Neonatal Indirect Hyperbilirubinemia

Nicole B. Anderson, MD,* Kara L. Calkins, MD, MS*

**Department of Pediatrics, Division of Neonatology and Developmental Biology, Neonatal Research Center of the UCLA Children's Discovery and Innovation Institute, David Geffen School of Medicine UCLA, Los Angeles, CA*

Practice Gaps

Neonatal indirect hyperbilirubinemia is a common diagnosis. Neonatologists should understand:

1. The physiology of bilirubin metabolism.
2. How altered bilirubin production and elimination contribute to severe neonatal indirect hyperbilirubinemia.
3. How prematurity and genetics contribute to severe indirect hyperbilirubinemia.
4. How to best screen, manage, and treat severe indirect hyperbilirubinemia to prevent complications associated with severe indirect hyperbilirubinemia, including kernicterus spectrum disorder.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
ABE	acute bilirubin encephalopathy
DAT	direct antigen testing
G6PD	glucose-6-phosphate dehydrogenase
HDFN	hemolytic disease of the fetus and newborn
Ig	immunoglobulin
IHB	indirect hyperbilirubinemia
IVIG	intravenous immunoglobulin
KSD	kernicterus spectrum disorder
NADP	nicotinamide adenine dinucleotide peptide
PT	phototherapy
RBC	red blood cell
Rh	Rhesus
TCB	transcutaneous bilirubin
TSB	total serum bilirubin
UGT	uridine diphosphoglucuronosyltransferase

Abstract

Neonatal indirect hyperbilirubinemia (IHB) is caused by an imbalance in bilirubin production and elimination. Approximately 60% of term and 80% of preterm infants develop jaundice in the first week of age. This review seeks to provide the reader with a thorough understanding of the physiology of bilirubin, etiology of IHB, and management of severe IHB. Phototherapy and exchange transfusion remain the mainstays of treatment for severe IHB. Noninvasive screening tools, innovative treatments, and a better understanding of how prematurity and genetics contribute to severe IHB have improved our understanding of IHB and may help eliminate the hazards associated with severe IHB, including kernicterus spectrum disorder.

Objectives After completing this article, readers should be able to:

1. Summarize the metabolism of bilirubin and causes of neonatal indirect hyperbilirubinemia.
2. Describe screening methods and treatment for indirect hyperbilirubinemia.
3. Identify why preterm infants are susceptible to brain injury from severe indirect hyperbilirubinemia.

4. Explain why specific genetic mutations increase the risk of severe indirect hyperbilirubinemia.

INTRODUCTION

Transient indirect hyperbilirubinemia (IHB) is an almost universal condition in the newborn. Clinically, IHB manifests as jaundice, or yellowing of the skin, sclera, and mucous membranes. Biochemically, IHB is defined by an increase in total serum bilirubin (TSB) as a result of an elevated indirect serum bilirubin. Although most neonates present with physiologic IHB, which is normal and benign, a subset of neonates will develop severe IHB warranting treatment. Each year, approximately 45,000 infants in the United States are evaluated for jaundice in emergency departments. (1) Sixty-five percent of all readmissions in the first week after birth, and 8% of readmissions in the second week after birth, are the result of severe IHB. (2) In cases of severe and untreated IHB, free bilirubin crosses the blood-brain barrier and causes brain injury. Premature infants and infants with Gilbert syndrome and glucose-6-phosphate dehydrogenase (G6PD) deficiency are particularly susceptible to severe IHB and kernicterus spectrum disorder (KSD). (3)(4)(5) Despite increased awareness, validated screening nomograms, and phototherapy (PT), KSD still occurs in highly resourced countries and is associated with a 10% mortality and 70% morbidity rate. (6)

BILIRUBIN PHYSIOLOGY

Bilirubin is a product of heme catabolism, which is primarily derived from hemoglobin in red blood cells (RBCs). Heme catabolism occurs in macrophages in the reticuloendothelial system. During RBC degradation, hemoglobin is broken down into globin and heme, which undergoes oxidation, producing biliverdin and carbon monoxide in equimolar amounts, along with Fe^{2+}. Carbon monoxide can be measured in the breath and serves as a biomarker for neonatal hemolysis, or increased bilirubin production. (7) Biliverdin is reduced to unconjugated bilirubin, which is released into the circulation. Because bilirubin is not water-soluble, bilirubin is transported in the plasma bound to albumin (Figure). Albumin's ability to bind bilirubin is determined by TSB concentrations and its capacity and affinity to bind bilirubin. In humans, the primary bilirubin isomer, IX-alpha (Z,Z), is lipophilic and crosses phospholipid membranes. The lipophilic nature of unbound, free bilirubin is why unbound bilirubin crosses the blood-brain barrier. In utero, unbound free bilirubin crosses the placenta for disposal by the maternal liver and, to a lesser extent, the maternal kidneys. Unlike the adult liver, the immature fetal liver is unable to conjugate and eliminate bilirubin via biliary excretion.

