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Neonatal Hyperbilirubinemia

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INTRODUCTION

Neonatal jaundice is the most common physiologic variant encountered in the newborn. More than 60% of healthy term neonates, and even a greater percentage of breastfed infants, display some degree of visible jaundice during the first week of life. Usually the body's regulatory mechanisms succeed in keeping the serum total bilirubin (STB) level within physiologic levels, and therefore at a concentration that is nontoxic. Indeed, STB concentrations within this range may even have beneficial antioxidant properties.

On occasion, STB levels may increase and significant hyperbilirubinemia may develop. Not all degrees of hyperbilirubinemia are necessarily dangerous, but because of the potential for the STB to continue to rise, phototherapy may be indicated. By facilitating bilirubin elimination, further rise of STB may be limited, thereby preventing the potential for bilirubin neurotoxicity. Rarely, the STB may increase to extreme levels at which bilirubin neurotoxicity may occur. In these cases, bilirubin—especially the unbound fraction—may enter vulnerable brain cells, especially the basal ganglia and auditory nerve tissue, causing acute bilirubin encephalopathy with the potential for progressing to the chronic form of bilirubin neurotoxicity, choreoathetoid cerebral palsy (kernicterus).

It is not our intention in this chapter to provide yet another all-inclusive treatise on neonatal hyperbilirubinemia. Rather, following some background information regarding neonatal hyperbilirubinemia, the reader will be presented with some actual clinical cases drawn from the authors' experience. The reader is encouraged to put himself or herself in the "driver's seat" and actually manage the patients, making clinical decisions from the options provided. The cases will provide the opportunity for in-depth discussions of the issues at hand and focus on practical issues that the practitioner may encounter on a daily basis.

THE SERUM TOTAL BILIRUBIN: WHAT DOES IT REPRESENT?

CASE 1

A 36 weeks' gestation, otherwise healthy infant aged 24 hours was being discussed on rounds in the regular newborn nursery. The STB was 15.0 mg/dL. The professor asked the residents what this value actually meant. The following possibilities were suggested.

Exercise 1

Question

Which answer do you think is correct?

A. One resident plotted the result on the hour-specific bilirubin nomogram. Because the value was greater than the 95th percentile, this resident concluded that increased hemolysis was present.
B. The second resident related to the late prematurity of this infant. The bilirubin conjugating system is immature, he claimed, resulting in the increased STB.
C. The third resident claimed that the pathogenesis of the high STB value was multifactorial and that both increased bilirubin production and hemolysis contributed to its development.

Answer

The third resident (C) supplied the correct answer. He correctly argued that several physiologic or pathophysiologic processes contributed to the STB. He claimed that no single process is responsible for an STB value at any point in time but that the STB value represents a combination of processes acting in tandem. The first resident's answer (A) was incorrect because although increased hemolysis may have been present, he did not take bilirubin elimination into account. Similarly, the second resident (B) correctly identified late prematurity with diminished conjugation ability of the infant as a risk factor but neglected to take the potential for increased hemolysis into account.

The STB: a Delicate Balance of Forces

Equilibrium Between Bilirubin Production and Elimination

The STB at any point in time, in any newborn, represents a combination of forces both affecting heme catabolism with subsequent bilirubin production, on the one hand, and bilirubin elimination—regulated by the processes of bilirubin conjugation and excretion—on the other. In the newborn, reabsorption of bilirubin from the bowel, as part of the enterohepatic circulation, adds to the bilirubin pool to be subsequently eliminated. As long as these processes remain in

equilibrium, the STB may rise to physiologic levels but should not pose a threat to an otherwise healthy term newborn without hemolysis.

Lack of Aforesaid Equilibrium

Should this delicate balance become compromised and bilirubin production exceed bilirubin elimination, the equilibrium will fail and hyperbilirubinemia may result. Severe hemolysis per se or immature bilirubin conjugation in and of itself may not necessarily result in hyperbilirubinemia. For example, an infant with blood type A, born to a woman with blood type O who has a positive direct antiglobulin test (DAT, also known as the Coombs test), can be expected to be a strong bilirubin producer but may not necessarily develop hyperbilirubinemia, should the bilirubin conjugation and elimination processes be well functioning. On the other hand, moderate hemolysis coupled with immaturity of UDP-glucuronosyltransferase 1A1 (UGT1A1, the bilirubin conjugating enzyme) as might occur in a late preterm infant, may result in lack of equilibrium between the aforementioned processes with resultant hyperbilirubinemia. A third cause of lack of equilibrium may result from nonfunction of the conjugation system in the absence of any hemolysis, as in Crigler-Najjar syndrome.

This concept has been likened to the filling of a kitchen sink with water. Provided the drainage is functional, an influx of water may not result in the water level increasing. Partial blockage of the drain may lead to a high water level even with a partly opened tap. Kaplan et al demonstrated this concept mathematically by using a production–conjugation index, which illustrates the contribution of the combined forces of bilirubin production and conjugation to the STB at any point in time. The blood carboxyhemoglobin concentration (corrected for inspired CO), an index of heme catabolism, and the serum total conjugated bilirubin (a reflection of intrahepatocytic conjugated bilirubin) have been used as components of this index. A rising index suggests an increasing lack of equilibrium between production and excretion.

It should be obvious that when evaluating a hyperbilirubinemic infant, both etiologic factors contributing to increased bilirubin production and diminished bilirubin conjugation should be taken into consideration. Given the unreliability of hematological indices to reflect hemolysis in the newborn, it may be difficult to distinguish disorders associated with increased production or increased excretion. These processes may include exaggerated heme catabolism (hemolysis), immaturity of UGT1A1, and reabsorption of bilirubin from the bowel to reenter the bloodstream. Immaturity in the enzyme UGT1A1 may be compounded by presence of the $(TA)_n$ polymorphism in the promoter of the *UGT1A1* gene (*UGT1A1*28*), resulting in diminished gene expression with decreased enzyme activity (Gilbert syndrome). Poor feeding may result in sluggish peristalsis and bowel stasis with increased reabsorption of bilirubin via the enterohepatic circulation. Factors affecting lack of equilibrium between the processes contributing to the serum total bilirubin are summarized in Table 5.1.

TABLE 5.1 Factors Affecting Lack of Equilibrium Between the Processes Contributing to the Serum Total Bilirubin at any Specific Point in Time

Increased hemolysis
Immaturity of the bilirubin conjugating enzyme, UDP-glucuronosyltransferase 1A1 (UGT1A1)
(TA)n promoter polymorphism of the encoding gene *UGT1A1* with resultant diminished gene expression and enzyme activity (associated with Gilbert syndrome in adults)
Enterohepatic circulation

Is the STB Predictive of Bilirubin Neurotoxicity?

Although, for practical purposes, the STB is used as the tool for the management of neonatal hyperbilirubinemia, including the indications for phototherapy and exchange transfusion, this test is actually not a good predictor of bilirubin-related neurologic outcome. Although it is unlikely that an otherwise healthy term infant with no obvious hemolytic condition will develop bilirubin neurotoxicity at STB levels under 25 mg/dL, there is actually no specific cutoff point at which an STB level will or will not be predictive of neurotoxicity. Certainly not all newborns with extreme hyperbilirubinemia go on to develop choreoathetoid cerebral palsy. For example, in one study of 140 newborns with STB values above 25 mg/dL who were treated with phototherapy or exchange transfusion, overall, 5-year outcomes were not significantly different from those of randomly selected controls. In a reanalysis of data from the Collaborative Perinatal Project, there was no relationship, overall, between maximum STB levels and subsequent IQ scores. However, in both these studies, the presence of a positive DAT resulted in a poorer prognosis. (See section on hemolysis.) Similarly, of 249 newborns admitted to a children's hospital in Cairo, Egypt, all of whom had STB values 25 mg/dL and above, there was little correlation between admission STB and acute bilirubin encephalopathy. However, in babies with hemolytic risk factors including Rh incompatibility, ABO incompatibility, and sepsis, the threshold STB for identifying babies with bilirubin encephalopathy was lower relative to those without these factors.

If the STB Is Not a Good Predictor of Bilirubin Neurotoxicity, Then What Is?

Predictive Value of Serum Unbound Bilirubin

Several studies have suggested that the unbound bilirubin fraction may be a more accurate predictor of bilirubin toxicity—including choreoathetoid cerebral palsy and sensorineural hearing loss—than STB, both in term and preterm infants. Use of the unbound fraction as an indication for

institution of phototherapy or for performing exchange transfusion would take much of the guesswork out of the decision-making process and permit better identification of the infant at risk for brain damage. Currently, however, unbound bilirubin determinations are in the main unavailable for routine clinical use, and STB remains the cardinal laboratory indication used for clinical decision making in hyperbilirubinemic newborns.

DEFINITIONS

Jaundice and Hyperbilirubinemia

The terms jaundice and hyperbilirubinemia are sometimes, incorrectly, used interchangeably.

Jaundice refers to a yellow coloring of the sclera, skin, and mucous membranes caused by infiltration from the serum of the yellow pigment bilirubin. *Hyperbilirubinemia*, on the other hand, relates to a measurement of serum or transcutaneous bilirubin, the result of which is greater than an accepted norm.

The Hour-Specific Bilirubin Nomogram

In infants 35 weeks' gestation or greater, a useful definition of hyperbilirubinemia is a STB value greater than the 95th percentile for age in hours on the Bhutani et al hour-specific bilirubin nomogram (Fig. 5.1). Use of the nomogram adjusts for the dynamic changes in STB during the first postnatal week and obviates the concept whereby a single STB value is regarded as representative of hyperbilirubinemia. Thus an infant with an STB value of 10.0 mg/dL at 12 hours will be regarded as hyperbilirubinemic, whereas the same concentration 48 hours later will have little significance.

Variations on This Definition

In newborns with lower gestational ages or with risk factors for hyperbilirubinemia, according to the 2004 AAP guidelines, phototherapy may be indicated at levels of STB below the 95th percentile. Thus many newborns receiving treatment may not actually meet these criteria for hyperbilirubinemia. Variations on this definition, to accommodate intervention with phototherapy, include use of an STB value within 1 mg/dL of the indications for phototherapy or an STB value exceeding the 75th percentile on the bilirubin nomogram.

