98 Mechanistic Aspects of Phototherapy for Neonatal Hyperbilirubinemia

Vinod K. Bhutani | Angelo A. Lamola

INTRODUCTION

The pathways by which light reduces levels of circulating bilirubin and how this mechanism leads to the reduction of possible toxic byproducts has been the subject of intense inquiry and debate since the 1960s.[1] In 1969, the first United States (US) national symposium on neonatal hyperbilirubinemia and phototherapy, convened by the March of Dimes Foundation, reported on the effect of light on bilirubin metabolism and delineated the potential clinical implications for application to neonatal practice.[2] The proceedings provided key recommendations for the clinical use of light with a directive to *"involve judgments similar to those made in deciding upon the clinical use of a new drug."* A new standard of care was then established for the use of phototherapy with consideration of its advantages and risks, the likelihood of injury from hyperbilirubinemia, and risks associated with alternative treatment strategies. Over the intervening years, the mechanism of action of phototherapy has been extensively studied, and sufficient evidence is available to guide its use in term and late-preterm neonates.[3-5] However, use of phototherapy in moderate or very preterm hyperbilirubinemic infants, although apparently effective, is confounded by preterm biology, state of maturation, concurrent disease, choice of light source, device design, and inconsistent clinical implementation.

The primary success of phototherapy has been attributed to its ability to reduce an infant's risk for bilirubin neurotoxicity (i.e., *kernicterus*) and the need for exchange transfusions.[6] When phototherapy is instituted as an emergency measure ("a crash-cart approach") in infants presenting with extreme hyperbilirubinemia or early neurologic symptoms, care is taken to maximize the intensity of phototherapy light and to concurrently reduce the enterohepatic circulation of bilirubin.[5,7,8] This approach, previously based only on hypothesis, has been validated by recent observations that 20% to 25% of total serum/plasma bilirubin (TB) levels can be converted to more water-soluble, and directly excretable, (configurational) photoisomers within 30 minutes of exposure to light of sufficient intensity.[9] Concomitantly, phototherapy generates structural isomers of bilirubin, called *lumirubins*, which are produced less efficiently but are excreted more rapidly. Both types of photoproducts are believed to be less likely than bilirubin to cross the blood-brain barrier (BBB), and some investigators have proposed that they may confer neuroprotection even without enhancing excretion.

Table 98-1 Indices for Optimal Administration of Phototherapy

Checklist	Recommendation	Implementation
Light source (nm)	Emission spectrum in 460-490 nm blue-green light region	Know the spectral output of the light source
Light irradiance ($\mu W/cm^2/nm$)	Irradiance: ≥30 $\mu Wcm^{-2}nm^{-1}$ within the 460-490 nm wavelength band	Measure irradiance over entire light footprint area to ensure uniformity
Body surface area (cm^2)	Expose maximal skin area (35-80%)	Reduce blocking of light
Timeliness of implementation	Urgent or "crash-cart" intervention for excessive hyperbilirubinemia	May perform other procedures while infant is under phototherapy
Continuity of therapy	May briefly interrupt for feeding, parental bonding, and nursing care	After confirmation of adequate TB decrease
Efficacy of intervention	Periodically measure rate of response in bilirubin load reduction	Degree of TB concentration decrease
Duration of therapy	Discontinue at desired bilirubin threshold; be aware of possible rebound increase	Serial TB measurements based on rate of decrease

Republished with permission from Bhutani VK, Committee on Fetus and Newborn, American Academy of Pediatrics: Phototherapy to prevent severe neonatal hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 128:1046–1052, 2011.

Prescription of phototherapy for neonatal hyperbilirubinemia is relatively simple and efficacious if properly applied. Disciplined efforts are now aimed at standardizing prescribing practices. Furthermore, a much better definition of the phototherapy "action spectrum" has emerged, taking into account improvements in light sources, variables affecting efficacy (such as dosimetry and hematocrit levels), and potential undesirable effects (such as heating by absorption of light wavelengths that are relatively useless therapeutically).[10-13] The advent of blue light-emitting diodes (LEDs) with their narrow bandwidths has significantly fostered the development of affordable and optimized phototherapy devices.