Postnatally, the role of bilirubin excretion transitions from the placenta to the neonatal liver. Bilirubin dissociates from albumin and is taken up by the liver. In the hepatocyte, uridine diphosphoglucuronosyltransferase (UGT)-1A1 conjugates bilirubin to glucuronic acid, producing a water-soluble product. Conjugated bilirubin is secreted into bile and then the intestine, where it is hydrolyzed and reduced by bacteria, yielding urobilinogen. Urobilinogen is oxidized by intestinal bacteria to urobilin and stercobilin, which are excreted in urine and stool, respectively. A portion of urobilinogen partakes in the enterohepatic cycle, a process by which bilirubin, bile acids, and specific drugs are reabsorbed from the small intestine, transported via portal circulation back to the liver, and re-excreted in bile (Figure).

Neonates develop IHB because of an increase in bilirubin preload and limited bilirubin disposal. Because of a shortened neonatal RBC lifespan, increased hematopoiesis, and enterohepatic circulation, neonatal bilirubin production is 2 to 3 times that of adult production. The neonatal RBC life span is approximately 70 to 90 days, compared with 120 days in adults. In comparison to children and adults, neonates, particularly preterm infants, have increased heme degradation of fetal hematopoietic tissues and increased cytochrome turnover. Complicating matters, neonatal UGT activity is only 1% of that of adults and does not reach adult levels until 3 months of age. (8) In addition, enterohepatic circulation is enhanced in neonates. This occurs for several reasons. First, meconium has a high concentration of bilirubin. Second, because of increased intestinal β-glucuronidase activity, bilirubin monoglucuronide and bilirubin diglucuronide are hydrolyzed, releasing bilirubin. Third, because of a lack of intestinal bacterial flora, conversion rates of bilirubin to urobilinogen are low.

CAUSES OF HYPERBILIRUBINEMIA

Jaundice is typically seen in an infant when the TSB level exceeds 5 mg/dL (85.5 μmol/L). Most often, this is because

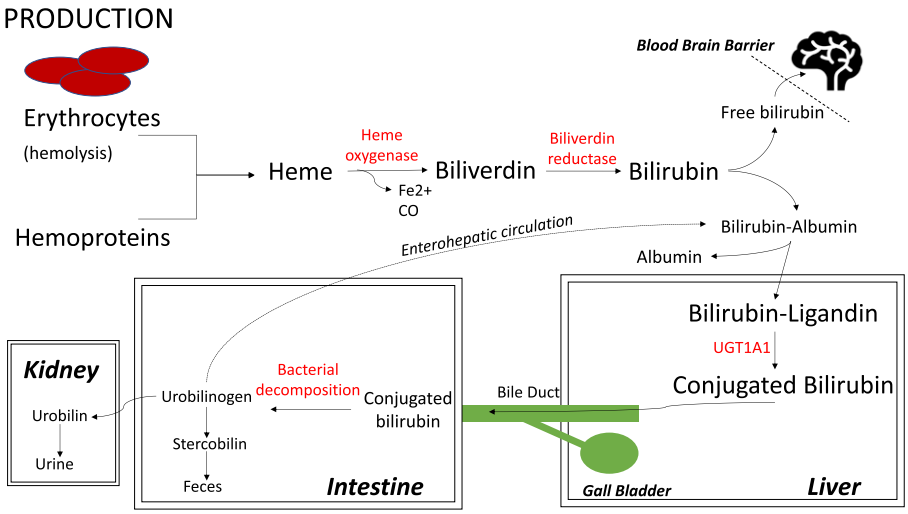

Figure. Bilirubin metabolism.

of unconjugated (indirect) hyperbilirubinemia. Less commonly, neonatal jaundice is the result of conjugated (direct) hyperbilirubinemia, also known as *cholestasis*. Unlike unconjugated hyperbilirubinemia, conjugated hyperbilirubinemia is always considered pathologic and deserves an appropriate and timely evaluation and treatment. Cholestasis is traditionally defined as a conjugated bilirubin concentration greater than 1.0 mg/dL (>17.1 μmol/L) when the TSB is less than or equal to 5 mg/dL (≤85.5 μmol/L), or more than 20% of TSB when the TSB is greater than 5 mg/dL (>85.5 μmol/L). Further discussion on neonatal cholestasis is outside the scope of this review.

IHB is often categorized as either physiologic or pathologic. Physiologic jaundice occurs because of neonatal bilirubin metabolism, appears after 24 hours of age, and usually resolves by approximately 2 to 3 weeks of age in full-term infants. On the other hand, IHB is considered pathologic if: 1) jaundice is observed in the first 24 hours of age, 2) the serum bilirubin level is higher than the 95th percentile for age in hours based on an hour-specific bilirubin nomogram, 3) the bilirubin level is increasing by more than 5 mg/dL (>85.5 μmol/L) per day or more than 0.2 mg/dL (>3.4 μmol/L) per hour, or 4) jaundice persists beyond 2 to 3 weeks of age in full-term infants. (3)

IHB can be divided into 4 primary categories: 1) increased enterohepatic circulation, 2) increased production, 3) decreased clearance, and 4) impaired conjugation (Table 1). In most cases, the etiology is multifactorial. Risk factors for severe IHB and neurotoxicity are listed in Table 2. The severity and incidence of severe IHB are inversely proportional to gestational age. (3)(4) Because of immature erythropoietic, hepatic, and gastrointestinal systems and delayed or limited enteral nutrition, premature infants typically have higher peak TSB concentrations and a prolonged course and slow resolution of IHB.