Bilirubin Encephalopathy and Kernicterus

The terms acute bilirubin encephalopathy and kernicterus are often used interchangeably, although the AAP recommends differentiating these two conditions (AAP, 2004). *Acute bilirubin encephalopathy* relates to the acute manifestations of bilirubin neurotoxicity seen during or immediately following an episode of extreme hyperbilirubinemia. Permanent features of choreoathetoid cerebral palsy may ensue, but reversal, when appropriately treated, has been reported.

Kernicterus, on the other hand, refers to chronic and permanent sequelae attributable to bilirubin neurotoxicity, the result of bilirubin deposition in the target nuclei of the brain.

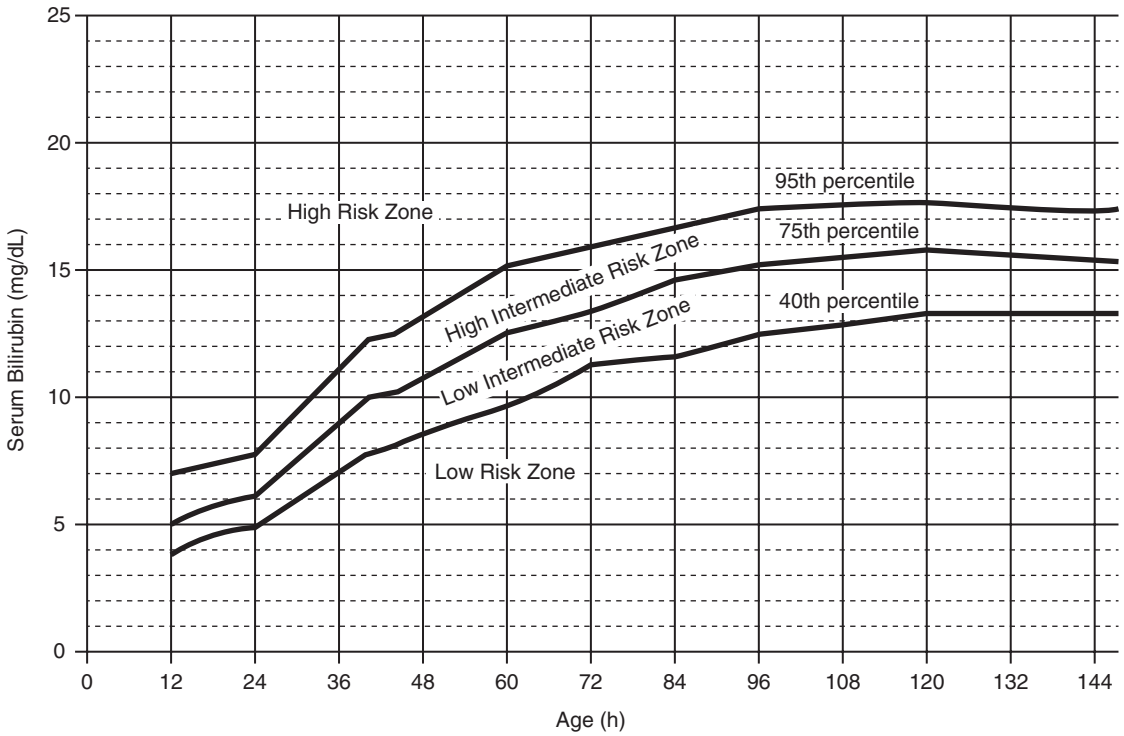


Fig. 5.1 Nomogram for designation of risk in 2840 well newborns at ≥36 weeks' gestational age with birth weight of ≥2000 g or ≥35 weeks' gestational age and birth weight of ≥2500 g based on the hour-specific serum bilirubin values. (Reproduced with permission from Bhutani VK, Johnson L, Sivieri EM, Predictive ability of a predischarge hour specific bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*;103:6–14, 1999.)

PHYSIOLOGY OF BILIRUBIN PRODUCTION AND METABOLISM

An understanding of the basic concepts of bilirubin physiology is necessary for perceptive management of the hyperbilirubinemic newborn. As detailed reviews of this subject are available in standard texts, only an outline will be provided here as a basis for comprehension of the subsequent portions of the chapter. Variations in bilirubin physiology peculiar to the newborn, contributing to the development of hyperbilirubinemia, are interspersed among the descriptions of basic bilirubin physiology.

A. Bilirubin Formation

Most heme is produced by the destruction of red blood cells (RBC) in the reticuloendothelial system, although some is produced from turnover of hemoproteins such as myoglobin. Heme itself is catabolized to biliverdin by the enzyme heme oxygenase 1 and thence to bilirubin. This bilirubin component is termed unconjugated or indirect bilirubin. In newborn infants, the RBC mass is larger, the turnover of the RBC is more rapid, and the cell lifespan is shorter than in adults. There is thus a relatively large heme load that contributes to the bilirubin pool.

B. Bilirubin Binding to Serum Albumin; Unbound Bilirubin

To facilitate transportation to the liver, indirect bilirubin is bound to serum albumin. This step is very important in our current understanding of the pathophysiology of bilirubin neurotoxicity. As long as the bilirubin molecule is bound to albumin, it is not expected to cross the blood–brain barrier and to cause bilirubin neurotoxicity. Should the albumin-binding sites be saturated and the bilirubin unable to bind, unbound, or free, bilirubin will result. The unbound bilirubin fraction is thought to be that capable of entering bilirubin-sensitive brain cells and causing neurotoxic damage. Potential causes of unbound bilirubin formation, raising the risk for neurotoxicity, should always be kept in mind when evaluating an infant for hyperbilirubinemia. Some causes potentiating unbound bilirubin formation are listed in Table 5.2.

TABLE 5.2 Some Causes of Unbound Bilirubin Formation

Hypoalbuminemia
Excessive hemolysis even in the presence of normal serum albumin concentrations
Metabolic acidosis
Hypothermia
Sepsis
Drugs such as sulfa-containing antimicrobials
Prematurity (possible)

C. Bilirubin Uptake

Uptake Genes

Uptake of bilirubin into the liver is controlled by the solute carrier organic anion transporter protein 1B1, *SLCO1B1,* also known as *OATP2.* Varying expression of this sinusoidal transporter gene, the result of polymorphisms, may affect bilirubin kinetics and metabolism. For example, the *SLCO1B1*1b* variant is associated with neonatal hyperbilirubinemia in Taiwanese newborns, especially when coupled with *UGT1A1* variants. Similarly, coexpression of *SLCO1B1*1b* with G6PD A− was associated with hyperbilirubinemia in a study from the United States.

D. Bilirubin Conjugation and Elimination

The Importance of UDP-Glucuronosyltransferase 1A1 (UGT1A1)

Following uptake into the hepatocyte, indirect bilirubin is conjugated with glucuronic acid to form water soluble mono- and diglucuronides. These complexes are known as conjugated or direct bilirubin. The enzyme controlling the conjugation process is UGT1A1. Immaturity of UGT is an important contributor to hyperbilirubinemia in both term and preterm infants. In term infants, activity of UGT is only about 1% that of adults, and it is even less in preterm infants. Developmental immaturity with slowing of the conjugation process is actually the bottleneck of the neonatal bilirubin elimination process and the reason that the majority of newborns exhibit some degree of visible jaundice during the postnatal period.

Genetic Control of Bilirubin Conjugation

There is increasing appreciation that the modulation of serum bilirubin levels and the development of hyperbilirubinemia may be under genetic control. A detailed account of all the genes contributing to bilirubin metabolism is beyond the scope of this text. Because of the practical nature of the enzyme UGT1A1, its genetic control is discussed in some detail.

The enzyme UGT1A1 is encoded by the gene *UGT1A1,* mapped to chromosome 2q37. This gene contains both a noncoding promoter region and a coding region. Polymorphisms of the promoter region, such as the $(TA)_n$ polymorphism, result in diminished expression of a normally formed enzyme and are associated with Gilbert syndrome. On the other hand, coding area mutations as seen in Crigler-Najjar syndrome result in an abnormally structured enzyme that has no or little conjugating ability. Coexpression of genes, presence of several mutations or polymorphisms, and interactions with environmental factors may potentiate the genetic contribution to the pathophysiology of neonatal hyperbilirubinemia. A paradigm of this concept may be found in the pathophysiology of neonatal hyperbilirubinemia in glucose-6-phosphate dehydrogenase (G6PD) deficient neonates, in which interaction between environmental factors (triggering hemolysis), the G6PD deficiency in and of itself, and $(TA)_n$ promoter polymorphisms of *UGT1A1 (UGT1A1*28)* may potentiate severe hyperbilirubinemia.

E. Excretion of Bilirubin Into the Bowel and the Enterohepatic Circulation

Direct bilirubin is secreted into the bile and then to the bowel from which it is excreted in the stool. The presence of the enzyme beta-glucuronidase in the colon deconjugates bilirubin-glucuronides and allows the reabsorption of bilirubin into the bloodstream, thereby adding to the bilirubin pool. A delay in enteral feeding or poor intake may diminish intestinal motility. The resultant increased bowel stasis with decreased elimination will allow for even greater reabsorption of bilirubin.

INCREASED HEMOLYSIS: A RISK FACTOR FOR HYPERBILIRUBINEMIA AND BILIRUBIN NEUROTOXICITY

Given the universal immaturity of the enzyme UGT1A1, it is fair to suggest that almost all newborns have suboptimal bilirubin conjugation. Taking the bilirubin production–conjugation equilibrium into account, it stands to reason that hemolysis must therefore be a cardinal factor in the pathogenesis of hyperbilirubinemia in many newborns.

ABO ISOIMMUNIZATION

CASE 2

Baby AB was born at term gestation to a blood group O, Rh-negative mother. On admission to the nursery, the nurses thought that the baby's skin had a yellow tinge. The physician believed this was only very mild jaundice and chose to ignore it. An astute nurse, however, took an STB at age 12 hours, the result of which was 9.2 mg/dL. "Not very high," responded the physician. By the next day (28 hours) the STB value was 15 mg/dL.

Exercise 2

Question

What would you do?

A. Observe the baby and repeat the STB in another 24 hours
B. Place the infant under intense phototherapy and repeat the STB in 4 to 6 hours
C. Begin phototherapy and proceed to exchange transfusion

Answer

The correct answer is B, but this baby had not been correctly managed from the outset. A baby born to a blood group O mother may be at risk for neonatal hyperbilirubinemia if the infant's blood type is A or B. The second risk factor for severe hyperbilirubinemia was the presence of jaundice shortly after birth, with an STB concentration significantly above the 95th percentile. Answers A and C are incorrect. There is no need at this point to proceed to exchange transfusion, as the rise in STB in many cases of ABO isoimmunization may be modulated by intense phototherapy and IVIG administration.

