Drug Therapy

NEONATAL HYPERBILIRUBINEMIA

Phyllis A. Dennery, M.D., Daniel S. Seidman, M.D., and David K. Stevenson, M.D.

Hyperbilirubinemia results from a predisposition to the production of bilirubin in newborn infants and their limited ability to excrete it. Infants, especially preterm infants, have higher rates of bilirubin production than adults, because they have red cells with a higher turnover and a shorter life span. In newborn infants, unconjugated bilirubin is not readily excreted, and the ability to conjugate bilirubin is limited. Together, these limitations lead to physiologic jaundice — that is, high serum bilirubin concentrations in the first days of life in full-term infants (and up to the first week in preterm infants and in some full-term Asian infants), followed by a decline during the next several weeks to the values commonly found in adults. The average full-term newborn infant has a peak serum bilirubin concentration of 5 to 6 mg per deciliter (86 to 103 µmol per liter). Exaggerated physiologic jaundice occurs at values above this threshold (7 to 17 mg per deciliter [104 to 291 µmol per liter]). Serum bilirubin concentrations higher than 17 mg per deciliter in full-term infants are no longer considered physiologic, and a cause of pathologic jaundice can usually be identified in such infants.

CAUSES

The predominant source of bilirubin is the breakdown of hemoglobin in senescent or hemolyzed red cells. Heme is degraded by heme oxygenase, resulting in the release of iron and the formation of carbon monoxide and biliverdin (Fig. 1). Biliverdin is further reduced to bilirubin by biliverdin reductase. Bilirubin then enters the liver and is modified to an excretable conjugated form that enters the intestinal lumen but can be deconjugated by bacteria so that the bilirubin is reabsorbed into the circulation.

Increased production of bilirubin, deficiency of hepatic uptake, impaired conjugation of bilirubin, and increased enterohepatic circulation of bilirubin account for most cases of pathologic jaundice in newborn infants. Increased production of bilirubin occurs in infants of various racial groups, as well as in infants with blood-group incompatibilities, erythrocyte-enzyme deficiencies, or structural defects of the erythrocytes (Table 1). The propensity toward hyperbilirubinemia in certain racial groups is not well understood.

Another reason for pathologic hyperbilirubinemia is deficient hepatic uptake of bilirubin, as occurs in patients with Gilbert’s syndrome. Deficiency of uridine diphosphate glucuronosyltransferase, the enzyme required for the conjugation of bilirubin, is another important cause of neonatal jaundice. Although all newborn infants are relatively deficient in this enzyme, those with Crigler–Najjar syndrome type I, in whom the deficiency is severe, have bilirubin encephalopathy in the first days or months of life. In contrast, encephalopathy is rare in infants with Crigler–Najjar syndrome type II, in which serum bilirubin values rarely exceed 20 mg per deciliter (342 µmol per liter). In glucose-6-phosphate dehydrogenase deficien-
Hemolysis and impaired conjugation of bilirubin.

Infants with Gilbert’s syndrome also have mildly decreased uridine diphosphate glucuronosyltransferase activity. This decrease has been attributed to an expansion of thymine–adenine (TA) repeats in the promoter region of the \textit{UGT1A1} gene, the principal gene encoding this enzyme. Racial variation in the numbers of TA repeats and a correlation with uridine diphosphate glucuronosyltransferase activity suggest that these polymorphisms contribute to variations in bilirubin metabolism. In Asians, a common DNA sequence variant (Gly71Arg), resulting in an amino acid change in the uridine diphosphate glucuronosyltransferase protein, is associated with neonatal hyperbilirubinemia. In addition, the combination of glucose-6-phosphate dehydrogenase deficiency and Gilbert’s syndrome increases the likelihood of severe hyperbilirubinemia.

Increased enterohepatic circulation of bilirubin in the fasting state can also exaggerate hyperbilirubinemia. Newborn infants who are not feeding well or who are exclusively breast-fed have low levels of the intestinal bacteria that are capable of converting bilirubin to nonresorbable derivatives and the enterohepatic circulation of bilirubin may be increased in such infants (Table 1).