In this chapter, we review the issues related to bilirubin photochemistry, photobiology, and photomedicine to delineate our understanding of how phototherapy light (photons) should be viewed as a drug that interacts with bilirubin molecules (Table 98-1). A review of selected terms related to photobiology products can be found in Box 98-1. In the spirit of *primum non nocere*, there is an obligation for clinicians to optimize therapy through translation of this science to clinical practice to deliver the safest and most effective care.

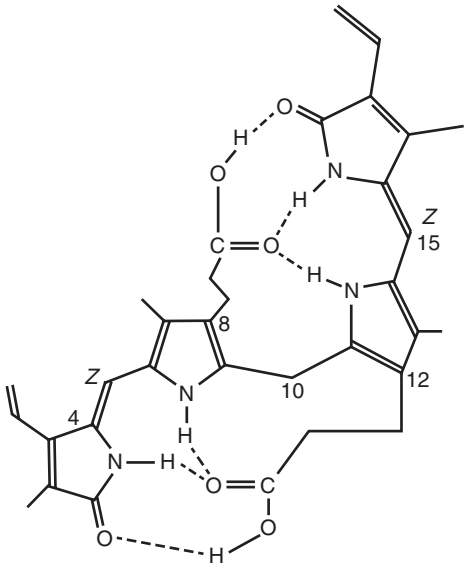

Figure 98-1 A representation of the structure of naturally occurring bilirubin, the *Z,Z*-configurational isomer. This configuration allows all the polar groups in the molecule to be internally hydrogen bonded to other polar groups. The structure presents only a carbon-hydrogen hydrophobic surface and greatly reduced water solubility. (From McDonagh AF, Lightner DA: 'Like a shrivelled blood orange'–bilirubin, jaundice, and phototherapy. *Pediatrics* 75:443–455, 1985.)

BACKGROUND

ORIGIN AND MEDICAL INNOVATION

Of the three naturally occurring biologic pigments (the red of hemoglobin, the yellow of bilirubin, and the green of chlorophyll), bilirubin (Figure 98-1) is unique as a developmental and life-modulating pigment that retains its photosensitivity.[1] Ancient and traditional knowledge of this yellow pigment and social practices to use natural sunlight to reduce circulating levels in newborns intersected with scientific inquiry in 1956 to 1958 at the Rochford General Hospital, Essex, United Kingdom, where the photoreactivity of bilirubin was originally observed.[14] The scientific community was first introduced to the photosensitivity of bilirubin at a meeting on 28 June 1957. The "device-biodesign innovation team" included Dr. R.J. Cremer (pediatrician in training), Dr. P.W. Perryman (biochemist), D.H. Richards (laboratory technician), and B. Holbrook (device engineer). They provided the "evidence for the reduction of circulating bilirubin levels in some cases of neonatal jaundice by exposing these infants to sunlight." Details were published in a landmark paper in *The Lancet*, which described their "cradle illumination machine."[15] It consisted "of a hemi-cylindrical stainless-steel reflector suspended on a movable gantry and adjustable for height. Eight 24-inch 40-watt blue fluorescent tubes (General Electric Corporation) at 2-inch separation were arranged around the curve of the reflector." The equipment was designed for use with a bassinet that was wheeled beneath the lights, and a switch was provided to allow illumination to be halved, if desired. Light in the region of 420 to 480 nm, filtered of any dangerous ultraviolet (UV) or x-ray components, was delivered at a very high intensity. Although *The Lancet* recognized this as a contribution of importance to merit publication, it received only limited attention both in Europe and North America. The breakthrough scientific concepts, novel prototype device, and change in clinical practice, however, subsequently made their way to Italy, Brazil, and other Latin American nations.[16] A decade after the original scientific publication, Dr. J.F. Lucey opined "no adverse effects had been

