CLINICAL THERAPEUTICS

Phototherapy for Neonatal Jaundice

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.*

A male infant weighing 3400 g was born at 37 weeks' gestation after an uncomplicated pregnancy. The mother is a 24-year-old primipara who has type A Rh-positive blood. The infant's course in the hospital nursery was uncomplicated. Although his mother needed considerable help in establishing effective breast-feeding, he was exclusively breast-fed. Jaundice was noted at the age of 34 hours. The total serum bilirubin level was 7.5 mg per deciliter (128 μmol per liter). The infant was discharged at the age of 40 hours and is seen in the pediatrician's office 2 days later, now with marked jaundice. The results of his physical examination are otherwise normal, but his weight, at 3020 g, is 11% below his birth weight. His total serum bilirubin level is 19.5 mg per deciliter (333 μmol per liter), and his conjugated (direct) bilirubin level 0.6 mg per deciliter (10 μmol per liter). The complete blood count and peripheral-blood smear are normal. The infant has type A Rh-positive blood. The pediatrician consults a neonatologist regarding the need for phototherapy.

THE CLINICAL PROBLEM

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Some 60% of normal newborns become clinically jaundiced sometime during the first week of life. Unconjugated (indirect) hyperbilirubinemia occurs as a result of excessive bilirubin formation and because the neonatal liver cannot clear bilirubin rapidly enough from the blood.[1,2] Although most newborns with jaundice are otherwise healthy, they need to be monitored because bilirubin is potentially toxic to the central nervous system. Sufficiently elevated levels of bilirubin can lead to bilirubin encephalopathy and subsequently kernicterus, with devastating, permanent neurodevelopmental handicaps.[3]

Fortunately, current interventions make such severe sequelae rare. But because neonatal jaundice is so common, many infants — most of whom will be unaffected — are monitored and treated to prevent substantial damage that would otherwise occur in a few. Data from 11 hospitals in the northern California region of the Kaiser Permanente medical system[4] and from the 18-hospital Intermountain Health Care system[5] suggest that the total serum bilirubin level is 20 mg per deciliter (342 μmol per liter) or higher in approximately 1 to 2% of infants born at a gestational age of at least 35 weeks. Hospital-based studies in the United States have shown that 5 to 40 infants per 1000 term and late-preterm infants receive phototherapy before discharge from the nursery and that an equal number are readmitted for phototherapy after discharge.[5-7] These data do not include the use of home phototherapy, which is prevalent in some regions.[8,9] In some hospitals and in other countries,[10] phototherapy is used more frequently.

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Bilirubin is normally cleared from the body by hepatic conjugation with glucuronic acid and elimination in bile in the form of bilirubin glucuronides (Fig. 1). Neonatal jaundice stems from a transient deficiency of conjugation (exacerbated in preterm infants) combined with increased turnover of red cells. Pathologic conditions that can increase bilirubin production include isoimmunization, heritable hemolytic disorders, and extravasated blood (e.g., from bruises and cephalhematomas).[11] Genetic disorders of bilirubin conjugation, particularly the common Gilbert's syndrome, can also contribute to neonatal hyperbilirubinemia.[12] The largest group of otherwise healthy infants at increased risk for hyperbilirubinemia are late-preterm infants and those who are exclusively breast-fed[7,13,14] (particularly if breast-feeding is not going well). Breast-feeding and the poor caloric intake associated with breast-feeding difficulties are both thought to cause an increase in the enterohepatic circulation of bilirubin.[15]

The goal of therapy is to lower the concentration of circulating bilirubin or keep it from increasing. Phototherapy achieves this by using light energy to change the shape and structure of bilirubin, converting it to molecules that can be excreted even when normal conjugation is deficient (Fig. 1 and 2).[17] Absorption of light by dermal and subcutaneous bilirubin induces a fraction of the pigment to undergo several photochemical reactions that occur at very different rates. These reactions generate yellow stereoisomers of bilirubin and colorless derivatives of lower molecular weight (Fig. 2). The products are less lipophilic than bilirubin, and unlike bilirubin, they can be excreted in bile or urine without the need for conjugation. The relative contributions of the various reactions to the overall elimination of bilirubin are unknown, although in vitro and in vivo studies suggest that photoisomerization is more important than photodegradation.[17] Bilirubin elimination depends on the rates of formation as well as the rates of clearance of the photoproducts. Photoisomerization occurs rapidly during phototherapy, and isomers appear in the blood long before the level of plasma bilirubin begins to decline.