Increased Enterohepatic Circulation

Breast milk jaundice and breastfeeding jaundice are 2 distinct entities. By definition, breast milk jaundice is a prolongation of physiologic jaundice in a breastfed infant with normal weight gain and normal patterns of passing stools and urinating. Breast milk jaundice occurs in up to 30% of breastfed infants. The TSB trajectory over the first 4 days of age in exclusively breastfed infants and formula-fed infants is similar. Thereafter, while TSB concentrations decline in formula-fed infants after the fifth day after birth, TSB concentrations increase in breastfed infants, generally peaking between 5 and 15 days after birth. In breastfed infants, TSB concentrations rarely exceed 25 mg/dL (427.6 μmol/L). IHB may persist beyond 4 weeks of age and sometimes up to 3 months of age. (9) Breast milk jaundice is generally benign, and it is safe to continue breastfeeding. Temporary cessation of breastfeeding may decrease breast milk production and interfere with exclusive breastfeeding.

The etiology of breast milk jaundice remains unclear. Many people hypothesized that specific breast milk metabolites (ie, progesterone, pregnane-3α,20β-diol) inhibited hepatic UGT. However, this theory has been disproven. Others postulate that free fatty acids in breast milk displace bilirubin from albumin, while others claim that high breast milk β-glucuronidase concentrations increase intestinal

TABLE 1. Causes of Neonatal Indirect Hyperbilirubinemia

UNCONJUGATED HYPERBILIRUBINEMIA		
Increased enterohepatic circulation	Breast milk jaundice Breastfeeding jaundice	
Increased production	***Immune-mediated*** Blood group incompatibilities (ABO, Rh)	***Non–immune-mediated*** Inherited RBC defects • Enzyme defects o Glucose-6-phospate o Pyruvate kinase deficiency • Membrane defects o Hereditary spherocytosis o Hereditary elliptocytosis • Hemoglobinopathies o Thalassemias o Sickle cell disease • Sequestration o Cephalohematoma o Subgaleal hemorrhage o Intracranial hemorrhage Polycythemia Infection
Decreased clearance	Gilbert syndrome	
Impaired conjugation	Crigler-Najjar 1 Crigler-Najjar 2	
Other	Maternal diabetes Pyloric stenosis Intestinal obstruction Congenital hypothyroidism Bilirubin displacers	

hydrolysis of bilirubin monoglucuronide and bilirubin diglucuronide. In animal studies, rats fed breast milk demonstrated increased intestinal reabsorption of bilirubin compared with rats fed formula, and free fatty acid concentrations and UGT activity were not correlated with TSB concentrations. (10) Other studies have demonstrated that intestinal UGT1A is induced by formula but inhibited by breast milk. (11) Genetics also contribute to breast milk

TABLE 2. Risk Factors for Severe Neonatal Hyperbilirubinemia and Neurotoxicity (3)

SEVERE INDIRECT HYPERBILIRUBINEMIA	NEUROTOXICITY
Predischarge bilirubin screening level in the high-risk or high-intermediate-risk zone for age	Isoimmune hemolytic disease
Prematurity (<38 weeks)	Glucose-6-phosphate dehydrogenase deficiency
Exclusive breastfeeding	Asphyxia
Isoimmune or other hemolytic disease	Significant lethargy
Older sibling with jaundice	Temperature instability
Cephalohematoma or significant bruising	Sepsis
East Asian race	Acidosis
	Albumin <3 g/dL (<30 gL)

jaundice. Approximately 50% of Japanese infants with breast milk jaundice had specific *UGT1A1* mutations. The most common *UGT1A1* mutation was the variant that causes Gilbert syndrome. (12)

In contrast to breast milk jaundice, breastfeeding jaundice is physiologic jaundice that is exaggerated by caloric deprivation and dehydration leading to excessive weight loss because of insufficient breast milk production and/or a poor latch. Hence, it is not breastfeeding itself, but inadequate breastfeeding, that causes "breastfeeding" jaundice. Breastfeeding jaundice is a common entity and peaks at the same time as physiologic jaundice. Because of a prolonged intestinal transit time and delayed meconium passage, enterohepatic circulation is increased. Management includes increased breastfeeding frequency, supplementation with breast milk via a bottle, and formula supplementation. After birth, frequent feedings and lactation support for mothers are key to preventing breastfeeding jaundice. (3)