**Cellular Toxic Effects of Bilirubin**

The primary concern with respect to exaggerated hyperbilirubinemia is the potential for neurotoxic effects, but general cellular injury also occurs. Bilirubin...
Bilirubin can enter the brain if it is not bound to albumin or is unconjugated or if there has been damage to the blood–brain barrier. Albumin can bind bilirubin at a molar ratio of up to 1 or a maximum of 8.2 mg of bilirubin per gram of albumin. Therefore, newborn infants with a serum albumin concentration of 3 g per deciliter may have a serum concentration of albumin-bound bilirubin of approximately 25 mg per deciliter. If the serum albumin concentration is low, the binding of bilirubin is compromised and the risk of kernicterus increases. In the 1950s, treatment of preterm infants with sulfisoxazole increased the risk of kernicterus, because the drug displaced bilirubin from albumin and therefore facilitates its entry into the brain. Benzyl alcohol, a preservative agent that was added to solutions of normal saline in the 1970s, may have caused kernicterus by the same mechanism. In the brain, the susceptibility to the neurotoxic effects of bilirubin varies according to cell type, brain maturity, and brain metabolism.

Unconjugated bilirubin is a substrate for an ATP-dependent plasma–membrane protein, P-glycoprotein, in the blood–brain barrier. In mice with a tar-

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### Table 1. Risk Factors for Neonatal Hyperbilirubinemia

<table>
<thead>
<tr>
<th>Maternal factors</th>
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<tr>
<td>Native American</td>
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<td>Genetic factors</td>
<td>Familial disorders of conjugation</td>
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<tr>
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<td>Other enzymatic defects</td>
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<td>Glucose-6-phosphate dehydrogenase deficiency</td>
<td>Pyruvate kinase deficiency</td>
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<td>Hexokinase deficiency</td>
<td>Congenital erythropoietic porphyria</td>
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<td>Spherocytosis</td>
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<td>Polycythemia</td>
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<td>Drugs</td>
<td>Streptomycin</td>
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<tr>
<td>Chloramphenicol</td>
<td>Benzyl alcohol</td>
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<tr>
<td>Sulfinpyrazone</td>
<td>Low intake of breast milk (early-onset breast-milk jaundice)</td>
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*Breast milk is a competitive inhibitor of hepatic uridine diphosphate glucuronyltransferase (late-onset breast-milk jaundice).

Table 1. Risk Factors for Neonatal Hyperbilirubinemia.

The concentration of bilirubin in the brain and the duration of exposure to bilirubin are important determinants of the neurotoxic effects of bilirubin, whereas the correlation between the serum bilirubin concentration and bilirubin encephalopathy is poor in infants without hemolysis. One reason for this weak correlation is that the duration of hyperbilirubinemia is also an important determinant of the brain's exposure to bilirubin. Serum bilirubin concentrations do not provide a reliable estimate of bilirubin production, tissue bilirubin concentrations, or serum concentrations of albumin-bound bilirubin. Furthermore, phototherapy, which alters the configuration of bilirubin and yields a photosomer that can be excreted, makes it difficult to equate serum bilirubin concentrations in treated infants with those in untreated infants. In contrast, peak serum bilirubin concentrations higher than 20 mg per deciliter usually predict a poor outcome in infants with Rh hemolytic disease, but some infants with concentrations of 25 mg per deciliter (428 μmol per liter) or higher are normal. Kernicterus was detected in 8 percent of infants with Rh-associated hemolysis who had serum bilirubin concentrations of 19 to 24 mg per deciliter (325 to 410 μmol per liter), 33 percent of infants with concentrations of 25 to 29 mg per deciliter (428 to 496 μmol per liter), and 73 percent of infants with concentrations of 30 to 40 mg per deciliter (513 to 684 μmol per liter).