Bilirubin absorbs light most strongly in the blue region of the spectrum near 460 nm (Fig. 3), a region in which penetration of tissue by light increases markedly with increasing wavelength. The rate of formation of bilirubin photoproducts is highly dependent on the intensity and wavelengths of the light used — only wavelengths that penetrate tissue and are absorbed by bilirubin have a phototherapeutic effect. Taking these factors into account, lamps with output predominantly in the 460-to-490-nm blue region of the spectrum are probably the most effective for treating hyperbilirubinemia.

A common misconception is that ultraviolet

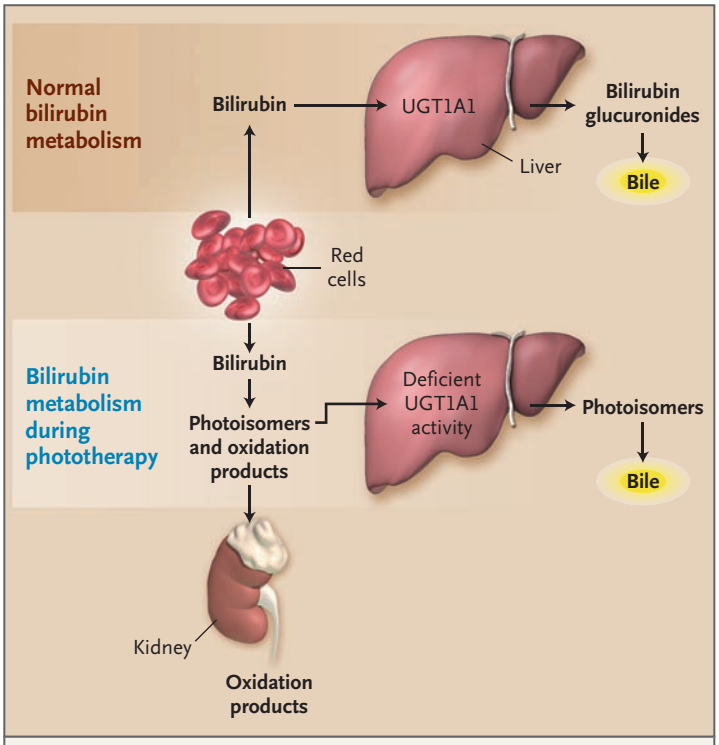

Figure 1. Normal Bilirubin Metabolism and Bilirubin Metabolism during Phototherapy.

In normal metabolism, lipophilic bilirubin, which results predominantly from the catabolism of red cells, circulates in blood mainly as a noncovalent conjugate with serum albumin. After uptake by the liver, it is converted into two isomeric monoglucuronides and a diglucuronide (direct bilirubin) by the enzyme uridinediphosphoglucuronosyltransferase 1A1 (UGT1A1). The water-soluble glucuronides are excreted in bile with the aid of a canalicular multidrug-resistance–associated transport protein, MRP2. Without glucuronidation, bilirubin cannot be excreted in bile or urine. In neonates, hepatic UGT1A1 activity is deficient and the lifetime of red cells is shorter than in adults, leading to accumulation and increased formation of bilirubin, with eventual jaundice. Phototherapy converts bilirubin to yellow photoisomers and colorless oxidation products that are less lipophilic than bilirubin and do not require hepatic conjugation for excretion. Photoisomers are excreted mainly in bile, and oxidation products predominantly in urine.