One hour after phototherapy began, these laboratory results were reported: Infant's blood group B, Rh positive, DAT strongly positive, Hb 12.0 g/dL, Hct 36%, reticulocyte count 6%. The anemia in association with an elevated reticulocyte count in a newborn with jaundice and hyperbilirubinemia noted before 24 postnatal hours suggests that hemolysis is occurring.

After 6 hours of intensive phototherapy, a repeat STB value is 18.3 mg/dL.

Question

What should be done now?

A. Continue phototherapy and repeat the STB in 12 hours
B. Exchange transfusion
C. Administer intravenous immune globulin (IVIG), 1 g/kg.

IVIG in Immune Hemolytic Anemia

Answer

In the authors' practice, we would choose option C. Answer A is incorrect because waiting 12 hours in the presence of hemolysis might allow the bilirubin to rise to a dangerous level. Answer B might be considered a valid option. However, in the authors' experience, administration of IVIG has dramatically reduced the need for exchange transfusion in infants with ABO incompatibility. In an infant with ABO incompatibility, administration of IVIG is very effective in preventing a further increase in STB and decreasing the need for exchange transfusion. In other isoimmunizations such as Rh, anti-c, or anti-E, IVIG therapy may be less effective but may be instrumental in slowing the rise in STB before blood products for exchange transfusion become available. In studies using measurement of carboxyhemoglobin (COHb), a sensitive index of heme catabolism, in responders to IVIG, the rate of hemolysis is diminished. IVIG therapy is recommended in the therapeutic armamentarium of the AAP guideline (2004) for the management of immune-mediated hemolysis.

In fact, this baby did respond to an infusion of IVIG. The rise in STB was curtailed and exchange transfusion avoided. In the authors' experience, an aggressive approach to ABO incompatible infants including (1) a high rate of awareness of babies born to blood group O mothers, (2) identification of early jaundice, (3) intense phototherapy according to AAP recommendations, and (4) IVIG administration should the STB continue to rise despite phototherapy has diminished the need for exchange transfusion in ABO incompatible newborns.

Increased Risk for Bilirubin Neurotoxicity Associated With Hemolysis

It is generally believed that neonates with hemolytic disease are at a higher risk for bilirubin-induced neurotoxicity than those whose hyperbilirubinemia is not due to a hemolytic process. Whereas an STB concentration of 20 to 24 mg/dL may be associated with bilirubin encephalopathy and kernicterus in a neonate with Rh isoimmunization, in the absence of a hemolytic condition, a healthy term infant will rarely be endangered by STB concentrations in that range. The mechanism by which hemolysis increases the risk of bilirubin neurotoxicity has not been elucidated. Because the unbound

bilirubin fraction is thought to be that which crosses the blood–brain barrier, it seems logical that babies with hemolytic conditions should have higher unbound bilirubin fractions than their nonhemolyzing counterparts. However, this has not been demonstrated to date. A high rate of bilirubin production over a short period, typical of increased hemolysis, may offset the effect of bilirubin distribution into the tissues, a process that may be effective in moderating the rise in STB.

Several studies support the concept of increased severity of bilirubin neurotoxicity in the face of hemolysis. In a study performed in Turkey, a positive DAT, used as a presumed marker of hemolysis in infants with Rh isoimmunization or ABO incompatibility, was associated with lower IQ scores and a higher incidence of neurologic abnormalities than in controls who were not DAT positive. A similar observation was made in Norway in the 1960s; DAT-positive males who had STB levels above 15 mg/dL for longer than 5 days had IQ scores lower than those observed in the general population. In the Jaundice and Infant Feeding Study, IQ values in the subgroup of DAT-positive infants with TSB above 25 mg/dL were significantly lower than hyperbilirubinemic infants who were DAT negative. Finally, in a reanalysis of the data from the Collaborative Perinatal Project, the presence of a positive DAT in infants with a TSB of 25 mg/dL and above was associated with decreased IQ scores.

Recent case series of infants with kernicterus from the United States, Canada, the United Kingdom and Ireland, and Denmark indicate that hemolysis (with or without isoimmunization) plays a major role in the etiology of hyperbilirubinemia. Hemolytic conditions including ABO incompatibility with or without a positive DAT and G6PD deficiency topped the list of conditions in which a specific etiology for the hyperbilirubinemia was determined. Although Rh isoimmunization is now rarely encountered in Western countries, the condition is still rampant in developing countries. On the other hand, immigration patterns, ease of travel, and the recent influx of Middle Eastern refugees to the West have made G6PD deficiency a condition no longer limited to the countries to which it was indigenous but potentially encounterable in virtually any country in the globe.

AAP Recommendations Regarding Babies With Hemolysis

In its 2004 guidelines, the AAP placed special emphasis on identifying neonates with hemolytic conditions. Infants with early jaundice (<24 hours postdelivery) or those who have rapidly increasing bilirubin values (that jump percentiles on the hour-specific bilirubin nomogram) should be suspected of having ongoing hemolysis. Similarly, blood group incompatibility with a positive DAT and other known hemolytic disease including G6PD deficiency are regarded as major risk factors for the development of severe hyperbilirubinemia. Although the complete blood count (CBC) may be helpful in detecting severe hemolysis in cases of isoimmunization, there may be overlap in values between babies with and without hemolysis, and the CBC may not be sufficiently sensitive to detect many cases of hemolysis in the early neonatal period.

TABLE 5.3 Some Important or Commonly Occurring Causes of Increased Hemolysis

A. Immune conditions
ABO immunization
Rh (D) isoimmunization (in the main eliminated in Westernized countries, still common in developing countries)
Some rarer immune conditions anti-c, anti-C anti-e, anti-E anti-Kell anti-Duffy anti-Kidd
B. Nonimmune conditions
Red cell enzyme deficiencies G6PD deficiency Pyruvate kinase deficiency Other rare RBC enzyme deficiencies
Red cell membrane defects Hereditary spherocytosis Elliptocytosis Ovalocytosis Stomatocytosis Pyknocytosis
Hemoglobinopathies Unstable hemoglobinopathies
General conditions Sepsis Extravasated blood (cephalhematoma, ecchymosis, adrenal hemorrhage, subdural hemorrhage)

G6PD deficiency is especially notorious in demonstrating normal hemoglobin and hematocrit values in the presence of extremely high STB values, most likely attributable to hemolysis.

In cases of overt hemolysis including isoimmune hemolytic disease and G6PD deficiency, the Subcommittee on Hyperbilirubinemia of the AAP recommends a more aggressive approach to management of hyperbilirubinemia, including initiation of phototherapy or performing of exchange transfusions at lower levels of STB than in neonates without obvious hemolytic etiologies. A list of some commonly occurring etiologies of hemolysis can be seen in Table 5.3. For a comprehensive listing, the reader is referred to standard textbooks.

G6PD DEFICIENCY: AN IMPORTANT CAUSE OF KERNICTERUS

CASE 3

Baby GP, a male infant, was born at term gestation in the United States to parents who were immigrants from Greece. The parents reported that a previous child in their family, also born in the United States, had been treated with phototherapy. At the time of discharge of the current baby at

48 hours, the STB was 11.0 mg/dL (the 75th percentile on the bilirubin nomogram). The infant was breastfeeding, apparently successfully.

Exercise 3

Question

What would you advise the parents?

A. See a pediatrician within 2 to 3 days in accordance with AAP guidelines (2004).
B. Assess the baby as being relatively risk free for hyperbilirubinemia. See a pediatrician by age 2 weeks.
C. This infant is at high risk for significant neonatal hyperbilirubinemia. He should be seen by a pediatrician or medical professional within 48 hours (or sooner should the infant become yellow).

Answer

None of these answers is correct. This infant was at high risk for severe hyperbilirubinemia based on the history of a sibling requiring phototherapy and the family's Mediterranean Basin origin. The discharging pediatrician did not recognize these risk factors. Furthermore, the STB was already in the intermediate high-risk zone. Based on these risk factors in a male, breastfeeding baby (additional risk factors), this infant should have had a repeat STB within 24 hours. The parents should have been instructed how to recognize jaundice and what to do should their infant become jaundiced.

At age 5 days, the baby became lethargic and refused to nurse. The parents called the pediatrician's office but were told that the first available appointment was at 2:00 p.m. the next day. Following onset of seizures, the parents took the baby to the emergency room. The triage nurse exclaimed: "This baby looks like a pumpkin!" While waiting to be seen by a doctor, the baby became apneic and required intubation and ventilation. Phenobarbital was administered, and 1.5 hours later the STB was reported as 35 mg/dL. The baby was admitted to the pediatric ward, an IV placed, antibiotics administered, and phototherapy commenced. Blood was ordered for an exchange but because of a technical problem, delivery of the blood was delayed for 3 hours.

Acute Bilirubin Encephalopathy: to Exchange or Not to Exchange?

Question

While waiting for the blood for the exchange transfusion, there was a discussion between the doctors attending to this case regarding the efficacy of performing an exchange transfusion in a baby who already had signs of bilirubin encephalopathy (apathy, poor feeding, seizures, apnea).

A. One physician argued that bilirubin encephalopathy is associated with irreversible neurologic injury (kernicterus). Therefore why perform a potentially dangerous procedure in a baby who is already damaged?
B. Another physician stated that the early signs of bilirubin encephalopathy can be reversed when the STB is promptly lowered by exchange transfusion and intense phototherapy. Some of these infants develop normally.

Answer

The second physician is correct. There have been reports of reversal of the bilirubin neurotoxicity process with prompt lowering of the STB by exchange transfusion, even in cases already manifesting signs of bilirubin encephalopathy. The AAP guideline (2004) recommends immediate performance of exchange transfusion should an infant manifest signs of acute bilirubin encephalopathy. (See later discussion.) The initiation of intensive phototherapy while waiting for the blood for the exchange transfusion is the correct response.

In the current case, exchange transfusion via the umbilical vein was commenced 7 hours after arrival at the emergency room. A G6PD assay on blood that had been sampled before the exchange transfusion was very low, indicative of G6PD deficiency. On questioning, it became apparent that a neighbor had prepared a traditional Mediterranean meal for the parents that included fava beans. The infant was probably exposed to the bean metabolites via breast milk. The child is currently 7 years old and has choreoathetotic cerebral palsy.