Increased Bilirubin Production

Hemolytic causes of severe IHB can be divided into immune and nonimmune. Blood group incompatibilities, such as ABO or Rh incompatibility, are the primary immune mechanisms for increased bilirubin production, leading to fetal and newborn hemolytic disease (HDFN). In HDFN secondary to ABO incompatibility, maternal immunoglobulin (Ig) G anti-A or anti-B antibodies cross the placenta and destroy fetal RBCs. HDFN occurs in only 4% of all newborns with ABO incompatibility. (13) Because IgG anti-A and -B antibodies also bind to antigens on non-RBC tissues and fetal RBC A and B glycoproteins are not fully developed, IHB is generally mild. IHB in these infants is characterized by a mild compensated hemolytic anemia, reticulocytosis, and microspherocytosis. The direct antigen titer (DAT), or Coombs test, is a commonly used test to diagnose HDFN. However, the sensitivity and positive predictive value of DAT for severe IHB is low. (14) This is most likely because DAT detects the presence of antibodies on the RBC, not the hemolytic potential of the antibodies. Hence, universal DAT testing is not recommended. (3)

D antigens are highly immunogenic, and, as a result, HDFN secondary to Rhesus (Rh) incompatibility can be severe and can cause hydrops fetalis. Prenatal maternal blood type testing is critical to identify pregnant women who are Rh-negative. If a fetus is Rh-positive and fetal blood is exposed to maternal Rh-negative blood, maternal anti-Rh antibodies are formed. Initially, the pregnant woman produces IgM antibodies, which do not cross the placenta. However, subsequent exposures lead to maternal IgG production, leading to erythroblastosis fetalis. Thus, the risk for HDFN increases with subsequent pregnancies with Rh-positive fetuses. This phenomenon is not observed with ABO incompatibility.

The American College of Obstetricians and Gynecologists (ACOG) recommends that all Rh-negative pregnant women, regardless of fetal blood type, receive RhD immune globulin at 28 weeks' gestation, and again after delivery if the infant is Rh positive or Rh unknown. (15) The incidence of maternal Rh alloimmunization dropped from 14% to 2% after the implementation of postnatal immunoprophylaxis in 1970, and even further to 0.1% after antenatal immunoprophylaxis was instituted. (16) Postnatally, intravenous immunoglobulin (IVIG) can be used to treat HDFN. (3) In some studies, particularly in Rh HDFN, IVIG has been shown to reduce PT duration, hospital stay, and the need for exchange transfusion. (17)(18) However, in a large meta-analysis, IVIG treatment was not associated with a clear benefit. (18)

Nonimmune causes of IHB are diverse and include inherited RBC defects, infections, sequestration, and polycythemia. RBC defects include enzyme defects, membrane defects, and hemoglobinopathies. The most common RBC enzyme defect is G6PD deficiency, an X-linked disease that afflicts over 300 million people worldwide. (19) G6PD converts glucose-6-phosphate to 6-phosphogluconate, which transfers a hydrogenion to nicotinamide adenine dinucleotide peptide (NADP). Reduced NADP is essential for maintaining glutathione, an important antioxidant. Over 200 mutations in the G6PD coding region have been identified. (20) These variants, which are usually the result of single amino acid substitutions, cause an accumulation of reactive oxygen species in the RBC, leading to RBC instability and hemolysis. G6PD deficiency is over-represented in neonates with severe IHB and bilirubin encephalopathy. (5)(19)(21) In female infants, severe IHB has been noted in both G6PD deficiency homozygotes and heterozygotes, particularly when combined with the *UGT1A1* gene bearing the variant promoter observed in Gilbert syndrome. (5) Cutoff values for enzyme assays for G6PD deficiency are dependent on the sex of the infant, the mutation, and whether the infant is a homozygote versus a heterozygote. (21) Next-generation sequencing has become an attractive tool to diagnosis these multigene hemolytic anemias.

RBC membrane defects include hereditary spherocytosis and hereditary elliptocytosis. Hereditary spherocytosis, the most common RBC structural defect causing IHB, is caused by various mutations in RBC membrane proteins, including spectrin, ankyrin, band 3, protein 4.2 (pallidin), and aquaporin-1. Seventy-five percent of mutations are dominantly inherited and the remaining 25% are inherited in a recessive fashion. (22) Hereditary elliptocytosis is caused by defects in

the RBC membrane scaffolding (ie, cytoskeletal) proteins, with α- and β-spectrin mutations being most common. Hereditary elliptocytosis is most commonly autosomal dominant, except for 1 autosomal recessive subtype called *hereditary pyropoikilocytosis*. Initial evaluation for a structural RBC defect includes a complete blood cell count with differential and a peripheral smear. In hereditary spherocytosis, the peripheral smear shows spherocytes without central pallor. In contrast, hereditary elliptocytosis is hallmarked by elliptocytes. Traditionally, the osmotic fragility test is used to diagnose RBC membrane disorders. However, flow cytometry is now commonly used to diagnose RBC membrane disorders.

Hemoglobinopathies less commonly contribute to neonatal IHB given the predominance of fetal hemoglobin at birth. The most common hemoglobinopathies that contribute to IHB in the newborn are thalassemias. Although presentation in the neonatal period is rare, sickle cell disease should be considered in cases of unexplained neonatal jaundice in Black infants. (23) Hemoglobinopathies are included in standard newborn screenings and are confirmed via hemoglobin electrophoresis.