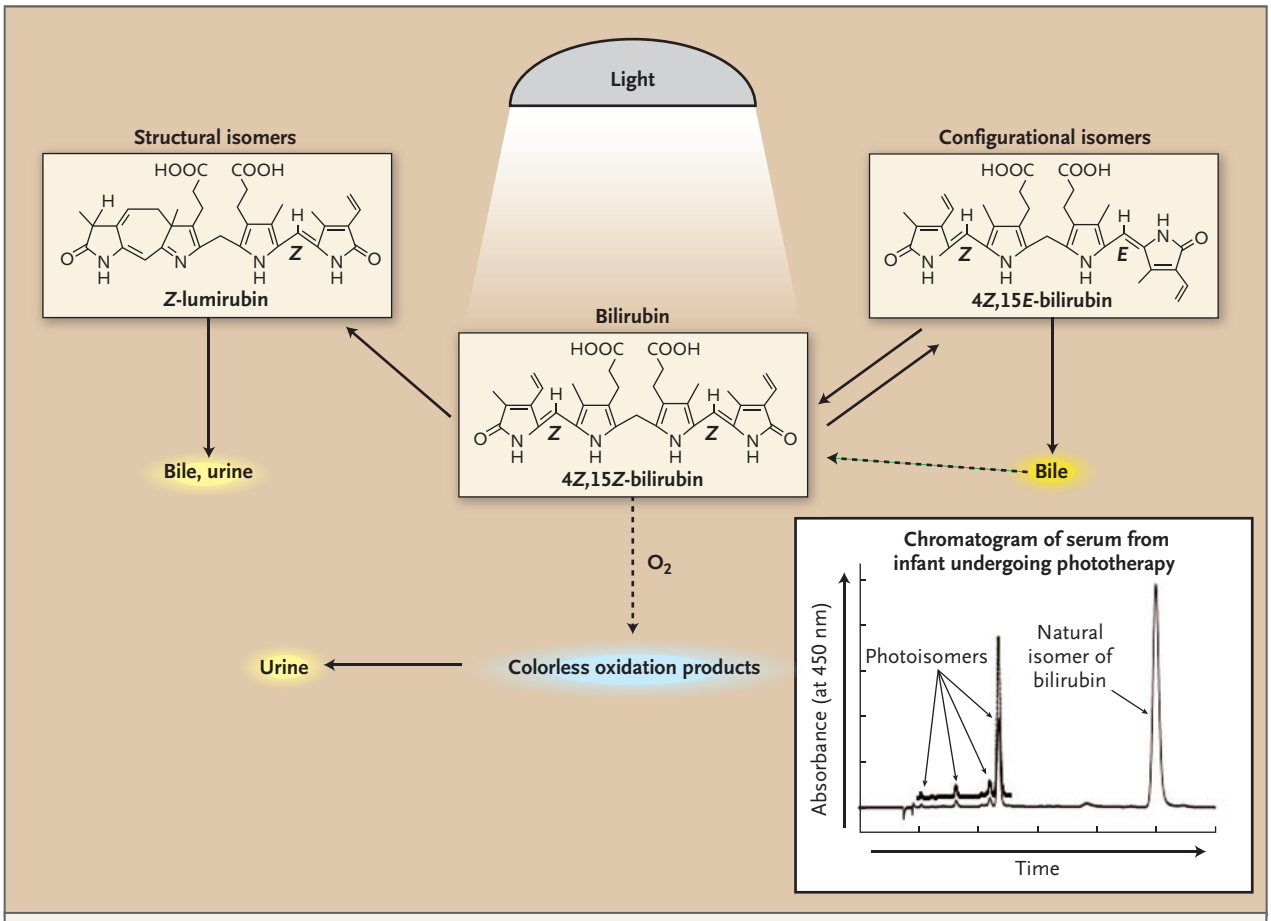

Figure 2. Mechanism of Phototherapy.