Bilirubin can enter the brain if it is not bound to albumin or is unconjugated or if there has been damage to the blood–brain barrier. Albumin can bind bilirubin at a molar ratio of up to 1 or a maximum of 8.2 mg of bilirubin per gram of albumin. Therefore, newborn infants with a serum albumin concentration of 3 g per deciliter may have a serum concentration of albumin-bound bilirubin of approximately 25 mg per deciliter. If the serum albumin concentration is low, the binding of bilirubin is compromised and the risk of kernicterus increases. In the 1950s, treatment of preterm infants with sulfisoxazole increased the risk of kernicterus, because the drug displaces bilirubin from albumin and therefore facilitates its entry into the brain. Benzyl alcohol, a preservative agent that was added to solutions of normal saline in the 1970s, may have caused kernicterus by the same mechanism. In the brain, the susceptibility to the neurotoxic effects of bilirubin varies according to cell type, brain maturity, and brain metabolism.

Unconjugated bilirubin is a substrate for an ATP-dependent plasma–membrane protein, P-glycoprotein, in the blood–brain barrier. In mice with a tar-

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Bilirubin also inhibits the 

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...inhibits mitochondrial enzymes and can interfere with DNA synthesis, induce DNA-strand breakage, and inhibit protein synthesis and phosphorylation. Bilirubin has an affinity for membrane phospholipids and inhibits the uptake of tyrosine, a marker of synaptic transmission. Bilirubin also inhibits the function of N-methyl-D-aspartate–receptor ion channels. This suggests that bilirubin can interfere with neuroexcitatory signals and impair nerve conduction (particularly in the auditory nerve). Bilirubin can inhibit ion exchange and water transport in renal cells, which may explain the neuronal swelling that occurs in the bilirubin encephalopathy associated with kernicterus. In immature rats, increased levels of lactate, decreased levels of cellular glucose, and impaired cerebral glucose metabolism are associated with hyperbilirubinemia.
geted deletion of P-glycoprotein, bilirubin influx into the brain is increased. Conditions that alter the blood–brain barrier, such as infection, acidosis, hyperoxia, sepsis, prematurity, and hyperosmolarity, may affect the entry of bilirubin into the brain. Once it is in the brain, precipitation of bilirubin at low pH may have toxic effects. Also, neurons undergoing differentiation are particularly susceptible to injury from bilirubin, suggesting that prematurity predisposes infants to bilirubin encephalopathy.

Clinical Features of Kernicterus

The clinical features of kernicterus vary, and up to 15 percent of infants have no obvious neurologic symptoms. The disease can be divided into an acute and a chronic form (Table 2). The acute form usually has three phases; the chronic form is characterized by hypotonia in the first year and by extrapyramidal abnormalities and sensorineural hearing loss thereafter. In a registry of full-term and nearly full-term infants born between 1984 and 1999, the mortality rate among infants with kernicterus was 4 percent. Specific changes on magnetic resonance imaging — namely, increased signal intensity in the globus pallidus on T2-weighted images — are closely correlated with the deposition of bilirubin in the basal ganglia.

In approximately 27,000 infants in the Collaborative Perinatal Project, neurodevelopment during the first year of life was correlated with the maximal serum bilirubin concentration soon after birth. In a multicenter Dutch survey, a dose–response relation between the maximal serum bilirubin concentration and the risk of impaired development was found at two years of age only among children who had weighed less than 1500 g at birth, and there was no correlation at five years of age. In a study of 50 full-term infants with moderate hyperbilirubinemia (serum bilirubin concentration, 10 to 20 mg per deciliter [171 to 342 µmol per liter]), the latency of brain-stem auditory evoked responses was longer in these infants than in those with lower serum bilirubin concentrations, and the abnormality was more pronounced in infants with higher bilirubin concentrations.