Box 98-1 Selected Definitions of Photobiology Products

1. Biliprotein: This is a molecular complex containing stoichiometric proportions of bile pigment and protein. The term is limited to molecules in the bile pigment.
2. Bilirubin: This term refers specifically, by convention, to the naturally produced 4Z,15Z-IXa isomer, unless indicated otherwise.
3. Chiral: A structure that is not superimposable on its mirror image is said to be chiral.
4. Configurational isomers: These are molecules that have the same sequence of atoms and bonds but different fixed three-dimensional arrangements of these atoms. They can only be interconverted by breaking and remaking chemical bonds between adjacent atoms.
5. Conformation isomers: These are molecules that can be interconverted by rotations about single bonds between atoms and without making or breaking covalent bonds between atoms. In general, conformational isomers interconvert very rapidly at room temperature and cannot be separated.
6. E/Z bilirubin: A nomenclature system for unambiguously designating the arrangement of atoms around double bonds in molecules is derived from the German words *entgegen* (opposite) and *zusammen* (together). Asymmetric substituted double bonds that are not contained within a ring system can have two possible configurations, which are designated as *E* and *Z.* Pairs of E/Z configurational isomers are also called *geometric isomers.*
7. Photo-bilirubins: A nonspecific term that has been used to designate several products obtained by irradiating bilirubin with light. Because the structures of most bilirubin photoproducts have been elucidated, the term is now redundant and may be abandoned except for use as a collective term to describe photo-isomers derived from bilirubin.
8. Photo-isomerization: This reflects conversion of a bilirubin molecule to an isomeric molecule by irradiation with light.

Data from McDonagh AF, Lightner DA: 'Like a shrivelled blood orange'–bilirubin, jaundice, and phototherapy. *Pediatrics* 75:443–455, 1985.

noted" with the use of phototherapy devices in Latin America.[17] His own studies led to serious debates about the effectiveness, timeliness, and safety of using phototherapy.[18,19] Dr. A.K. Brown then conducted the pivotal National Institutes of Health (NIH)-sponsored clinical study of the effectiveness of phototherapy to prevent exchange transfusions in preterm infants.[20,21]

DEFINING BILIRUBIN LOAD: PRODUCTION AND ELIMINATION

Catabolism of heme from senescent or shortened-lifespan fetal red blood cells occurs in the reticuloendothelial system, where heme oxygenase degrades heme to biliverdin, which is then rapidly reduced to the lipid-soluble unconjugated bilirubin. Almost all of the bilirubin in blood is reversibly bound to its transport protein, albumin, in a form that can be distributed to a variety of tissues.[6] The bilirubin-binding capacity (BBC) of albumin controls a dynamic relationship between an infant's levels of bound and unbound ("free") bilirubin (UB) and his/her ability to "tolerate" increasing bilirubin loads.[22] The ability of albumin to bind bilirubin is influenced by a variety of molecular, biologic, and metabolic factors that include: the rate of bilirubin production, an infant's gestational age, and the presence of circulating competitive antagonists. The circulating UB, in dynamic equilibrium with albumin-bound bilirubin, is a form in which bilirubin can cross membranes and enter cells. The cellular uptake of bilirubin is considered a reversible, passive diffusion process, such that bilirubin can be "pulled out of cells" by increasing the extracellular BBC. The normal lipid- to water-soluble conversion of unconjugated bilirubin is mediated through a process of conjugation occurring in the liver. The uridine diphosphate glucuronosyltransferase (UGT) family of microsomal enzymes mediates active glucuronidation. Once conjugated, the now water-soluble bilirubin is excreted into urine or bile. Phototherapy-induced conversion of bilirubin to more water-soluble and colorless products bypasses this hepatobiliary excretion process.[1]

CURRENT MEASURES OF BILIRUBIN NEUROTOXICITY

Direct neurologic measures that quantify bilirubin toxicity have remained elusive. Precise assessment of neurotoxicity must address multiple domains of sensory processing. Table 98-2 lists current and prospective biomarkers for identifying infants most at risk for neurotoxicity. In clinical practice, the ability to use phototherapy more effectively and to reduce the need for exchange transfusion warrants development of an evidence-based risk assessment paradigm to replace the current

Table 98-2 Biomarkers Utilized To Assess Risk for Bilirubin Neurotoxicity and To Provide Thresholds for Phototherapy