The absorption of light by the normal form of bilirubin (4*Z*,15*Z*-bilirubin) generates transient excited-state bilirubin molecules. These fleeting intermediates can react with oxygen to produce colorless products of lower molecular weight, or they can undergo rearrangement to become structural isomers (lumirubins) or isomers in which the configuration of at least one of the two *Z*-configuration double bonds has changed to an *E* configuration. (*Z* and *E*, from the German *zusammen* (together) and *entgegen* (opposite), respectively, are prefixes used for designating the stereochemistry around a double bond. The prefixes 4 and 15 designate double-bond positions.) Only the two principal photoisomers formed in humans are shown. Configurational isomerization is reversible and much faster than structural isomerization, which is irreversible. Both occur much more quickly than photooxidation. The photoisomers are less lipophilic than the 4*Z*,15*Z* form of bilirubin and can be excreted unchanged in bile without undergoing glucuronidation. Lumirubin isomers can also be excreted in urine. Photooxidation products are excreted mainly in urine. Once in bile, configurational isomers revert spontaneously to the natural 4*Z*,15*Z* form of bilirubin. The graph, a high-performance liquid chromatogram of serum from an infant undergoing phototherapy, shows the presence of several photoisomers in addition to the 4*Z*,15*Z* isomer. Photoisomers are also detectable in the blood of healthy adults after sunbathing.[16]

(UV) light (<400 nm) is used for phototherapy. Phototherapy lights in current use do not emit significant erythemal UV radiation. In addition, the plastic cover of the lamp and, in the case of preterm infants, the incubator, filter out UV light.

CLINICAL EVIDENCE

Phototherapy was evaluated in a number of randomized trials conducted from the 1960s through the early 1990s.[18,19] Although these trials helped to establish the efficacy of phototherapy as it was used during this period, none used the relatively high light doses used today. Current ethical standards would prevent any trial comparing phototherapy with placebo.

Since the only effective alternative to phototherapy in infants with severe jaundice is exchange transfusion, a measure of the efficacy of phototherapy is the dramatic reduction in the number of exchange transfusions being performed.[20-23] This effect has been particularly noticeable in in-