Some of these changes disappear spontaneously or can be reversed with exchange transfusion. In most infants with moderate-to-severe hyperbilirubinemia, the evoked responses become normal by six months of age; the abnormalities were permanent in only 4 of 60 infants in one study, but in another study they persisted in 7 of 30 infants, and 3 of those 7 infants also had neurologic abnormalities. A 17-year follow-up study revealed an association between severe hyperbilirubinemia (serum bilirubin concentration of 20 mg per deciliter or higher) and low IQ in boys, but not in girls. The finding that boys are more susceptible than girls to the adverse effects of neonatal hyperbilirubinemia was substantiated in a historical cohort study of 31,759 untreated infants, in which it held true even among those infants with a serum bilirubin concentration of less than 20 mg per deciliter.

PREDICTION OF THE RISK OF SEVERE HYPERBILIRUBINEMIA

An increasing number of newborn infants are discharged from the hospital within 48 hours after birth, and it is therefore not surprising that hyperbilirubinemia is detected before discharge less often than it was in the past. The need for phototherapy is one of the most commonly reported reasons for readmission of newborn infants, suggesting the need for early detection of hyperbilirubinemia and follow-up after discharge.

Clues to an infant’s propensity for severe hyperbilirubinemia can be obtained from characteristics of the mother and perinatal and neonatal factors (Table 1). The evaluation of serum bilirubin concentrations in newborn infants by means of a percentile-based nomogram allows physicians to predict the risk of hyperbilirubinemia. In one study, infants who had serum bilirubin concentrations in the high-risk category (higher than the 95th percentile) 18 to 72 hours after birth had a 40 percent probability of subsequent, moderately severe hyperbilirubinemia (serum bilirubin concentration of more than 17 mg per deciliter), whereas infants with concentrations in the low-risk category (lower than the 40th percentile) had a probability of zero. Some caution is needed in interpreting these data, since meaningful follow-up data after hospital discharge were available for only 2976 of 13,003 eligible infants. Nonetheless, nomograms can identify infants who are at risk for severe hyperbilirubinemia and can guide follow-up.

Transcutaneous Measurement of Bilirubin

Estimates of serum bilirubin concentrations that are based solely on clinical examination are not reliable. Noninvasive techniques for transcutaneous measurement have been developed for this purpose, but older devices are affected by variation in the pigmen-
tation of the skin.66,67 Newer devices that use multi-
 wavelength spectral reflectance can eliminate this var-
 iability.68 In 897 newborn infants from various racial
 and ethnic groups, the serum bilirubin concentration
 ranged from 2 to 28 mg per deciliter (34 to 479 µmol
 per liter), and the results of transcutaneous measure-
 ments of bilirubin correlated well with the serum con-
 centrations ($r^2 = 0.88$).68 These devices could help re-
 duce the need to draw blood and improve follow-up
 for infants at home.

**Measurement of Carbon Monoxide to Evaluate Bilirubin Production**

Hemolysis and bruising increase the production of bilirubin.15 Although the degree of jaundice and the rate of production of bilirubin are not always cor-
 related because the rate of elimination of bilirubin varies among infants, early identification of infants in whom large amounts of bilirubin are produced is im-
 portant. Because carbon monoxide and bilirubin are produced in equimolar amounts when heme is de-
 graded, measurement of carbon monoxide in exhaled
 air can be used as an index of bilirubin production
 (Fig. 1). Exhaled carbon monoxide can be measured reproducibly in newborn infants as well as in adults.69
Since infants with hemolytic disease have high values
 for exhaled carbon monoxide,70 measuring end-tidal carbon monoxide may allow physicians to identify
 such infants.