Biomarkers	Specifications	Clinical use
Total serum/plasma bilirubin[6]	Consensus threshold values	Adjusted for maturity
Rate of bilirubin rise[38]	Increased; at any age	≥0.2 mg/dL/hr
Bilirubin production rate[2]	Exhaled carbon monoxide (ETCOc)	>3.5 ppm
Bilirubin production rate	Carboxyhemoglobin (COHbc)	>2.5%
Unbound bilirubin[22]	≥10 nmol/L	Phototherapy threshold
Unbound bilirubin[22]	≥18 nmol/L	"Crash-cart" phototherapy threshold or exchange
Utilized bilirubin-binding capacity[22]	≥45%	Phototherapy threshold
Utilized bilirubin-binding capacity[22]	≥65%	"Crash-cart" phototherapy threshold or exchange

Data from Behrman RE, Hsia DY: Summary of a symposium on phototherapy for hyperbilirubinemia. *J Pediatr* 75: 718–726, 1969; 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; Lamola AA, Bhutani VK, Du L, et al: Neonatal bilirubin binding capacity discerns risk of neurological dysfunction. *Pediatr Res* 77: 334–339, 2015; Slusher TM, Vreman HJ, Olusanya BO, et al: Safety and efficacy of filtered sunlight in treatment of jaundice in African neonates. *Pediatrics* 133: e1568–e1574, 2014.

consensus-based TB thresholds modulated by gestational age, clinical signs of hemolysis, and the bilirubin-albumin molar ratio.[6,23]

PHOTONS, PHOTOCHEMISTRY, AND ABSORPTION SPECTRA: LIGHT AS A DRUG

Light absorption by bilirubin in the vasculature and extravascular space in the skin transforms the native toxic, nonpolar *Z,Z*-bilirubin into more readily excretable polar photoisomers: the configurational isomers *Z,E*- and *E,Z*-bilirubin and the structural isomers *Z*- and *E*-lumirubin.[4] The matching of the absorption spectrum of a bilirubin-albumin solution in vitro with a source of blue light with a peak emission of approximately 460 nm is now considered the global standard of treatment for hyperbilirubinemia.[6] The understanding of light and photochemistry that underlies this connection is as follows.

The perception of light as a continuous energy stream obscures the reality that it comprises discrete packets (quanta) of energy called *photons*. The energy *(E)* carried by a photon (quantum) is inversely proportional to the wavelength (λ) of the light as follows,

$$E = hc/\lambda$$

where *h* is Planck's constant, and *c* is the velocity of light. From this equation, it can be seen that a photon at 400-nm wavelength (visibly blue) contains approximately 25% more energy than one at 500-nm wavelength (visibly green)—that is, for the same light exposure measured in energy units (such as $\mu W/cm^2$), there are approximately 25% more photons at 500 than at 400 nm. All photochemical reactions require, in ordinary circumstances, the absorption of single photons by individual molecules. The absorption spectrum is a plot of the probability of light absorption as a function of the wavelength of the light. Figure 98-2 shows the absorption spectra of hemoglobin and bilirubin. Bilirubin appears yellow-orange in white light because it absorbs the blue light portion of the visual spectrum (as well as the UV portion that we cannot "see") and thus the yellow and red portions remain. Figure 98-2 also shows that hemoglobin strongly absorbs light throughout most of the region of the bilirubin spectrum. The spectrum in this illustration is actually that of bilirubin bound to albumin, which is the form of virtually all the bilirubin in blood. Photons are analogous to the molecules of a drug. Therefore the wavelength (color) of light (drug) designed to interact with the molecular target (bilirubin) can be predicted by determining its absorption by the molecular target. Additional specificity of the wavelength range may be dictated by the avoidance of untoward side effects. For example, bilirubin absorbs UV light, as do almost all biologic molecules, such as proteins and nucleic acids. UV light absorption by the latter can lead to photochemical alterations that can be deleterious. However, nucleic acids and proteins without prosthetic groups do not absorb blue light; therefore it is possible to have blue light absorbed by bilirubin without affecting proteins and nucleic acids. The number of therapeutic photons absorbed by the molecular target is analogous to the dose of a drug. The intensity or irradiance (photons per unit time) of the light is analogous to the drug dose rate. One way absorbed light generally differs from molecular drugs is in the deposition of heat. When a photon is absorbed by a molecule of bilirubin, the energy of the photon is transferred to the molecule and transformed into heat that is quickly transferred to the surrounding environment. These principles of molecular photochemistry are well described.[24]