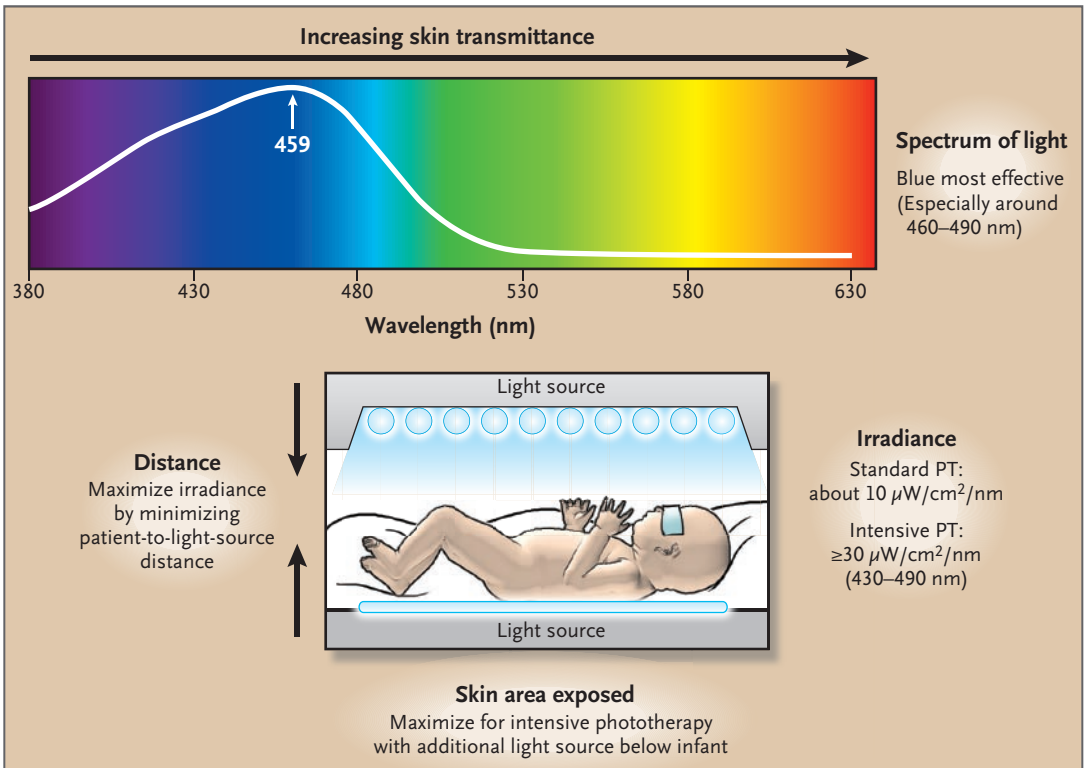

Figure 3. Important Factors in the Efficacy of Phototherapy.

The absorbance spectrum of bilirubin bound to human serum albumin (white line) is shown superimposed on the spectrum of visible light. Clearly, blue light is most effective for phototherapy, but because the transmittance of skin increases with increasing wavelength, the best wavelengths to use are probably in the range of 460 to 490 nm. Term and near-term infants should be treated in a bassinet, not an incubator, to allow the light source to be brought to within 10 to 15 cm of the infant (except when halogen or tungsten lights are used), increasing irradiance and efficacy. For intensive phototherapy, an auxiliary light source (fiber-optic pad, light-emitting diode [LED] mattress, or special blue fluorescent tubes) can be placed below the infant or bassinet. If the infant is in an incubator, the light rays should be perpendicular to the surface of the incubator in order to minimize loss of efficacy due to reflectance.

fants with very low birth weight, for whom exchange transfusions, once common procedures in the neonatal intensive care unit, are now rare.[20-23] Studies have shown that when phototherapy was withheld, 36% of infants with birth weights of less than 1500 g required an exchange transfusion.[24] When phototherapy was used, only 2 of 833 such infants (0.24%) received exchange transfusions.[23] Between January 1988 and October 2007, no exchange transfusions were needed in the neonatal intensive care unit at William Beaumont Hospital, in Royal Oak, Michigan, for 2425 infants who weighed less than 1500 g at birth.

CLINICAL USE

In term and late-preterm infants, phototherapy is typically used according to guidelines published by the American Academy of Pediatrics in 2004.[25] These guidelines take into consideration not only the level of total serum bilirubin but also the gestational age of the infant, the age of the infant in hours since birth, and the presence or absence of risk factors, including isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase deficiency, asphyxia, lethargy, temperature instability, sepsis, acidosis, and hypoalbuminemia (Fig. 4). In preterm infants, phototherapy is used at much lower total serum bilirubin levels,[26] and in some units it is used prophylactically in all infants with birth weights of less than 1000 g.

The efficacy of phototherapy depends on the irradiance (energy output) of the light source. Irradiance is measured with a radiometer or spectroradiometer in units of watts per square centimeter or in microwatts per square centimeter per