**PREVENTION**

**Reduction of Bilirubin in the Enterohepatic Circulation**

Newborn infants who do not feed adequately prob-
 ably have increased enterohepatic circulation of bili-
 rubin, because fasting causes increased accumulation
 of bilirubin in animals.28 Since increasing the num-
 ber of oral feedings allows for more rapid excretion
 of bilirubin, early, frequent nursing or supplemental
 feedings with formula may be effective in reducing
 serum bilirubin concentrations in breast-fed infants
 who are undergoing phototherapy.71 In contrast, sup-
 plementation with water or dextrose may disrupt the
 mother’s production of milk, resulting in higher se-
 rum bilirubin concentrations.72

No drugs or other agents that decrease the entero-
 hepatic circulation of bilirubin are available. In rats, ac-
 tivated charcoal binds bilirubin and promotes its ex-
cretion, but the efficacy of charcoal in infants has not been tested.73 In one study, the administration of
agar as an adjunct to phototherapy in newborn in-
fants with hyperbilirubinemia significantly reduced
the duration of phototherapy from 48 hours with-
out the use of agar to 38 hours with its use.74 Choles-
teryramine, used to treat obstructive jaundice, in-
creases bilirubin excretion by binding to bile acids in
the intestine and forming a nonabsorbable complex.
However, in a study involving full-term infants who
were receiving phototherapy, treatment with choles-
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**tyramine, given at a dose of 1.5 g per kilogram of
body weight, did not result in serum bilirubin con-
centrations that were lower than those achieved with
phototherapy alone.75**

**Inhibition of Bilirubin Production**

Synthetic metalloporphyrins in which the central
iron is replaced by other metals76 limit the produc-
tion of bilirubin by competitively inhibiting heme
oxygenase. In 517 preterm infants who weighed 1500
to 2500 g, one intramuscular dose (6 µmol per kil-
ogram) of tin-mesoporphyrin given within 24 hours
after delivery reduced the requirement for photo-
therapy by 76 percent and lowered the peak serum
bilirubin concentration by 41 percent.77 The only
untoward effect was transient erythema due to pho-
totherapy. In other randomized trials involving a to-
tal of 84 full-term and nearly full-term infants treat-
ced with tin-mesoporphyrin (6 µmol per kilogram),
the need for phototherapy was completely eliminated,
and among the full-term newborns, the duration of
in-hospital observation was significantly shorter for
the infants treated with tin-mesoporphyrin than for
those treated with phototherapy alone (a difference of
more than 30 hours).77,78 Furthermore, in one of these
studies, all the infants who received tin-mesoporphyr-
lin had a peak serum bilirubin concentration that was
less than 19.6 mg per deciliter (335.2 µmol per li-
ter).79 Although they are promising, metalloporphyr-
ins are not currently approved for use in newborn
infants. Whether one metalloporphyrin is more effec-
tive and safer than the others is not known,80,82 and
none are available for oral administration.

**TREATMENT**

**Phototherapy**

Phototherapy has remained the standard of care
for the treatment of hyperbilirubinemia in infants for
four decades.83 Efficient phototherapy rapidly reduc-
es the serum bilirubin concentration. The formation
of lumirubin, a water-soluble compound, is the rate-
limiting step in the elimination of bilirubin by pho-
totherapy.84 Two factors determine the rate of lumiru-
bin formation: the spectrum85,86 and the total dose of
light delivered.87,88 Because bilirubin is a yellow pig-
ment, it is likely to absorb blue light (with a wave-
length of approximately 450 nm).87,88 Thus, blue
lamps are most effective in reducing hyperbilirubi-

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bulbs are used to deliver 6 to 12 \( \mu \text{W} \) per square centimeter of body-surface area exposed per nanometer of wavelength. Fiberoptic blankets have a small effective surface area but generate little heat and can therefore be positioned nearer the infant, providing up to 50 \( \mu \text{W} \) per square centimeter per nanometer. A new device that uses high-intensity gallium nitride light-emitting diodes can generate more than 200 \( \mu \text{W} \) per square centimeter per nanometer, resulting in high rates of photodegradation of bilirubin in vitro.