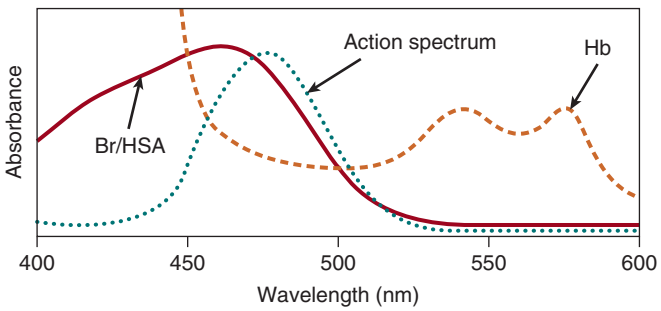

Figure 98-2 The absorption spectrum of bilirubin: bound to albumin *(solid line)* and that of hemoglobin (Hb) (at 75% oxygenation, the average between venous and arterial blood in the skin) *(dashed line)*. The relative magnitudes of the two spectra represent that for total serum/plasma bilirubin at 15 mg/dL and blood *Hb* at 16.5 g/dL (hematocrit = 50%) except that the bilirubin spectrum is enhanced by a factor of four for easier visualization. It is easily seen that the Hb can effectively compete with bilirubin for light absorption. The *dotted line* is the relative fraction of light absorbed by the bilirubin and, as such, represents the first order *action spectrum* (relative efficacy as a function of *wavelength*) for bilirubin photochemistry in the blood. *Br/HSA*, Bilirubin bound to human serum albumin.

THE ACTION SPECTRUM FOR BILIRUBIN PHOTOTHERAPY

The action spectrum of a light-driven process is a measure of its efficacy as a function of the wavelength of the light.[24] The measure of efficacy might be, for example, the rate of formation of a photochemical product for a given irradiance. For a sufficiently dilute solution of a photochemically reactive material, the action spectrum generally is identical to the absorption spectrum. This follows the basic law of photochemistry that states that light must be absorbed for a photochemical reaction to occur.[25] There are, however, many factors that can cause the action spectrum to differ, such as inhomogeneity of the material, as has been observed for a solution of bilirubin bound to albumin. In complex environments, such as in vivo, other materials present in tissues may compete for the light, acting as filters to block some wavelengths. Hemoglobin in the skin of adults and newborns is the main absorber of visible light, especially blue light, and is, in fact, an effective filter.[13] As shown in Figure 98-3, the probability of blue light absorption by hemoglobin overwhelms the light absorption by bilirubin for the range of TB and hematocrit levels commonly found in infants. Recently, Lamola and colleagues proposed a semi-empirical model for the calculation of the action spectrum for bilirubin photochemistry in vivo using available data on skin optics.[13] The model is based upon one used to develop advanced transcutaneous bilirubinometers that can relate light reflected from the skin to assess the TB. In the model, key factors include: the diffuse nature of light entering the skin, the wavelength dependence of back scatter of light from the skin, the absorbance due to melanin in the epidermis, the wavelength dependence of bilirubin photochemistry, the oxygenation level of the blood, the hemoglobin and bilirubin levels, and both the vascular and extravascular bilirubin. The calculations based on the model showed that the effect of competitive absorption of light by hemoglobin remains the predominant factor controlling the light that is absorbed by the bilirubin. The result is that the probability of light-driven alteration of bilirubin in the skin of neonates as a function of wavelength (i.e., the action spectrum for phototherapy of neonatal jaundice) is predicted to be that shown in Figure 98-2.[13] The spectrum peaks near 476 nm rather than at the maximum of the bilirubin-albumin absorption

spectrum (460 nm). A corollary of the predominance of light absorption by hemoglobin in the range of light used in phototherapy is a predicted dependence of phototherapy efficacy upon the hemoglobin level of the infant; the higher the hemoglobin concentration, the lower the expected efficacy.[13,26]

PHOTOTHERAPY EFFICACY: LIGHT SOURCES, IRRADIANCE, AND DOSE

It is evident that the wavelength range of the light source must overlap the action spectrum for phototherapy to be effective. Almost from the beginning of the development of phototherapy, it was recognized that blue light should be effective because the visible absorption spectrum of bilirubin, presumed to reflect the action spectrum, is mainly in the blue region.[15] It is well known that UV light is deleterious and should be avoided. The spectral region currently recommended is 400 to 520 nm, but more specifically 460 to 490 nm to exclude the UV light.