Polycythemia also contributes to IHB. Studies have shown that postnatal placental transfusions are associated with reduced postnatal anemia and improved developmental outcomes among term and preterm infants. These findings have led to the widespread practice of delayed cord clamping and milking. (24)(25) In a meta-analysis of 7 trials that compared early versus delayed cord clamping in term infants, early cord clamping was associated with a lower risk for PT (relative risk 0.62, 95% confidence interval 0.41–0.96). (24) In contrast, in a randomized controlled trial of 1,570 preterm infants of less than 30 weeks' gestation, the timing of cord clamping was not associated with an increased risk for PT or exchange transfusion, but a 2.7% increase in hematocrit was noted in those with delayed cord clamping. (26) Given the potential benefits of placental transfusions, the widespread availability, and low side effect profile of PT, many agree that the benefits of placental transfusions outweigh any potential or theoretical risks. It should be noted, however, in 1 randomized controlled study of preterm infants of less than 32 weeks' gestation, when cord milking was compared to delayed cord clamping, cord milking was associated with a significantly increased risk of severe intraventricular hemorrhage, particularly in infants of less than 27 weeks' gestation. (27)

Decreased Bilirubin Clearance

Gilbert syndrome affects 6% to 9% of the population. Because of poor bilirubin uptake and decreased hepatic UGT activity, bilirubin clearance is decreased, causing chronic IHB. This autosomal recessive condition is most commonly caused by the presence of additional TA repeats in the promoter region (TATAA box) of the *UGT1A1* gene. *UGT1A1* is structurally normal, but its expression is reduced because the noncoding promoter region is affected. In the Asian population, mutations usually involve exon 1 in the *UGT1A1* gene. A hallmark of Gilbert syndrome is mild jaundice during times of stress in the absence of hemolysis or liver dysfunction. In the neonatal period, patients with G6PD deficiency and superimposed Gilbert syndrome or HDFN are at high risk for severe IHB and KSD. (5)

Crigler-Najjar type 1 is inherited in an autosomal recessive pattern and results in the complete absence of UGT activity. Intense jaundice is seen soon after birth, and bilirubin encephalopathy and neurologic impairment is common. Treatment includes phenobarbital, cyclic PT, and exchange transfusions. Response to PT declines over time, and liver transplantation is the only curative treatment. In contrast, Crigler-Najjar type 2 is characterized by an autosomal recessive or autosomal dominant mode of inheritance and is more common than type 1. In type 2, because UGT activity is reduced to less than 10% to 20% of normal function, TSB rarely exceeds 20 mg/dL (342 μmol/L) and bilirubin encephalopathy is rare. Treatment includes PT and phenobarbital. Crigler-Najjar types 1 and 2 are differentiated by clinical presentation, phenobarbital response, and diagnostic evaluation. Bile is pale in patients with type 1 because of complete absence of UGT in liver tissue, but pigmented in patients with type 2. Children with type 1 have mutations in exons 2 and 5 (type 1A) and bilirubin specific A1 exon (type 1B). Children with type 2 have single base pair mutations.

Other Causes

Other causes of neonatal IHB with complex mechanisms include maternal diabetes, pyloric stenosis, intestinal obstruction, and congenital hypothyroidism. Infants of insulin-dependent diabetic mothers are at an increased risk for severe IHB. (3) The degree of bilirubin production in these infants has been shown to be directly related to the degree of macrosomia. (28) Infants of diabetic mothers have increased erythropoiesis secondary to increased erythropoietin production and are more likely to be born preterm than infants born to mothers without diabetes. (29) Furthermore, there is some evidence that, for unclear reasons, diabetic

mothers produce more β-glucuronidase in their breast milk compared with nondiabetic mothers. (30)

Jaundice is common in infants with hypothyroidism and gastrointestinal obstructions, such as pyloric stenosis, volvulus, malrotations, intestinal atresias, Hirschsprung disease, and meconium ileus. In congenital hypothyroidism, impaired bilirubin hepatic uptake and decreased UGT activity along with slowed gut motility contribute to IHB. However, the exact mechanism remains unknown. Intestinal obstructions lead to increased bilirubin absorption because of lack of enteral nutrition, intestinal stasis, and bilirubin recycling via the enterohepatic cycle.