The pattern of use of phototherapy in full-term infants has changed along with postpartum discharge practices. In many instances, by the time jaundice is diagnosed, the infant has already been discharged, and serum bilirubin concentrations of more than 25 mg per deciliter per day are not exceptional among hospitalized infants. Intensive phototherapy may eliminate the need for exchange transfusion. For example, phototherapy (irradiance, 11 to 14 \( \mu \text{W} \) per square centimeter per nanometer) and feeding on demand with formula or breast milk lowered serum bilirubin concentrations by more than 10 mg per deciliter within two to five hours in four infants admitted with serum bilirubin concentrations of 30 mg per deciliter or higher. However, the neurologic outcome was not assessed in these few infants, so the safety of this practice has not been established. Currently, many infants receive phototherapy in a dose that is well below the optimal therapeutic range, yet this therapy is safe, and its effect can be maximized by increasing the exposed body-surface area and the intensity of the light.

An infant being treated with phototherapy is placed (preferably naked) under a bank of lights (eight fluorescent bulbs), and the eyes are shielded. Temperature and hydration status should be monitored. When dehydration is suspected, intravenous fluids are infused. Otherwise, the infant receives only oral fluids. Phototherapy can be discontinued for periods of one to two hours to allow family visits and feeding.

The time at which phototherapy is initiated varies according to the infant's gestational age and the cause of the jaundice. Full-term infants with no evidence of hemolysis should be treated according to the guidelines of the American Academy of Pediatrics. No guidelines have been published for preterm infants, but we suggest following the published recommendations that are based on gestational age, birth weight, and relative health. Phototherapy can be discontinued once the serum bilirubin concentration has been reduced by about 4 to 5 mg per deciliter (68 to 86 \( \mu \text{mol} \) per liter). Phototherapy may not reduce the serum bilirubin concentration in breast-fed infants as rapidly as in bottle-fed infants, because the former may have greater degrees of enterohepatic recirculation, but supplementing breast-feeding with formula reduces recirculation and allows for continued breast-feeding even in infants with severe hyperbilirubinemia.

There is a common belief that the discontinuation of phototherapy is associated with rebound hyperbilirubinemia. In a recent study, 264 healthy newborns who weighed 1800 g or more had lower serum bilirubin concentrations as long as 30 hours after the discontinuation of phototherapy than they did immediately after discontinuation, suggesting that rebound hyperbilirubinemia is rare. Whether this finding can be extrapolated to smaller preterm infants or infants with hemolysis is not clear. Overall, phototherapy is an effective way to decrease serum bilirubin concentrations.

Exchange Transfusion

Exchange transfusion was the first successful therapy for severe neonatal jaundice. This technique rapidly eliminates bilirubin from the circulation. Circulating antibodies that target the erythrocytes are also removed. Exchange transfusion is especially beneficial in infants who have ongoing hemolysis from any cause. One or two central catheters are placed, and small aliquots of blood are removed from the infant and replaced with similar aliquots of red cells from a donor, mixed with plasma. This procedure is repeated until twice the blood volume has been replaced. During the procedure, serum electrolytes and bilirubin should be measured periodically. The amount of bilirubin removed from the circulation varies according to both the amount of bilirubin stored in tissues that reenters the circulation and the rate of hemolysis. In some cases, the procedure needs to be repeated to lower the serum bilirubin concentration sufficiently. Infusion of salt-poor albumin at a dose of 1 g per kilogram one to four hours before exchange transfusion increases the mean amount of bilirubin removed from 8.7 to 12.3 mg per kilogram of birth weight, demonstrating the importance of albumin in binding bilirubin.

Many complications of exchange transfusions have been reported, including thrombocytopenia, portal vein thrombosis, necrotizing enterocolitis, electrolyte imbalance, graft-versus-host disease, and infection. In a recent retrospective study spanning 15 years, 2 percent of 106 infants with a variety of illnesses died after exchange transfusion, and 12 percent had severe complications. All 81 infants with jaundice who were otherwise healthy survived, although necrotizing enterocolitis developed in 1. Therefore, exchange transfusion should be reserved for infants with hemolysis in whom intensive phototherapy (i.e., with the maximal area of exposure and at an irradiance of more than 12 \( \mu \text{W} \) per square centimeter per nanometer) has failed or in whom the rate at which the serum bilirubin concentration is rising suggests that it will probably reach 25 mg per deciliter within 48 hours, and for whom the risk of encephalopathy exceeds the risk of complications and death from the procedure. Use of exchange transfusion greatly
decreased after the introduction of phototherapy, and the optimization of phototherapy may further reduce its use.