Severe Hyperbilirubinemia Associated With G6PD Deficiency: Unpredictable and Unpreventable

The AAP regards kernicterus as a condition that should generally be preventable. G6PD deficiency, however, may be one important reason that this goal may be unreachable. G6PD deficient newborns sometimes have acute episodes of severe jaundice in which STB rises in an exponential fashion. These episodes are by and large unpreventable and unpredictable and occur even when all preventive measures are undertaken and exposure to known triggers of hemolysis avoided. However, had the diagnosis been made and the parents appropriately educated, much could have been done to facilitate treatment in the early stages of the hyperbilirubinemia, before the onset of signs of bilirubin encephalopathy, or at a point when bilirubin encephalopathy may still have been reversible with appropriate treatment.

What went wrong? This baby was inadequately managed and evaluated by the pediatricians both in the hospital and in the community setting. Some pediatricians in North America regard G6PD deficiency as a condition prevalent in the Middle East or Mediterranean Basin, with little relevance to their own practices. Although the indigenous distribution of G6PD deficiency characteristically includes Central and West Africa, Mediterranean countries, the Middle East, and parts of Asia, G6PD-deficient individuals are found throughout the world. About 12% of African American males are G6PD deficient. G6PD deficiency comprised more than 20% of the 125 cases reported in the US-based Kernicterus Registry, confirming its overrepresentation in its contribution to bilirubin neurotoxicity. Similar contributions of G6PD deficiency to extreme hyperbilirubinemia and kernicterus have been reported from Canada and the United Kingdom and Ireland. A list of population subgroups in the United States at risk for G6PD deficiency appears in Table 5.4.

TABLE 5.4 Population Subgroups at Risk for G6PD Deficiency in the United States

African American
Italian
Greek
Immigrants from the Middle East, India, South-East Asia and China
Sephardic Jews especially of Middle Eastern origin
Central and Western Africa descent
Brazil

Will G6PD Screening Help?

The parents of this baby should have been warned of the high-risk nature of their ethnic background with regard to the potential for G6PD deficiency. Had the baby been born in Greece, G6PD deficiency would have been screened for as part of a national screening program and the parents given preventive instructions even before the screening results becoming available. Several countries with a high incidence of G6PD deficiency have reported screening programs—in combination with parental education—with observational evidence of a decreased number of cases of kernicterus. With the exception of Washington, DC, and Pennsylvania in the United States, there is no obligation to screen otherwise healthy babies for this condition. Discussions have, however, commenced regarding the feasibility and whether it is economically worthwhile to establish such a program in the United States. Screening will not prevent the acute hemolytic attacks, but knowledge that their infant is G6PD deficient, in combination with parental education, should heighten parental and medical caretaker awareness, facilitate earlier referral to medical centers, and result in earlier institution of effective therapy. Many infants with bilirubin encephalopathy were readmitted at or around 5 days of age and had been discharged from birth hospitals as "healthy." It will therefore be important to perform screening for G6PD deficiency, obtain the results, and instruct the parents before discharge from the birth hospital. Recent studies in Cleveland, Ohio, have shown that this goal is feasible in the United States. In the authors' institution, targeted screening aimed at ethnic groups known to be at high risk for G6PD deficiency has been ongoing for decades.

Although the trigger of hemolysis in G6PD-deficient babies frequently cannot be identified, the parents of this baby should have been warned of the dangers of eating fava beans, using clothes that had been stored in naphthalene containing mothballs, or of using drugs or medications without consulting a doctor beforehand. The office pediatrician should have given instructions to his staff that an infant whose parents complain of jaundice should be seen immediately and not be given an appointment for the following day. Similarly, the emergency room triage nurse who recognized the extreme jaundice in this baby should have recognized the emergent nature of the situation and called a physician immediately. An STB should have been taken stat and intensive phototherapy started even before the results becoming available. Attention to these details may have prevented permanent bilirubin neurotoxicity.

Moderate G6PD Deficiency Associated Hyperbilirubinemia: a Potentially High-Risk Condition

Some G6PD-deficient infants develop a more moderate form of hyperbilirubinemia. We do not know the natural history of this form, as most infants are treated with phototherapy with good response, although a few do require exchange transfusion. The pathophysiology of the jaundice is attributed to a moderate degree of increased heme catabolism, as demonstrated by studies of endogenous carbon monoxide production, in combination with diminished bilirubin conjugation, the result of presence of a promoter polymorphism of *UGT1A1,* associated with Gilbert syndrome (*UGT1A1*28*). These infants are at risk for severe hyperbilirubinemia as the imbalance between bilirubin production and conjugation may be exacerbated should the infant come in contact with a hemolytic trigger or if prematurity further diminishes the bilirubin conjugation ability.

Falsely Normal G6PD Testing

If taken during an acute hemolytic episode, a G6PD test may be reported as falsely normal even in a severely G6PD deficient individual. The reason for this apparent discrepancy is that during hemolysis, older RBCs that have lower levels of G6PD activity are destroyed, leaving younger RBCs with higher G6PD activity intact. Such newborns should be regarded as G6PD deficient for the purpose of management. An accurate G6PD result can be expected several months later when RBCs have regenerated. Genetic analysis is another option but may not always be feasible.

Female heterozygosity may also lead to equivocal results on quantitative G6PD testing. Because of nonrandom X chromosome inactivation, the phenotype will usually give intermediate results but may range from low (deficient) to normal. It may be prudent to regard females from high-risk ethnic groups with intermediate or even normal G6PD enzyme values as G6PD deficient for the purpose of evaluation and treatment of hyperbilirubinemia.

CLINICAL EFFECTS OF SEVERE NEONATAL HYPERBILIRUBINEMIA

Kernicterus: a Never Event?

Kernicterus has been regarded as a preventable condition, but despite formulation of comprehensive guidelines in the United States, Canada, and other countries (including the United Kingdom, South Africa, Israel, Netherlands, and Norway), kernicterus continues to occur in Westernized countries with well-organized healthcare systems. Kernicterus is not surprising in low- and middle-income countries with poorly functioning health systems. Although the incidence of kernicterus relative to the number of deliveries in any developed country is low, the results of bilirubin neurotoxicity are permanent and long lasting, with major

implications for the affected infants, their families, and society. The incidence of extreme hyperbilirubinemia and kernicterus in industrialized countries varies. Kernicterus is estimated to occur in Denmark at the rate of 1 in 64,000 (1994–1998) or 1 in 79,000 (1994–2003), the United Kingdome and Ireland 1 in 150,000, Canada 1 in 43,000, and California 0.44 in 100,000. The incidence of severe neonatal hyperbilirubinemia in Canada decreased from 1 in 2480 in 2002 to 2004 to 1 in 8352 in 2011 to 2013, a factor of 3.5 (95% confidence interval 2.72–4.47). This decrease was attributable to introduction of Canadian hyperbilirubinemia guidelines in 2007 combined with increased physician awareness of severe hyperbilirubinemia.

Bilirubin toxicity—manifest as acute bilirubin encephalopathy with the potential for kernicterus or the less devastating bilirubin auditory neuropathy and bilirubin-induced neurologic dysfunction (BIND)—most likely will not have been encountered by the majority of readers. On the other hand, pediatricians and neonatologists spend much of the time devoted to newborns in predicting, monitoring, and treating hyperbilirubinemia to prevent the STB from reaching a neurotoxic level. Although a comprehensive account of bilirubin neurologic disease is beyond the scope of this chapter, we will in the ensuing paragraphs briefly describe the clinical picture of newborns who have been exposed to and affected by high levels of STB.

Acute Bilirubin Encephalopathy

The early clinical features giving rise to the suspicion of acute bilirubin encephalopathy include severe lethargy and poor feeding in a very icteric baby who has previously been feeding well. Granted, these signs are nonspecific, but in the presence of severe jaundice, encephalopathy should be suspected and therapy instituted without delay. Spasm of the extensor muscles results in opisthotonus and back arching. Muscle tone may fluctuate between hypo- and hypertonia, and a high-pitched cry frequently develops. Impairment of upward gaze results in the setting-sun sign, and fever, seizures, apnea, and death may follow.

Associated with acute bilirubin encephalopathy may be a kernicteric facies (Fig. 5.2). These facial features include a combination of features: (1) the setting-sun sign (paresis of upward gaze), (2) eyelid retraction, and (3) facial dystonia. In combination, these signs make the infant seem stunned, scared, or anxious. A fourth sign, dysconjugate or wandering eyes, may also occur. Recognition of this peculiar facial pattern should help identify a baby who is developing bilirubin encephalopathy.

Chronic Athetoid Cerebral Palsy: Kernicterus

The clinical picture of acute and chronic bilirubin neurotoxicity is due to deposition of bilirubin in the basal ganglia neural tissue. Kernicterus comprises a tetrad including:

- Abnormal muscle control, movements and muscle tone typical of choreoathetoid cerebral palsy
- Auditory processing disturbance, with or without hearing loss

Fig. 5.2 Kernicteric facies in a baby with acute bilirubin encephalopathy. Note the setting-sun sign (paresis of upward gaze), eyelid retraction, and facial dystonia, making the infant seem stunned, scared, or anxious. (Photograph courtesy Tina Slusher, MD, from that physician's personal collection, taken in Nigeria with mother's permission.)

- Oculomotor impairments resulting in paralysis of upward gaze
- Enamel dysplasia of the teeth

The following description of 25 cases of kernicterus in California portrays the dismal picture of these chronically affected children. Seventy-two percent were male. At a mean (SD) age of 7.8 (3.9) years, 60% did not walk at all, and only 16% were able to walk independently. Only 52% could self-feed, and a feeding tube was in place in 12%. Severe or profound mental retardation or severe disablement was found in 36%. There was no evidence of mental retardation in 32%. Epilepsy was found in 20%. Severe, profound, or untestable visual or hearing impairment was documented in 25% and 56% of cases, respectively, and only 36% had normal hearing. Motor spasticity was seen in 32%, ataxia and dyskinesis in 12% each, and hypotonia in 8%.