Pharmacologic agents can affect albumin binding with many medications acting as exogenous bilirubin displacers (Table 3). (31) Notably, ibuprofen, a pharmacologic treatment for patent ductus arteriosus, can displace bilirubin from albumin. Potential sources of infant exposure to bilirubin displacers include maternal medications taken during pregnancy, breast milk, and medications directly given to the infant (eg, sulfa drugs, ibuprofen, and cefazolin). Free fatty acids can act as an endogenous source of a bilirubin displacer. Premature infants, unlike their term counterparts, ineffectively clear free fatty acids. In extremely premature infants, the dose of the intravenous lipid emulsion was correlated with unbound free bilirubin and free fatty acids were inversely correlated with albumin affinity. (32)

BILIRUBIN NEUROTOXICITY

High TSB concentrations can quickly overwhelm the neonate's immature metabolic processes. The incidence of kernicterus ranges by report and country (0.5–1.3 per 100,000 births). (33) A study in Sweden estimated that 85% of kernicterus cases were preventable and could have been avoided with evidence-based practices. (33) Risks for bilirubin encephalopathy include displaced bilirubin and a damaged or weak blood-brain barrier. Both can occur in asphyxia, acidosis, and sepsis. (3) Acute bilirubin encephalopathy (ABE) should be considered if the TSB is greater than 25 mg/dL (427.6 μmol/L) in any term or near-term infant.

Preterm infants have a more permeable blood-brain barrier. Also, albumin in preterm infants is characterized by a decreased binding affinity and capacity. As a result, premature infants can develop bilirubin toxicity and long-term neurologic sequelae at much lower TSB levels compared with term or near-term infants. In a retrospective study of 2,575 extremely low birthweight infants, TSB in the first 14 days after birth correlated positively with hearing loss and death or neurodevelopmental impairment at 2 years of age. (34) Preterm infants do not display the initial classic clinical signs of ABE. Thus, close monitoring and high index of suspicion are required when caring for preterm infants.

Early ABE, or phase I, presents as poor suck, hypotonia, lethargy, and jitteriness. Intermediate ABE, or phase II, includes retrocollis, hypertonia, and opisthotonos. Advanced ABE, or phase III, includes intermediate signs plus seizures, apnea, and possible death. Phase I is reversible, whereas phases II and III may be reversible, depending on treatment timing. The term *kernicterus* traditionally refers to the neuropathology that is a consequence of bilirubin neurotoxicity. Historically, the diagnosis of kernicterus was made on autopsy with a yellow staining pattern

TABLE 3. **Bilirubin Displacers**

STRONG DISPLACERS	WEAK DISPLACERS
Sulfa drugs	Nafcillin
Ceftriaxone	Ampicillin
Cefotetan	Oxacillin
Cefazolin	Aminophylline
Carbenicillin	Furosemide
Moxalactam	Phenobarbital
Dicloxacillin	Papaverine
Methicillin	
Ibuprofen	

of the brainstem nuclei and cerebellum, with bilirubin-induced cell apoptosis and neuronal necrosis. Chronic bilirubin encephalopathy develops gradually over time, with most infants demonstrating clinical manifestations within the first year of age.

KSD includes a spectrum of neurologic sequelae caused by bilirubin neurotoxicity, including ABE and chronic bilirubin encephalopathy. (35) However, the term kernicterus is most often used in reference to chronic bilirubin encephalopathy. Classic KSD includes choreoathetoid cerebral palsy, an upward gaze, sensorineural hearing loss, and dental dysplasia of the deciduous teeth. Classic KSD can be diagnosed in infants with a history of elevated bilirubin who demonstrate abnormal tone on physical examination, auditory brainstem response diagnostic of auditory neuropathy or dys-synchrony, and bilateral basal ganglia lesions on magnetic resonance imaging. (36) Cognitive function is relatively spared in KSD, but these patients may be perceived as being more cognitively impaired because of extrapyramidal movement disorders and hearing loss. It is now widely recognized that there are more subtle cases of chronic bilirubin encephalopathy, such as auditory, learning, and behavioral disorders, and fine and gross motor incoordination.

HYPERBILIRUBINEMIA SCREENING

The American Academy of Pediatrics (AAP) recommends universal bilirubin screening in all neonates within the first 72 hours of age via TSB or transcutaneous bilirubin (TCB) measurement. (3) Implementation of screening guidelines has led to a decrease in the incidence of extreme IHB in the United States and other countries. (33)(37) When measuring TSB in the newborn nursery, a screening direct or conjugated bilirubin measurement should be obtained. When infants who were later diagnosed with biliary atresia were compared with healthy, term infants, neonates with biliary atresia had a higher direct or conjugated bilirubin in the first 24 to 48 hours after birth (1.4±0.43 vs 0.019±0.75 mg/dL [23.9±7.3 vs 0.32±12.8 μmol/L], $P<.0001$). (38)

Bilirubin is most commonly measured via the diazo method. This method provides 2 qualitative measurements, the total bilirubin and the "direct" bilirubin level. The "indirect" bilirubin is calculated by subtracting the direct from the total bilirubin. The direct bilirubin level is an estimate of the conjugated bilirubin level, but it can overestimate the true conjugated bilirubin level because the diazo reagent reacts with both conjugated bilirubin and bilirubin bound to albumin (δ-bilirubin). Similarly, the indirect bilirubin is an estimation of unconjugated bilirubin, but it tends to underestimate unconjugated bilirubin because a portion of the unconjugated bilirubin reacts with the diazo reagent. Thus, quantitative methods, such as high-performance liquid chromatography, direct spectrophotometry, and enzymatic assays, are considered more accurate. (39) Given the altered bilirubin-albumin binding capacities in premature infants, unbound free bilirubin may be a more sensitive and specific predictor of bilirubin-induced neurotoxicity. (40) Free bilirubin can be measured using the modified peroxidase method. Unfortunately, this test is not available in the clinical setting.