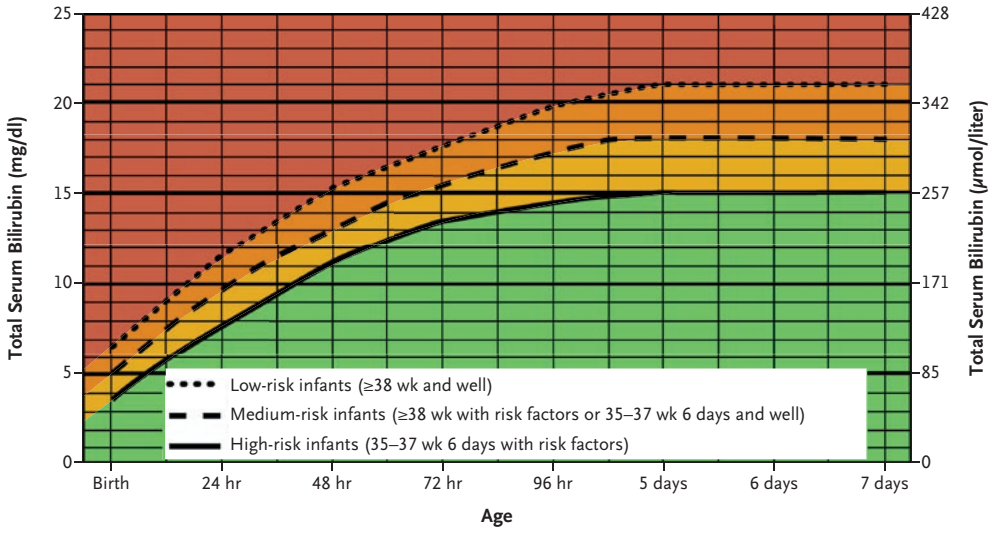

Figure 4. Guidelines for Intensive Phototherapy in Hospitalized Infants Born at a Gestational Age of 35 Weeks or More.

The guidelines are based on limited evidence. Intensive phototherapy should be used when the level of total bilirubin (not total minus direct) falls above the appropriate risk-group line for the infant at a particular age. Risk factors include isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase deficiency, asphyxia, lethargy, temperature instability, sepsis, acidosis, and an albumin level of less than 3.0 g per deciliter. For conventional phototherapy in the hospital or for home phototherapy, total serum bilirubin levels that are 2 to 3 mg per deciliter (34 to 51 μmol per liter) below those shown should be used. Home phototherapy should not be used for any infant with risk factors. Adapted from the American Academy of Pediatrics.[25]

nanometer over a given wavelength band. When positioned 20 cm above the infant, conventional or standard daylight phototherapy units should deliver a spectral irradiance (measured at the level of the infant) of 8 to 10 μW per square centimeter per nanometer in the 430-to-490-nm band, whereas special blue fluorescent lamps will deliver 30 to 40 μW per square centimeter per nanometer.[27] The American Academy of Pediatrics defines intensive phototherapy as a spectral irradiance of at least 30 μW per square centimeter per nanometer over the same bandwidth delivered to as much of the infant's body-surface area as possible.[25] This may be achieved by using light sources placed above and beneath the infant (Fig. 3). There is a direct relationship between the irradiance used and the rate at which the level of total serum bilirubin declines.[28] The guidelines recommend standard phototherapy for total serum bilirubin levels that are 2 to 3 mg per deciliter (34 to 51 μmol per liter) lower than the range for which intensive phototherapy is recommended (Fig. 4).[25]

The dose of phototherapy should be checked with the use of a commercially available radiometer designed for that purpose. Unfortunately, no single standardized method is in general use for reporting phototherapy dosages in the clinical literature,[25,29] making it hard to compare published studies, and different radiometers often produce markedly different results when irradiance is measured from the same phototherapy system.[29] Therefore, clinicians should use the radiometer recommended by the manufacturer of the light source. Using ordinary photometric or colorimetric light meters or relying on visual estimations of brightness is inappropriate. Because of spatial variation, irradiance should ideally be measured at several sites under the area illuminated by the unit, and the measurements averaged. Since this is not often done, the American Academy of Pediatrics recommends that measurements be performed below the center of the lights.[25]

The dose and efficacy of phototherapy are affected by the type of light source. Commonly used phototherapy units contain daylight, white, or blue fluorescent tubes. However, when total serum bilirubin levels approach the range at which intensive phototherapy is recommended,[25] it is particu-

larly important to use lamps with blue emission for the reasons outlined above. The American Academy of Pediatrics currently recommends special blue fluorescent lamps or light-emitting diode (LED) lights that have been found to be effective for phototherapy in clinical studies.[30,31] Filtered halogen lights, often incorporated into fiber-optic devices, are also used.