SUBTLE BILIRUBIN ENCEPHALOPATHY AND AUDITORY NEUROPATHY

Bilirubin-Induced Neurologic Dysfunction (BIND)

Bilirubin encephalopathy may not always manifest as the classic, chronic picture of kernicterus. In some, BIND may result in subtle bilirubin encephalopathy. These children have less severe injury than those with classic kernicterus but nevertheless show signs attributable to bilirubin neurotoxicity. The spectrum of neurologic manifestations in BIND includes subtle disturbances of hearing, disorders of auditory processing known as auditory neuropathy/dyssynchrony, visual motor paralysis, and disorders of speech, language, and cognition. Hearing loss or auditory neuropathy may be isolated or in combination with additional manifestations of kernicterus. Cognitive disturbances may also be evident.

Auditory Neuropathy/Dyssynchrony

Auditory neuropathy associated with hyperbilirubinemia is not simply a sensorineural hearing loss but is the result of dysfunction at the level of the auditory brainstem or nerve. Thus the cochlear hair cells remain intact, but the central auditory nerve tissue or auditory brain center are affected. Functionally, auditory neuropathy or dyssynchrony is characterized by absent or abnormal brainstem auditory evoked potentials but with normal inner ear function. In these cases, hearing screening using automated auditory brainstem responses (testing neural tissue) will identify the condition. However, evoked otoacoustic emission studies, reflecting cochlear hair cell inner ear function, may be normal. If the latter technology is used exclusively, the auditory neuropathy may remain undiagnosed. Affected patients may be able to hear, as documented on audiogram, and to respond to sounds appropriately, but their ability to decode speech and language and interpret the sounds they are hearing may be hindered. Awareness of bilirubin auditory neuropathy is of practical importance, as cochlear implantation has been used successfully in children with this condition.

LATE PREMATURITY

CASE 4

A 36-week gestation, male breastfed infant was to be discharged at 48 hours. The predischarge STB was 11.0 mg/dL. Both mother's and infant's blood groups were O, Rh positive. The parents are Caucasian.

Exercise 4

Question

Which of the following physicians is correct in their assessment?

A. The first pediatrician was not concerned, as the STB was not very high, in his evaluation. He claimed that this was a case of nonhemolytic jaundice.
B. His partner, in contrast, insisted that this baby has risk factors for neonatal hyperbilirubinemia and requires very close observation.

Every STB Value Should Be Plotted on the Bilirubin Nomogram

Answer

The pediatrician did not plot the STB value on the nomogram. Had he done so, he would have seen that the value was on the 75th percentile (the beginning of the intermediate high-risk range). Because of bilirubin dynamics during the first week of life, it is essential to plot every STB value on the nomogram. A value of 11.0 mg/dL at 24 hours will be above 95th percentile, in the high-risk zone; at 48 hours, it will fall on the 75th percentile, at the beginning of the intermediate high-risk zone; and at 72 hours on the 40th percentile, bordering on the low-risk zone. Each percentile has different risk values for the potential to develop severe hyperbilirubinemia. Regardless of the actual STB value, the higher the hour-specific percentile value, the greater the risk for subsequent hyperbilirubinemia. Furthermore, should more than one STB determination be available, the STB trajectory can be evaluated. A trajectory running parallel to the graph may be cautiously reassuring, whereas a trajectory that is jumping percentiles may be indicative of hemolysis and predictive of subsequent hyperbilirubinemia. Although the low-risk zones on the nomogram (<75th percentile) have traditionally been regarded as minimal or moderate risk for subsequent hyperbilirubinemia, this may not be entirely true. Recent studies of newborns readmitted for hyperbilirubinemia determined a false negative predischarge bilirubin screen in many instances. For example, in a study from Israel, Bromiker et al reported that of 143 infants readmitted for hyperbilirubinemia, 4.2% had predischarge STB values in the 40th percentile or below range (low-risk zone), and 28% were in the intermediate low-risk zone (41st–75th percentile) predischarge. These and other results support the AAP recommendation that every newborn should be seen by a health authority within a few days of discharge to detect those developing jaundice, or with preexisting jaundice that is increasing, that is not recognized by the parents.

In this case, the pediatrician did not take some risk factors into consideration. As discussed earlier, the conjugating ability of newborns 37 weeks' and earlier gestation is low. Even early term newborns (37–38 weeks' gestation) exhibit a decreased ability to conjugate bilirubin and therefore are at higher risk for hyperbilirubinemia than those born after 38 weeks' gestation. Studies have demonstrated that a combination of predischarge STB in conjunction with gestational age has an excellent predictive accuracy for subsequent hyperbilirubinemia (see discussion later). Breastfeeding and male sex further add to the complexities of this case and compound the risk for hyperbilirubinemia.

Physician B was correct. Although it is not mandatory to observe this infant in hospital, he should have been seen by a healthcare professional within 1 or 2 days of discharge. Whether the jaundice in this infant was nonhemolytic or not will be discussed later.

Jaundice Associated With Prematurity

Jaundice in premature infants is more common and severe than in full-term neonates. STB concentrations peak around the fifth day of life. The major reason for the frequency of jaundice in premature infants is developmental immaturity of the UGT1A1 bilirubin-conjugating enzyme. In premature infants, bilirubin toxicity may occur at lower concentrations of bilirubin than in term infants, and any visible jaundice in a preterm infant should be closely monitored.

Jaundice Associated With Late Preterm Infants

Late preterm gestation (newborns born between $34^{0}/_{7}$ and $36^{6}/_{7}$ completed weeks) is another important risk factor for the development of severe neonatal hyperbilirubinemia. An immature bilirubin conjugative capacity is implied in the potential severity of jaundice in these infants. Coexpression of late prematurity with additional icterogenic factors such as

G6PD deficiency may enhance the jaundice. Management of late preterm infants as if they were term infants, with early discharge and lack of appropriate follow up, may be a major contributor to the bilirubin-related morbidity in these cases.

"Nonhemolytic Jaundice": Is There Such an Entity?

In the absence of known or obvious etiologies for neonatal hyperbilirubinemia, some pediatricians have used the term "nonhemolytic jaundice." Although there may be some cases of true nonhemolytic jaundice, such as breastfeeding jaundice or Crigler-Najjar syndrome, categorization of hyperbilirubinemic newborns as nonhemolytic may lessen the degree of concern regarding the potential for bilirubin neurotoxicity. The presence of a hemolytic condition does not categorically imply that the jaundice or hyperbilirubinemia is necessarily due to this condition. Conversely, absence of an identifiable etiology does not necessarily imply that increased hemolysis is not part of the pathophysiology of the jaundice. Studies using the endogenous production of CO have demonstrated that many jaundiced babies do, in fact, have a hemolytic component to their jaundice, even in the absence of a defined hemolytic condition. In a multicenter, multinational study using end-tidal CO concentration corrected for ambient CO (ETCOc), Stevenson et al reported the mean ETCOc value for 1370 infants who completed the study was 1.48 ± 0.49 ppm. The 120 newborns who developed any TSB concentration above 95th percentile on the hour-specific nomogram had significantly higher ETCOc values than those who did not (1.81 ± 0.59 ppm vs. 1.45 ± 0.47 ppm, $p < 0.0001$).

However, high bilirubin production was not a prerequisite for the development of hyperbilirubinemia. Some babies with low bilirubin production nevertheless did develop hyperbilirubinemia, whereas others with high production rates did not. These findings confirm that both bilirubin production and its elimination contribute to the STB at any point in time. Additional studies using both ETCOc and blood carboxyhemoglobin (COHbc) levels have demonstrated greater endogenous production of CO, reflective of increased heme catabolism in many newborns, even in the absence of a specific diagnosis associated with increased hemolysis. It appears, therefore, that many hyperbilirubinemic babies do have some degree of increased heme catabolism with the potential of bilirubin neurotoxicity. Using new generation sequencing, Christensen et al provided a diagnosis for hemolysis in cases that previously would have been regarded as idiopathic. Absence of an obvious etiology associated with increased hemolysis for hyperbilirubinemia should not result in us labeling newborns as nonhemolytic. This practice may result in a sense of complacency and lack of recognition of babies with increased potential for bilirubin neurotoxicity.

Recent re-availability of a device for noninvasive bedside testing for ETCOc should contribute to the detection of hemolysis and identify neonates at higher risk for extreme hyperbilirubinemia and bilirubin neurotoxicity. Study of ETCOc in combination with STB or transcutaneous bilirubin (TcB) should help determine whether the pathophysiology of hyperbilirubinemia in a specific newborn is primarily hemolytic or due to elimination disorders. A recent study by Bhutani et al concluded that high ETCOc implies increased hemolysis, whereas high STB in the face of a normal ETCOc implies a predominantly conjugative deficiency.

TABLE 5.5 Some Important Causes of Hyperbilirubinemia Due to Diminished Bilirubin Conjugation

Prematurity
Late prematurity
Hypothyroidism
Pyloric Stenosis
Gilbert syndrome
Crigler-Najjar syndromes types 1 and 2

DIMINISHED BILIRUBIN CONJUGATION AND NEONATAL HYPERBILIRUBINEMIA

Diminished bilirubin conjugation may result in hyperbilirubinemia independently or in conjunction with increased bilirubin production. Some important causes of hyperbilirubinemia due to diminished conjugation are found in Table 5.5.

Gilbert Syndrome

Gilbert syndrome is a benign disorder that produces mild unconjugated bilirubinemia in about 6% of adults. Both defective hepatic uptake of bilirubin and decreased hepatic UGT activity have been demonstrated. In individuals with Gilbert syndrome, the UGT1A1 conjugating enzyme is normally structured but not fully functional because of diminished gene expression. This is because the noncoding, rather than coding, area of the gene is affected. In Caucasian populations, the genetic basis of the reduced gene expression lies in the presence of additional TA repeats ($[TA]_7$ or occasionally $[TA]_8$ instead of the wild type $[TA]_6$] in the TATAA box in the promoter region of the *UGT1A1* gene (*UGT1A1*28*). In and of itself, the $(TA)_7$ promoter polymorphism has not been associated with severe hyperbilirubinemia, but it may in combination with additional factors. Kaplan et al demonstrated that a dose-dependent genetic interaction between G6PD deficiency and $(TA)_7$ promoter polymorphism increased the incidence of a TSB above 15 mg/dL dramatically when these two factors occurred together. In Asian populations, interaction between G6PD deficiency and coding area *UGT1A1* mutations *(UGT1A1*6)* exacerbate hyperbilirubinemia. An interaction between $(TA)_7$ promoter polymorphism and hereditary spherocytosis increasing hyperbilirubinemia has been documented.