Noninvasive bilirubin measurement tools include the transcutaneous bilirubinometer as well as via pulse oximetry (spectrophotometry). Emerging novel techniques include exhaled carbon monoxide spectroscopy and optical imaging of conjunctiva. In term and late preterm infants, TCB measurements are quick and accurate, provide a painless estimation of TSB, and are associated with less blood sampling and a decreased incidence of anemia, particularly in very low-birthweight infants. (41)(42) TCB measurements are influenced by the TCB device, gestational age, TSB, postnatal age, race/ethnicity, and measurement site. (41)(42)(43) Because TCB underestimates TSB, in term infants, the AAP recommends measuring the TSB when considering a therapeutic intervention if: 1) the TCB is at 70% of the TSB level recommended for PT, 2) the TCB is above the 75th percentile on the Bhutani nomogram, or 3) the postdischarge TCB value is higher than 13 mg/dL (222.3 μmol/L). (4) In very low-birthweight infants, TCB reliably estimates TSB; the difference between TSB and TCB values is small and correlation coefficients are high. (41)(42)(43)(44) During PT, the TSB and TCB difference increases. Because PT bleaches the skin, covering a small patch of skin with a photo-opaque patch or other measure improves TCB accuracy. (42)(44)

HYPERBILIRUBINEMIA TREATMENT

The ultimate goal of recognizing and treating unconjugated HB is to prevent bilirubin neurotoxicity. In 2004 and 2009, the AAP provided evidence-based guidelines to reduce the incidence of severe IHB and bilirubin-induced encephalopathy in infants of gestational age greater than or equal to 35 weeks. (3)(4) The guidelines incorporate an hour-specific bilirubin nomogram for assessing the risk of IHB, and PT recommendations for hour-specific treatment thresholds. (45) Online calculators, such as BiliTool™, have been created based on these guidelines. (46)

TABLE 4. **Suggested Guidelines for Starting Phototherapy in Premature Infants (47)**

GESTATIONAL AGE	TSB THRESHOLD FOR PHOTOTHERAPY (mg/dL)	TSB THRESHOLD FOR EXCHANGE TRANSFUSION (mg/dL)
<28 weeks	5–6	11–14
28–29 6/7 weeks	6–8	12–14
30–31 6/7 weeks	8–10	13–16
32–33 6/7 weeks	10–12	15–18
34–34 6/7 weeks	12–14	17–19

TSB=total serum bilirubin.

Low-birthweight and premature infants were excluded from the 2004 AAP guideline, given the paucity of evidence. However, a consensus-based approach to IHB in infants of less than 35 weeks' gestational age was published in 2012, which includes recommendations for initiation of PT and exchange transfusion based on gestational age and TSB (Table 4). (47) Similar to BiliTool, online calculators have been created based on these recommendations, such as Stanford University's Premie BiliRecs. (48)

Phototherapy

PT reduces serum bilirubin primarily via geometric (irreversible) isomerization of unconjugated bilirubin to lumirubin, a water-soluble substance that is excreted via bile and urine without conjugation. Photoisomerization (reversible) and photo-oxidation of bilirubin also contribute to its treatment effect. PT is indicated when the bilirubin level is approaching a possible toxic range. Bilirubin absorbs light most effectively in the blue region of the spectrum (460–490 nm). High-intensity light-emitting diodes have been shown to be the most effective light sources for bilirubin degradation. Conventional PT and intensive PT have irradiances of 6 to 12 $\mu W/cm^2$ per nanometer, and at least 30 $\mu W/cm^2$ per nanometer, respectively. The PT "dose" is affected by the distance of the infant from the light source, as well as the surface area exposed. The recommended distance of the infant from the light source is 12 to 16 inches (~30 to 40 cm). Skin exposure should be maximized by providing light above and below the infant, who should be naked (except for a diaper) in a servo-controlled incubator. The infant can be removed from the light for breastfeeding.

PT should be initiated when the TSB is at or above PT threshold based on the infant's age and risk factors and considered when the bilirubin level is within 2 to 3 points from the PT threshold. Typically, one expects a decrease in TSB of approximately 0.5 mg/dL (8.5 μmol/L) within the first 4 to 8 hours of treatment. Although the AAP does not provide recommendations on bilirubin monitoring during PT, when to discontinue treatment, and bilirubin measurements after PT, the UK National Institute for Health and Clinical Excellence recommends checking TSB levels 4 to 6 hours after initiation of PT, and every 6 to 12 hours once the TSB is stable or trending downward. (49) There is no universal agreement on when to discontinue PT. However, when the TSB is at least 3 points below light level or decreases to less than or equal to 14 mg/dL (239.4 μmol/L), the risk for severe IHB requiring PT is rare. (50)(51) The usefulness of rebound TSB measurements, or TSB measurements after PT discontinuation, does not appear to have any value for term and late preterm infants. (50) Because premature infants and infants with HDFN have a high risk for rebound IHB, these infants warrant additional monitoring.