The dose and efficacy of phototherapy are also affected by the infant's distance from the light (the nearer the light source, the greater the irradiance[27]) and the area of skin exposed (Fig. 3), hence the need for a light source beneath the infant for intensive phototherapy. Although controlled trials have demonstrated that the more surface area exposed, the greater the reduction in the total serum bilirubin level,[32-34] it is usually unnecessary to remove the infant's diaper. If, however, the total serum bilirubin level continues to rise despite treatment, the diaper should be removed until there is a clinically significant decline. Aluminum foil or white cloth placed on either side of the infant to reflect light will also improve the efficacy of phototherapy.[35,36] Because light can be toxic to the immature retina, the infant's eyes should always be protected with opaque eye patches.[37]

The effectiveness of treatment depends not only on the light dose but also on the cause and severity of the hyperbilirubinemia. During active hemolysis, the total serum bilirubin level will not decline as rapidly as it would in an infant without hemolysis. On the other hand, because phototherapy works on bilirubin present in the skin and superficial subcutaneous tissue, the more bilirubin present at those sites (i.e., the higher the total serum bilirubin level), the more effective phototherapy will be.[38] In some infants with a total serum bilirubin level greater than 30 mg per deciliter (513 μmol per liter), intensive phototherapy can result in a decline of as much as 10 mg per deciliter (171 μmol per liter) within a few hours.[39]

Hemolysis is more likely to be the cause of hyperbilirubinemia in infants treated with phototherapy during the birth hospitalization than in those readmitted for such treatment,[2,40,41] and phototherapy in infants treated during the birth hospitalization is initiated at a lower total serum bilirubin level (Fig. 4). For both of these reasons, the level of total serum bilirubin tends to fall relatively slowly in such infants. Although there are no firm standards for discontinuing treatment, phototherapy can be safely stopped in infants treated during the birth hospitalization when the total serum bilirubin falls below the level at which phototherapy was initiated. In contrast, in infants readmitted for phototherapy, hemolysis is less often the cause of their hyperbilirubinemia[40,41] and treatment is begun at a higher initial level of total serum bilirubin (Fig. 4). In these patients, intensive phototherapy can result in a decrement of 30 to 40% in the first 24 hours,[40] with the most pronounced decline occurring in the first 4 to 6 hours; phototherapy can be discontinued when the total serum bilirubin level has fallen below 13 to 14 mg per deciliter (222 to 239 μmol per liter).[25]

A rebound in the total serum bilirubin level of 1 to 2 mg per deciliter (17 to 34 μmol per liter)[40,42] — and occasionally more[41] — can occur after phototherapy is discontinued. Infants at increased risk of a clinically significant rebound are those born at less than 37 weeks' gestation, those with hemolytic disease, and those treated with phototherapy during the birth hospitalization.[40,41] It is usually unnecessary to keep an infant in the hospital to check for rebound,[40,43] but for infants who require phototherapy during their birth hospitalization and for those with well-defined hemolytic disease, a follow-up bilirubin level should be obtained 24 hours after discharge.

The principal expense of phototherapy is that associated with hospital admission. In one report from the United States, the estimated daily cost in 2002 dollars was less than $1,000.[44] Home phototherapy is an option that avoids separation of mother and infant, facilitates the maintenance of breast-feeding, and is cheaper than hospitalization. It can be used safely, provided that the total serum bilirubin level is monitored regularly.[8,9,45] However, most home phototherapy devices are less efficient than those available in hospitals, making home phototherapy more appropriate for infants with total serum bilirubin levels that are 2 to 3 mg per deciliter below those recommended for hospital phototherapy[25] (Fig. 4). Newer home phototherapy devices that have special blue or LED lights should be more effective.

Sunlight will lower the serum bilirubin level,[46] but the practical difficulties involved in safely exposing a naked newborn to the sun either inside or outside (and avoiding sunburn) preclude the use of sunlight as a reliable therapeutic tool.