BREASTFEEDING AND BREAST MILK JAUNDICE

CASE 5

A male term infant was born to parents who were second cousins. The infant was breastfed. The STB was 20.0 mg/dL

on day 3 of life. Phototherapy was instrumental in decreasing the STB value, and the baby was discharged only to be readmitted 3 days later with an STB value of 23.0 mg/dL.

Exercise 5

Question

What is the most likely diagnosis?

Answer

At this point, the leading diagnosis is *breastfeeding jaundice.* Breastfeeding jaundice occurs in the first postnatal days. Lack of proper technique, engorgement, cracked nipples, small amounts of milk, and fatigue may impair effective breastfeeding on the part of the mother. Neonatal factors such as an ineffective suck may be common in late-preterm infants. The result may be ineffective breastfeeding, underhydration, delayed meconium passage, and intestinal stasis leading to an increased enterohepatic circulation and increased bilirubin load.

Breast milk jaundice, on the other hand, occurs after the first 3 to 5 days of life. Mutations of the *UGT1A1* gene, including a $(TA)_7$ promoter polymorphism *(UGT1A1*28)*, or the G71R mutation *(UGT1A1*6)* can contribute to the development of hyperbilirubinemia in breastfed infants. More severely affected neonates may achieve peak levels as high as 20 to 30 mg/dL with no obvious evidence of hemolysis or illness. Interruption of nursing and substitution with formula feeding for 1 to 3 days usually causes a prompt decline of the STB concentration, especially when STB concentrations reach levels that might be of danger to the infant. On resumption of nursing, the STB does not usually increase. Most infants with breast milk jaundice can be observed without other interventions. However, if prolonged, one must determine that other pathology is not existent, and fractionation of bilirubin, thyroid testing, and urine cultures should be considered.

In the baby presented here, the sequence of readmission and phototherapy repeated itself several more times. Laboratory investigations revealed a normal CBC, a direct bilirubin value 0.3 mg/dL, normal thyroid function tests, and no evidence of infection. Both maternal and newborn blood groups were A Rh positive and the DAT was negative.

Question

What if anything, should be done next?

A. This is clearly a nonhemolytic situation and no further testing or interventions are necessary.
B. Indirect hyperbilirubinemia in a breastfed infant indicates breastfeeding jaundice. Breastfeeding should be discontinued.
C. Pay attention to the family history: The parents are second cousins. Consider evaluation for Crigler-Najjar syndrome. Treat the baby with phototherapy to prevent the STB concentrations from rising to potentially neurotoxic levels.

Crigler-Najjar Syndrome

Answer

C is the correct answer. Although breastfeeding jaundice definitely should be taken into consideration, it does not usually result in in a sequence of readmissions for hyperbilirubinemia. Response B would have been the correct response early on in this baby's management, but the repeated readmissions should have made the breastfeeding jaundice an unlikely possibility. The UGT1A1 gene was sequenced in the baby and both parents. A coding area mutation associated with Crigler-Najjar syndrome was found, homozygous in the baby and heterozygous in both parents.

Crigler-Najjar syndrome type I is a rare autosomal recessive disease characterized by an almost complete absence of hepatic UGT activity. In this situation, the coding area of the UGT gene is mutated, resulting in a structurally abnormal enzyme with no or little bilirubin-conjugating ability. Severe unconjugated hyperbilirubinemia may develop and kernicterus may occur should the STB not be vigorously controlled with phototherapy. The diagnosis can now be obtained by sequencing the UGT1A1 gene. Liver transplant offers definitive treatment for the disease, but in a multicenter report, 7 of 21 (33%) transplanted children had already developed some form of brain damage by the time of their transplantation.

Crigler-Najjar syndrome type II is more common than type I disease and is typically benign. The occurrence of kernicterus is rare. Unconjugated hyperbilirubinemia occurs in the first days of life and may be exacerbated by fasting, illness, and anesthesia. Phenobarbital may be used as a simple clinical tool to differentiate between type II and type I diseases. Jaundiced neonates with type II disease respond to oral administration of phenobarbital with a sharp decline in STB, whereas individuals with type I disease do not respond in this way. Beyond the neonatal period, there should be no long-term risk of kernicterus.

Hypothyroidism

About 10% of congenitally hypothyroid neonates may develop prolonged jaundice due to diminished UGT activity, and testing for thyroid function should be performed in these cases. This form of jaundice is encountered less frequently than in the past, because with modern methods of routine metabolic screening the diagnosis of hypothyroidism and institution of therapy should be available in the first postnatal days. The mechanism of this association may be impairment of hepatic uptake and reduced hepatic ligandin (carrier protein) concentrations. Absence of thyroid hormone may delay hepatic bilirubin enzyme and transport development.

EFFECT OF RACE AND ETHNIC BACKGROUND ON NEONATAL HYPERBILIRUBINEMIA

CASE 6

A male term infant was born to African American parents. There was no blood group incompatibility. The infant was breastfed and apparently healthy. At 50 hours of life, a predischarge STB result was 10.0 mg/dL. When plotted on the hour-specific nomogram, it fell between the 40th and 75th percentiles.

Exercise 6

Question

Which of the following statements is correct?

A. This is a term infant with an STB value in the intermediate low-risk range. He can be safely sent home; there are no special concerns.
B. This infant is of African American heritage and at very low risk for neonatal hyperbilirubinemia.
C. This infant is potentially at high risk and should be followed according to AAP guidelines with the same vigilance as a Caucasian infant.

Answer

C is the correct answer. Within the African American population, there is a subset at risk for extreme hyperbilirubinemia and kernicterus. Additional risk factors in this case include male sex and breastfeeding. Until recently, black heritage has been regarded as protective against hyperbilirubinemia. Indeed, the AAP (2004) statement on hyperbilirubinemia lists black ethnicity among conditions *decreasing* the risk of hyperbilirubinemia. However, black race does seem to contribute to the development of kernicterus. Black ethnicity comprises 25% of the US-based Kernicterus Registry and was overrepresented in the UK and Ireland survey. Some of these cases may be due to concurrent G6PD deficiency and others due to disadvantaged social status. Kernicterus is rampant in West and Central Africa. In a recent study from California, Wickremasinghi et al confirmed a lower incidence of moderate hyperbilirubinemia (STB ≥20 mg/dL) in black infants, an equal incidence of STB 25 mg/dL or above in black and Caucasian infants, and an increased incidence of hazardous hyperbilirubinemia (STB ≥30 mg/dL) in black neonates compared with white infants. Low-risk categorization of black newborns may therefore no longer be appropriate, and answers A and B are incorrect

Additional Racial Aspects of Hyperbilirubinemia

Asians are another population group at risk for neonatal hyperbilirubinemia. Some of the increased risk may be due to a high incidence of the G71R mutation of UGT1A1, *(UGT1A1*6)* associated with Gilbert syndrome, in Asian populations. Native Americans are also at high risk for neonatal hyperbilirubinemia.

PREDISCHARGE EVALUATION FOR PREDICTION OF HYPERBILIRUBINEMIA

In normal, healthy term babies, there is a natural progression of STB levels during the first days of life to a peak between the third and fifth postnatal day. Current practice in many countries is to discharge babies around 48 hours (or earlier). This means that the peak STB will be reached when the infant is already at home, thereby placing much of the onus for recognition of hyperbilirubinemia on the parents and community services. It is therefore essential to assess every infant for the risk of developing subsequent hyperbilirubinemia and to ensure adequate follow-up to detect developing hyperbilirubinemia.

Universal Predischarge Screening

In their clarification to the 2004 AAP guideline, Maisels et al recommend universal predischarge bilirubin screening using either STB or TcB readings to assess the risk of subsequent severe hyperbilirubinemia. These authors suggest a structured approach incorporating not only the bilirubin reading reflected as a percentile value but also gestational age and the presence or absence of risk factors. The underlying basis for this approach is that the higher the predischarge bilirubin percentile, the lower the gestational age, and the higher the number of risk factors, the greater will be the chance of developing subsequent hyperbilirubinemia. These recommendations are not evidence based but representative of expert opinion. The risk factors that are most predictive of significant hyperbilirubinemia include:

- Lower gestational age
- Exclusive breastfeeding, the latter especially if the nursing is not going well and there is excessive weight loss
- Jaundice appearing in the first 24 hours
- Bilirubin trajectory crossing percentiles on the nomogram
- Hemolytic conditions
  - Isoimmune hemolytic disease of the newborn
  - G6PD deficiency
- Older sibling who had jaundice
- Cephalohematoma or ecchymosis
- East Asian race

A Practical Approach to Follow up for Hyperbilirubinemia

To ease the screening process and facilitate formulation of a follow up plan, Maisels et al provide an algorithm for the predischarge screen. Those neonates who do not meet the AAP criteria for phototherapy are followed up according to a suggested protocol based on predischarge STB or TcB risk zone, gestational age 35 to 37 weeks or 38 weeks and above, and the presence of risk factors.

False Negative Predischarge Bilirubin Screening

As already pointed out, recent studies have shown that some infants readmitted for significant hyperbilirubinemia had a predischarge bilirubin screen in the low-risk zones on the nomogram, indicating a false negative screen. A predischarge screen in the low-risk zones should not, therefore, result in complacency, and the results of these studies confirm the AAP (2004) recommendations that every newborn should be evaluated for developing jaundice within 2 to 3 days of discharge.