Pharmacologic Therapies

Phenobarbital has been used since the mid-1960s to increase the conjugation and excretion of bilirubin, but it is not effective immediately. In a study involving 1310 women whose infants were at risk for jaundice, the administration of phenobarbital at doses of more than 1 mg daily for the last week of pregnancy reduced the incidence of severe jaundice (defined as a serum bilirubin concentration of more than 16 mg per deciliter [274 µmol per liter]) and reduced the need for exchange transfusion by a factor of six.

However, in rats, phenobarbital diminishes the oxidative metabolism of bilirubin in neural tissues, suggesting an increased risk of neurotoxic effects.

Unconjugated bilirubin is metabolized by bilirubin oxidase. When human or rat blood is passed through a filter containing bilirubin oxidase, more than 90 percent of the bilirubin is degraded in a single pass. This procedure may prove useful in the treatment of neonatal hyperbilirubinemia, but it has not yet been tested in clinical trials. Moreover, it may pose a risk of allergic reaction because the enzyme is derived from a fungus.

PREVENTION OF BILIRUBIN ENCEPHALOPATHY

Once bilirubin has accumulated, raising the brain pH may help prevent encephalopathy, because bilirubin is more soluble in alkaline states. In primates with hyperbilirubinemia, correction of respiratory acidosis results in the complete reversal of abnormalities in auditory evoked potentials. In newborn infants with severe hyperbilirubinemia, moderate alkalization (pH, 7.45 to 7.55) may be attempted either by infusing bicarbonate or by using ventilatory strategies to lower the partial pressure of carbon dioxide and thus raise the pH.

APPROACH TO JAUNDICE

Many variables affect the severity of hyperbilirubinemia in infants, making it difficult to develop a simple algorithm for intervention. The current recommendations for initiating treatment are based on clinical practice, and important unknowns preclude the development of a universally applicable approach. The designation of a specific serum bilirubin concentration at which therapy is warranted is controversial, because estimates of safe concentrations are based primarily on historical data from infants with a disease that is rarely seen now (Rh-hemolytic disease). In addition, serum bilirubin concentrations of more than 25 mg per deciliter are rarely encountered today. Therefore, clinical trials of therapy would be difficult to conduct because of the large population of patients that would be required. To complicate matters further, there is substantial variability among hospitals in the methods of testing for hyperbilirubinemia and the laboratory values they report. Furthermore, the concentration and duration of exposure at which bilirubin is neurotoxic are not known; very premature or sick infants and those with hemolytic disease are at greater risk for neurotoxic effects.

For full-term infants with no evidence of hemolysis, the American Academy of Pediatrics recommends initiating phototherapy according to a threshold for serum bilirubin that depends on the infant’s age: 15 mg per deciliter (257 µmol per liter) at 49 to 72 hours; 18 mg per deciliter (308 µmol per liter) at 49 to 72 hours; and 20 mg per deciliter (342 µmol per liter) at 72 hours or more. Unfortunately, these values are not based on large prospective studies and may not apply to all infants. Furthermore, the absence of hemolysis can be difficult to gauge in the first days of life. Last, these recommendations should not be extrapolated to preterm or sick infants because of the higher risk of toxic effects in these infants.

Therefore, for preventing the development of pathologic jaundice, we can recommend only a careful history taking to elicit information on risk factors, early measurement of serum bilirubin, tests to rule out hemolysis, and prudent feeding practices (early breastfeeding and frequent supplementation with breast milk or formula to prevent dehydration). The serum bilirubin concentration is merely a marker of possible neurotoxic effects and should be evaluated in the context of the infant’s overall condition. For example, the physician should take into consideration the presence or absence of hypoxemia, acidosis, hypalbuminemia, and sepsis. If severe hyperbilirubinemia is detected, phototherapy should be initiated immediately. We also strongly recommend early follow-up (within 48 hours after discharge) to detect severe jaundice.