ADVERSE EFFECTS

Reports of clinically significant toxicity from phototherapy are rare.[47,48] In infants with cholestasis

(direct hyperbilirubinemia), phototherapy can produce the bronze baby syndrome, in which the skin, serum, and urine develop a dark, grayish-brown discoloration.[49,50] The pathogenesis of this condition, which occurs only in infants with cholestasis, is not fully understood. When phototherapy is stopped and cholestasis resolves, the coloration disappears. Rare purpuric and bullous eruptions have also been reported in infants with severe cholestatic jaundice who are receiving phototherapy,[51,52] probably as a result of sensitization by accumulating porphyrins. An erythematous rash can occur in infants treated with tin-mesoporphyrin (an experimental drug used to prevent and treat hyperbilirubinemia) who are subsequently exposed to sunlight or daylight fluorescent bulbs.[53] Congenital porphyria, a family history of porphyria, and concomitant use of photosensitizing drugs or other agents are absolute contraindications to phototherapy; severe blistering and agitation during phototherapy could be a sign of congenital porphyria.[54]

Conventional phototherapy can produce an acute change in the infant's thermal environment, leading to an increase in peripheral blood flow and insensible water loss.[55,56] This finding has not been studied with LED lights, which, because of their relatively low heat output, should be much less likely to cause insensible water loss. In term infants who are nursing or feeding adequately, additional intravenous fluids are usually not required.

A recent study suggested that intensive phototherapy might increase the number of atypical melanocytic nevi identified at school age,[57] although other research has not shown this association.[58] Intensive phototherapy does not cause hemolysis.[59] Swedish studies have suggested that phototherapy is associated with type 1 diabetes[60] and, possibly, asthma.[61] Because bilirubin is a powerful antioxidant,[62,63] lowering total serum bilirubin levels, particularly in an infant with very low birth weight, could have undesirable consequences,[29] but none have yet been clearly identified.

AREAS OF UNCERTAINTY

The fact that exchange transfusions are now so rare confirms the efficacy of phototherapy for regulating plasma bilirubin concentrations. The price of this success may be that many infants are treated whose levels of total serum bilirubin would not have reached the threshold for exchange transfusion had phototherapy been withheld.

Historically, the goal of phototherapy has been to reduce circulating levels of bilirubin by accelerating its elimination; phototherapy does this effectively, albeit sometimes rather slowly. Observations that phototherapy rapidly converts a substantial fraction (up to approximately 25%) of the bilirubin in the circulation to a less lipophilic and possibly less toxic isomer raises the possibility that an unrecognized benefit of treatment might be partial detoxification of bilirubin even before it is eliminated.[64,65] On the other hand, there is limited evidence regarding the possible toxicity of photoisomers. The precise contributions of the different photochemical pathways to the elimination of bilirubin during phototherapy are also unknown.

GUIDELINES

Figure 4 shows the American Academy of Pediatrics guidelines for the use of phototherapy in infants with a gestational age of 35 weeks or more. These guidelines, however, are not evidence based but are primarily the result of expert opinion. The use of phototherapy in infants with low birth weight is prophylactic, similarly arbitrary, and based on either birth weight or gestational age.[26]

RECOMMENDATIONS

The infant described in the vignette was born at 37 weeks' gestation and has no documented hemolytic disease. With a total serum bilirubin level of 19.5 mg per deciliter, he meets the American Academy of Pediatrics criteria for hospital admission and intensive phototherapy (defined as an irradiance of at least 30 μW per square centimeter per nanometer in the blue spectrum delivered to the maximum surface area) (Fig. 3).[27] We concur with this recommendation. Such therapy can be expected to reduce the level of total serum bilirubin by 30 to 40% in 24 hours.[40] We recommend that treatment continue until the level falls below 13 to 14 mg per deciliter. In addition, the loss of 11% of his birth weight suggests inadequate caloric intake and possibly hypernatremic dehydration. Depending on electrolyte measurements, this infant might need intravenous fluids. Breast-feeding should be continued, although in view of his weight loss, he will probably need supplementa-

tion with formula while in the hospital. It is very important to review the process of breast-feeding with the mother and to provide her with guidance and support so that effective breast-feeding can be established and continued.

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