TRANSCUTANEOUS BILIRUBINOMETRY

Transcutaneous bilirubinometry (TcB) is a technology for the noninvasive, instantaneous point-of-care estimation of the STB. To date, this technique has been used primarily in the hospital setting but has been successful in the outpatient setting as well. Visual inspection, which was for decades the mainstay for deciding which infant needs a bilirubin test performed, is notoriously inaccurate. TcB takes the guesswork out of bilirubinometry. TcB should be regarded as a screening tool and not as a substitute for actual STB measurement. The

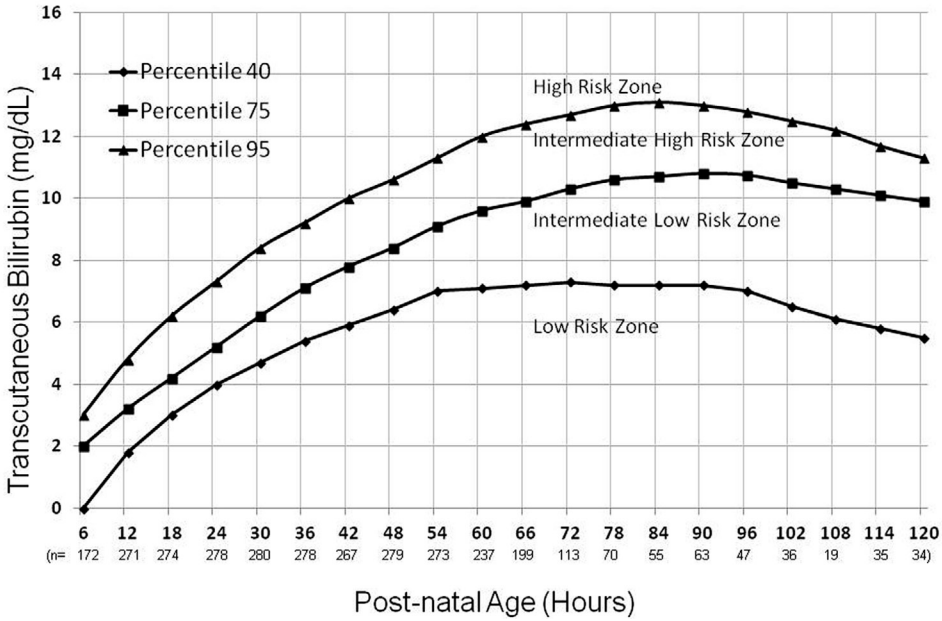


Fig. 5.3 An example of a transcutaneous bilirubin nomogram (constructed in Israel). (Reproduced with permission from Bromiker et al: Israel transcutaneous bilirubin nomogram predicts significant hyperbilirubinemia. *J Perinatol* 37[12]:1315–1318, 2017.)

technique involves a flash of light entering the skin and subcutaneous tissues and measurement of the degree of yellowness. After correcting for skin color and hemoglobin, an estimated STB level is reported.

In general, TcB tends to underestimate the actual STB, although in a Nigerian study it was shown to overestimate the STB reading in black African neonates. In their clarification to the 2004 AAP guidelines, Maisels et al suggest measuring STB if (1) the TcB is 70% of the STB value recommended for phototherapy, (2) the TcB is above the 75th percentile on the bilirubin nomogram or above the 95th percentile on a TcB nomogram, and (3) a postdischarge TcB value is above 13 mg/dL.

TcB nomograms have been constructed from several population groups, an example of which can be seen in Fig. 5.3.

TREATMENT OF NEONATAL HYPERBILIRUBINEMIA

Newborns 35 Weeks' Gestation and Above

The mainstays of treatment for neonatal hyperbilirubinemia include phototherapy and exchange transfusion, AAP-generated graphs for which can be seen in Fig. 5.4. The indications, technologies, and equipment required have been comprehensively described in the 2004 AAP hyperbilirubinemia guidelines with clarifications in the 2009 statement of Maisels et al, and a 2011 technical report on phototherapy by Bhutani et al from the Committee on the Fetus and Newborn. These statements relate to infants of 35 weeks' gestational age and above and are still applicable. The indications take into account not only the actual STB value but also the time and percentile of this value, gestational age, and the presence of risk factors. The higher the STB percentile, the lower the gestational age, and the greater the number of risk factors, the sooner treatment should be initiated. The 2004 AAP guidelines emphasize that in considering the indications for phototherapy and exchange transfusion, the direct-reacting (or conjugated) bilirubin level should **not** be subtracted from the total. However, the statement continues, in unusual circumstances in which the direct bilirubin is above 50% of the total bilirubin, consultation with an expert in the field is recommended as there are no data to provide guidance for therapy.

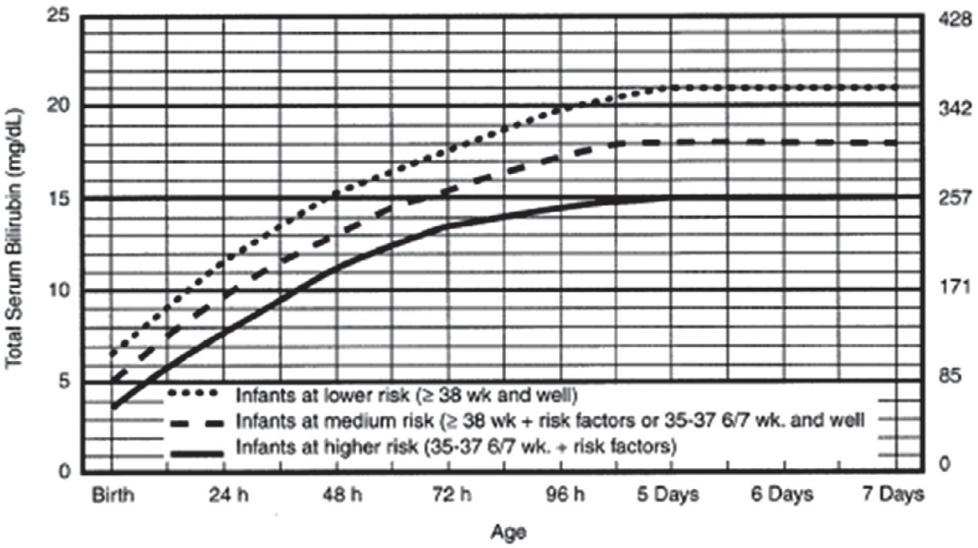
With regard to phototherapy, the 2009 clarification emphasizes the need to take risk factors for bilirubin neurotoxicity into account when making the decision to initiate phototherapy or perform an exchange transfusion. Neurotoxicity risk factors may increase the risk of neurologic damage in infants with severe hyperbilirubinemia. Neurotoxicity risk factors listed in the statement include

- Isoimmune hemolytic disease
- G6PD deficiency
- Asphyxia
- Sepsis
- Acidosis
- Albumin ≤3.0 mg/dL

The statement also provides algorithms that give recommendations for management, phototherapy, and follow-up taking into account not only bilirubin measurements but also gestation and risk factors for subsequent hyperbilirubinemia (Fig. 5.5).

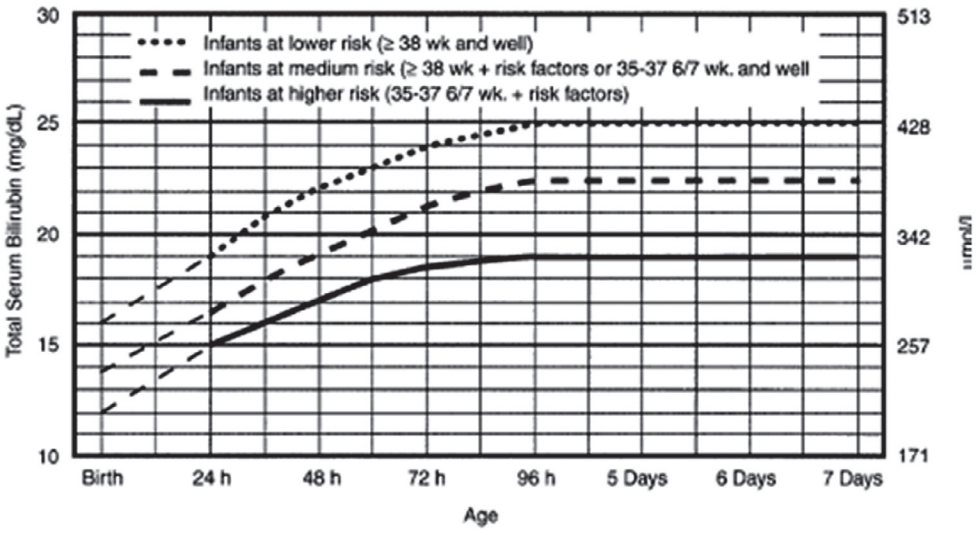
Cardinal points of the 2011 Committee on Fetus and Newborn technical report include that the effectiveness of phototherapy light is enhanced by:

- Emission of light in the blue–green range that overlaps the in vivo plasma bilirubin absorption spectrum (460–490 nm)



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/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 wks 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 (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

A



- The dashed lines for the first 24 hours 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 B/A ratio (See legend)
- 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.

B

Fig. 5.4 (A) AAP-generated graph of indications for phototherapy for neonates ≥35 weeks' gestation. The graph includes three sets of indications based on gestational age and the presence or absence of risk factors. (Redrawn with permission from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, *Pediatrics* 114:297–316, 2004.) (B) AAP-generated graph of indications for exchange transfusion for neonates ≥35 weeks' gestation. The graph includes three sets of indications based on gestational age and the presence or absence of risk factors. (Redrawn with permission from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, *Pediatrics* 114:297–316, 2004.)