CONCLUSIONS

With our altered perception of the toxicity of bilirubin and an emphasis, driven by managed care, on shortened hospital stays, the incidence of kernicterus has again increased. Thus, health care providers must reexamine their procedures for follow-up of newborn infants. Evaluating the serum bilirubin concentration early for all infants with the use of a percentile-based nomogram and possibly screening for genetic conditions should facilitate the anticipation and diagnosis of pathologic jaundice before discharge. Improved phototherapy and the use of metalloporphyrins may decrease the need for exchange transfusion and even make possible the successful treatment of hyperbilirubinemia at home. All newborn infants who are discharged 48 hours or less after delivery should meet the criteria of the American Academy of Pediatrics for early discharge and should be examined for jaundice within two to three days after discharge.
Ultimately, serious consideration should be given to a universal screening program for hyperbilirubinemia in the first 24 to 48 hours after delivery, with the establishment of a registry to assess the severity of bilirubin toxicity. Kernicterus is a condition that leads to devastating neurologic injury. This complication occurs infrequently and can be prevented by continued vigilance and available therapies.

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REFERENCES


50. van de Bor M, van Zeben-van der AA TM, Verloove-Vanhorick SP, Brand R, Ruys JH. Hyperbilirubinemia in preterm infants and neurodevelopment at 4 years of age: results of a national collaborative sur-

51. van de Bor M, Ens-Dokkum M, Schreuder AM, Veen S, Brand R, Ver-

52. Vohr BR, Karp D, O'Dea C, et al. Behavioral changes correlated with brain-stem auditory evoked responses in term infants with moderate hyper-

53. Gupta AK, Mann SB. Is auditory brainstem response a bilirubin tox-

54. Agrawal VK, Shukla R, Misra PK, Kapoor RK, Malik GK. Brainstem auditory evoked response in newborns with hyperbilirubinemia. Indian Pa-

55. Seidman DS, Paiz I, Stevenson DK, Laor A, Danon YL, Gale R. Neo-


58. Maises MJ, Kring E. Length of stay, jaundice, and hospital readmis-


60. Stanley TA. A case of kernicterus in New Zealand: a predictable trag-


62. Bhutani VK, Johnson HJ, Siveri EM. Predictive ability of a predisch-


67. Gale R, Dranitzki Z, Dollberg S, Stevenson DK. A randomized, con-


70. Vreman HJ, Wong RJ, Stevenson DK, et al. Bilirubin production in healthy term newborns with the inhib-


72. Odell GB, Cohen SN, Gordes EH. Administration of albumin in the management of severe hyperbilirubinemia in full-term newborns with the inhib-

73. Martinez KC, Garcia HO, Otheguy LE, Drummond GS, Kappas A. Control of severe hyperbilirubinemia in full-term newborns with the inhib-

74. Vreman HJ, Wang RJ, Williams SA, Stevenson DK. In vitro heme ox-

75. Kappas A, Drummond GS, Henschke C, Valeta T. Direct comparison of Sn-mesophosphoryl, an inhibitor of bilirubin production, and photother-
apy in controlling hyperbilirubinemia in term and near-term newborns. Pa-

76. Johnson HJ, McKee L, Henschke C, Valeta T. The use of metallopor-

77. Valeta T, Petmezakis S, Henschke C, Drummond GS, Kappas A. Con-
trol of jaundice in preterm newborns by an inhibitor of bilirubin produc-

78. Kappas A, Drummond GS, Henschke C, Valeta T. Direct comparison of Sn-mesophosphoryl, an inhibitor of bilirubin production, and photother-
apy in controlling hyperbilirubinemia in term and near-term newborns. Pa-


114. Newborns’ and Mothers’ Health Protection Act of 1996, tit. 6 (Departments of Veterans Affairs and Housing and Urban Development, and Independent Agencies Appropriations (1997)) (brochure).