PT is an essential part of IHB management, but PT is not entirely benign. Although high concentrations of unbound free bilirubin cause neuronal apoptosis, mildly elevated levels of unconjugated bilirubin have antioxidant and anti-inflammatory properties. In term infants, some studies have associated PT with a slightly increased risk of cancer in infancy. (52) PT may induce oxidative injury to cell membranes and DNA, particularly in extremely low-birthweight infants who have extremely translucent skin. (53) For these reasons, ongoing research is investigating alternative PT strategies, including lower irradiances and cycled PT for very premature infants. (54)

"Aggressive" PT, or prophylactic PT, is often used for infants at risk for HDFN and preterm infants. Aggressive PT refers to initiating or continuing PT at lower bilirubin thresholds or initiating PT without measuring bilirubin. On the other hand, "conservative" PT, or conventional PT, refers

to starting PT at standard bilirubin thresholds. In a single-site study, full-term infants with ABO incompatibility and a positive DAT were randomized to either prophylactic PT initiated in the first 4 hours of age or routine PT. When infants who received prophylactic PT were compared with infants who received standard care, infants who received prophylactic PT had longer hospital stays without any clinical benefit. (55) Hence, the potential benefits and risks of PT overtreatment should be carefully considered in all infants.

Although animal studies suggest that PT may cause retinal damage, the risk to humans is unknown. Regardless, eye shields should be worn. The "bronze baby" syndrome is seen in infants with conjugated HB who receive PT. The urine and skin turn a bronze color because of the photodestruction of copper porphyrins. This syndrome is generally benign. PT is contraindicated in congenital erythropoietic porphyria, which is a rare disease in which exposure to high-intensity light causes severe bullous lesions and can lead to death.

Exchange Transfusion

Exchange transfusion is indicated in any infant with ABE, and should be considered when TSB reaches the exchange transfusion threshold. (3) Continued rise in TSB despite PT treatment often indicates an ongoing hemolytic process. If exchange transfusion is being considered, albumin concentration in conjunction with TSB level should be measured. Bilirubin/albumin ratios act as a surrogate for free bilirubin, and high bilirubin/albumin ratios are associated with neurologic dysfunction. (3)

Double-volume exchange transfusion is performed via apheresis. The process involves drawing the patient's blood, then separating and removing the RBCs, effectively removing circulating bilirubin and maternal antibodies. The removed RBCs are replaced with the same quantity of donor RBCs, free of maternal antibodies. This process replaces approximately 85% of circulating RBCs and decreases the bilirubin level by about 50%. Exchange transfusion is not without risks, including infection, thrombocytopenia, coagulopathies, graft-versus-host disease, necrotizing enterocolitis, portal vein thrombosis, electrolyte disturbances, cardiac arrhythmias, and a mortality rate of approximately 0.5% to 2%. (56)

Drugs

Potential pharmacologic modalities to prevent or treat IHB include phenobarbital and metalloporphyrins. Phenobarbital increases hepatic uptake and conjugation of bilirubin. However, phenobarbital is no longer recommended as a treatment for severe IHB because of its side effect profile. Metalloporphyrins, such as mesoporphyrin, inhibit the production of heme oxygenase and appear to be a promising drug treatment. Mesoporphyrin may help prevent hospitalization, PT, and exchange transfusion in severe IHB. (57) However, as of the time of this publication, mesoporphyrin is not approved by the US Food and Drug Administration.

CONCLUSION

Bilirubin is a breakdown product of heme catabolism and is found in physiologically high levels in the neonate. Severe and untreated IHB can result in KSD, a preventable complication. It is essential that health care professionals are able to recognize infants at risk for severe IHB and KSD. Competency in IHB screening, prevention, and treatment are critical to newborn care and optimizing neonatal outcomes.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know bilirubin physiology, including pathways of synthesis, transport, and metabolism, in the fetus and neonate.
- Know the factors, including red cell life span, enzyme defects, and red cell structural abnormalities, associated with an increase in bilirubin production.
- Know the factors associated with a decrease in neonatal serum bilirubin excretion, including those that affect the enterohepatic circulation of bilirubin.
- Know the differences between physiologic and nonphysiologic jaundice.
- Know the pathologic findings of kernicterus.
- Know the factors affecting the binding of bilirubin to albumin and know the pharmacologic agents which affect binding.
- Know the factors that increase the risk of the development of kernicterus.
- Know the clinical features of acute bilirubin encephalopathy in newborn infants.
- Know the clinical features of kernicterus.
- Know the mechanisms for physiologic jaundice.
- Know the course of physiologic jaundice in the newborn infant.
- Know the range of normal serum bilirubin concentration and the effects of an infant's age, race, and feeding circumstances on serum bilirubin.
- Know the pathogenesis, clinical course, diagnosis, and management of breastfeeding jaundice.

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