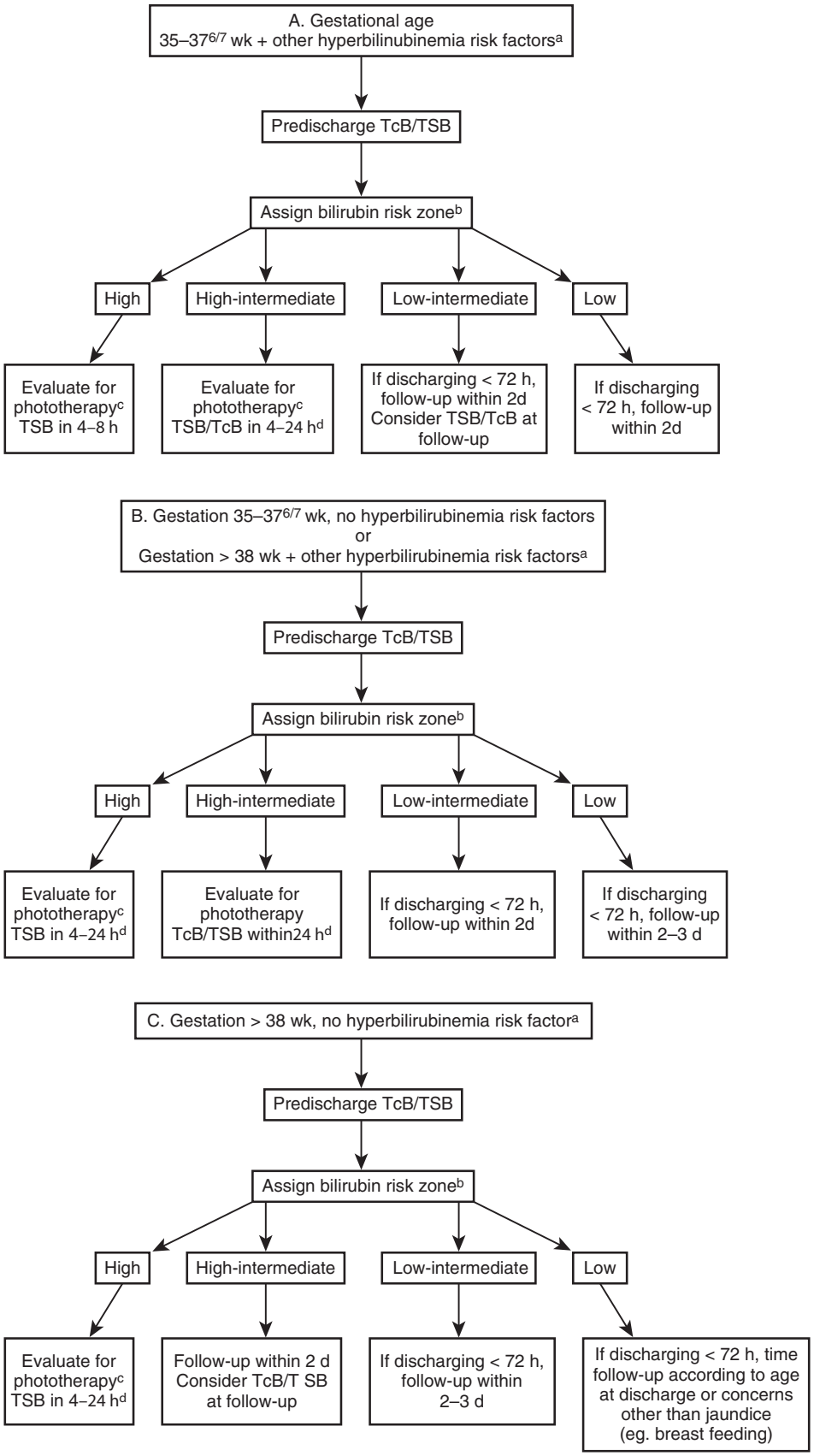


Fig. 5.5 Algorithms providing recommendations for management and follow-up according to predischarge bilirubin measurements, gestation, and risk factors for subsequent hyperbilirubinemia. (Reproduced with permission from Maisels et al, Hyperbilirubinemia in the newborn infant > or =35 weeks gestation: an update with clarifications. *Pediatrics* 124:1193–1198, 2009.)

- Irradiance of at least 30 $\mu W/cm^{-2}/nm^{-1}$ (confirmed with an appropriate irradiance meter calibrated over the appropriate wavelength range). The report adds that much higher irradiance (>65 $\mu W/cm^{-2}/nm^{-1}$) might have (as yet unidentified) adverse effects. Therefore the irradiance should be limited to that controlling any further increase in the STB and facilitating its decrease.
- Illumination of maximal body surface
- Demonstration of a decrease in total bilirubin concentrations during the first 4 to 6 hours of exposure

Additional points in the technical report include measurements of serial bilirubin measurements based on the rate of decrease. Phototherapy should be introduced urgently in cases of excessive hyperbilirubinemia, and procedures should be conducted while the infant receives phototherapy. Phototherapy may be interrupted briefly for feeding, parental bonding, or nursing care once a decrease in serum bilirubin has been detected. Possible rebound should be taken into consideration following discontinuation of phototherapy. Factors increasing the risk of clinically significant rebound include DAT positivity, gestational age under 37 weeks, and commencement of phototherapy at 72 postnatal hours or earlier.

Premature Infants <35 Weeks' Gestation

Management of hyperbilirubinemia in the premature infant under 35 weeks has been unclear, with a wide range of STB values suggested for various gestational ages and birth weights. Recently a suggested protocol—albeit nonevidence based—has been proposed that will hopefully standardize the treatment delivered to these infants (Table 5.6) (Maisels et al, 2012). Other protocols including guidelines for premature infants include the UK-based NICE guidelines and Norwegian, Dutch, and South African guidelines.

TABLE 5.6 Guidelines for Phototherapy and Exchange Transfusion in Premature Infants[a]

	Phototherapy	Exchange Transfusion
Gestational age (wk)	***Initiate phototherapy total bilirubin (mg/dL)***	***Total serum bilirubin (mg/dL)***
<27⁰⁄₇	5–6	11–14
28⁰⁄₇ – 29⁶⁄₇	6–8	12–14
30⁰⁄₇ – 31⁶⁄₇	8–10	13–16
32⁰⁄₇ – 33⁶⁄₇	10–12	15–18
34⁰⁄₇ – 34⁶⁄₇	12–14	17–19

In a footnote to their table, the authors of these guidelines make clarifications, some of which are summarized below:

1. The levels of STB at which phototherapy or exchange transfusion is recommended are not based on good evidence.
2. The wide ranges and overlapping of values between gestational age groups reflect a degree of uncertainty in the formulation of these guidelines.
3. Use the lower values in any given range for babies at high risk for bilirubin neurotoxicity, including lower gestational age, sepsis, clinical instability, serum albumin level <2.5 g/dL, or rapidly rising STB levels suggestive of hemolysis.
4. Indications for exchange transfusion apply to infants in whom STB levels continue to rise to exchange transfusion levels despite intense phototherapy.
5. Exchange transfusion is indicated in a baby who shows signs of acute bilirubin encephalopathy.
6. Use the total bilirubin value for decision making. Do not subtract the direct or conjugated bilirubin value from the total value.
7. Use the postmenstrual (adjusted) age for phototherapy indications.
8. Prophylactic phototherapy is an option in premature infants ≤26 weeks' gestation.
9. In infants <1000 g birth weight, because of possible increased mortality associated with phototherapy in this group, start with lower levels of irradiance and increase this should the STB levels continue to rise.

[a]Suggested by four US-based neonatologists who were involved in the preparations of the 2004 AAP guidelines, the 2009 clarification, or both.

From Maisels MJ, Watchko JF, Bhutani VK, et al: An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation, *J Perinatol* 32:660–664, 2012.

Low Bilirubin Kernicterus

Low bilirubin kernicterus occurs in premature infants at levels of bilirubin lower than one would expect to be associated with neurotoxicity and at levels lower than those indicating phototherapy or exchange transfusion. Therefore this condition may be unpreventable even if current phototherapy and exchange transfusion guidelines are strictly abided by.

Low bilirubin kernicterus is a condition that was encountered in the past in autopsy examinations of premature infants in whom the serum bilirubin did not reach levels that were thought to be neurotoxic. It is still encountered today in premature infant survivors who did not have very high serum bilirubin levels but who do have clinical and magnetic resonance imaging (MRI) evidence of kernicterus. Low bilirubin kernicterus has been defined as the occurrence of kernicterus at serum bilirubin levels below commonly recommended exchange transfusion thresholds. Because of the low nature of the serum bilirubin in this situation, in the range not necessarily obligating phototherapy, the condition is unpredictable and the consequences refractory. It is not known what factors potentiate bilirubin neurotoxicity at low levels of serum bilirubin. Some factors that have been implicated include low serum albumin (almost ubiquitous in sick, unstable premature infants) and comorbid central nervous system injury, including intraventricular hemorrhage, periventricular leukomalacia, and infection. Given the occurrence of the condition at low levels of serum bilirubin, it is unlikely that the condition will be eliminated, barring a significant lowering of exchange transfusion thresholds, with the potential of bringing in its wake a plethora of complications (infections, hemorrhage, blood pressure instability, and necrotizing enterocolitis) associated with this procedure, especially in unstable preterm infants.

SPECIAL INVESTIGATIONS IN KERNICTERUS

MRI Findings in Kernicterus

The MRI pattern seen in infants affected with kernicterus is typified by the appearance of hyperintensity of the globus pallidus, subthalamic nucleus, and other brainstem nuclei and is frequently bilateral. It is not known, however, whether these MRI changes are apparent in all cases of kernicterus and what their relationship is to long-term prognosis. For example, in a recent Canadian study, MRI findings consistent with kernicterus were initially present in three infants who were subsequently clinically and developmentally normal. On the other hand, the same authors report two infants with a normal MRI early on who subsequently had abnormal developmental outcomes on follow-up.

Brainstem Auditory Evoked Response (BAER)

Because auditory neural tissue is sensitive to the effects of bilirubin toxicity, the brainstem auditory evoked response (BAER) offers an early and sensitive measure of bilirubin-induced CNS dysfunction. Early signs include increased latency and decreased amplitude of waves III and V, progressing to absence of these waveforms, and finally to complete absence of all activity. Automated ABR can be used at the bedside as a rapid test of auditory function in a neonate with severe hyperbilirubinemia. Absence of automated ABR, or a change from "pass" before the hyperbilirubinemia, may be indicative of bilirubin neurotoxicity.

Cochlear Implants

Development of the cochlear implant technique may offer a ray of light to those affected by auditory bilirubin neurotoxicity. Although the cochlear itself is unaffected by bilirubin neurotoxicity, cochlear implantation has been successful in restoring hearing to sufferers of bilirubin auditory nerve toxicity. The mechanism of its function in bilirubin auditory neuropathy is not clear, but it is thought that direct stimulation of the auditory nerve improves nerve function in a way that regular cochlear stimulation cannot. Shapiro and Popelka noted that premature infants with bilirubin auditory neuropathy have responded well to cochlear implantation, adding hope to the improvement of auditory function in this group of children.

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Abstract: Neonatal jaundice is a commonly occurring condition. Usually the serum total bilirubin remains within physiologic levels but may increase to potentially dangerous concentrations and on occasion to extreme levels with the danger of bilirubin neurotoxicity. Neonatal hyperbilirubinemia is the most common cause for readmission in the neonatal period. Imbalance between the bilirubin production and elimination processes—the results of increased hemolysis relative to bilirubin excretion—upsets the equilibrium and results in hyperbilirubinemia. Phototherapy is the mainstay of therapy, with exchange transfusion held in reserve for those not responding to that treatment.

Keywords: Bilirubin, bilirubin encephalopathy, hemolysis, kernicterus, bilirubin conjugation, phototherapy, exchange transfusion