FLUORESCENT LAMP SOURCES

Because direct sunlight contains wavelengths of light that are potentially harmful (e.g., UV light), artificial light sources, which exclude harmful wavelengths, have been developed. Figure 98-3 shows the emission spectrum of a lamp (Philips/52) that is typical of the "super" blue fluorescent lamps that have been used for phototherapy. This spectrum has very good overlap with the bilirubin-albumin absorption spectrum. Also shown is the emission spectrum of a turquoise colored fluorescent lamp (Osram Turquoise), which has less overlap with the bilirubin-albumin spectrum. Yet several studies have shown that lamps utilizing green lights are equally or more effective than the blue lamps.[3,18,19,25] This observation is in quantitative agreement with the calculated expectation based upon the action spectrum of Figures 98-2 and 98-3, but not the bilirubin-albumin absorption spectrum.[25,27]

LED LIGHT SOURCES

The observations discussed above strongly support the action spectrum of Figure 98-3 and infer that a narrow-band source, such as LEDs with peak wavelength near 476 nm, would be most efficacious.[13,25,27] The use of an LED light source with peak emission near 460 nm is gaining in popularity; however, LEDs with a spectral output centered at 476 nm should be approximately 15% more efficacious than those centered at 460 nm at equal irradiance (Table 98-3). One can, however, increase the rate of TB reduction by simply increasing the irradiance (dose) by increasing lamp input power, adding more lamps, moving lamps closer to the infant, or increasing the light footprint. Therefore if the irradiance of a 460-nm light source was increased by 15%, it should equalize the rate of bilirubin photo-alteration by a 476-nm light source. The risk-benefit ratio of that approach versus using longer-wavelength light (476 nm) would need to be ascertained to inform clinical decisions.

The use of a source that is the most effective at providing wavelengths of light that are maximally absorbed by bilirubin while reducing therapeutically useless and possibly harmful light absorption by other entities, a priori, should underscore clinical practice.[5] For example, it is calculated that for equal therapeutic efficacy, use of the typical blue fluorescent source "heats" the infant at a rate 1.5 times greater than a 476-nm LED source because of the absorption of "therapeutically useless"

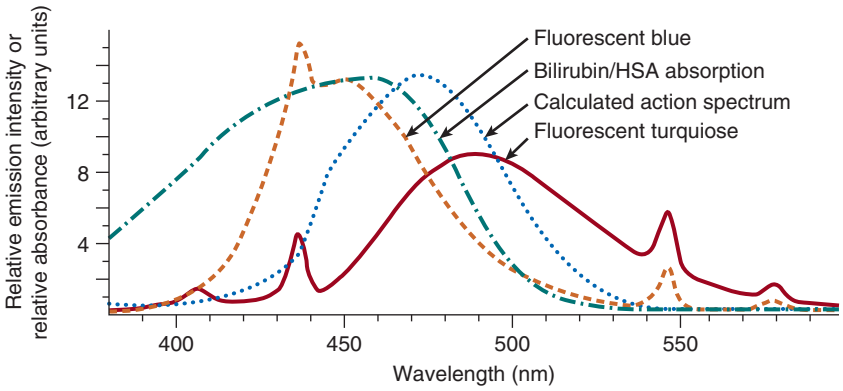

Figure 98-3 The absorption spectrum of bilirubin bound to human serum albumin and the "action spectrum" for bilirubin photochemistry. Both are taken from Figure 98-2, superimposed on the emission spectra of blue and turquoise fluorescent lamps. Although the blue lamp emission overlaps better with the bilirubin absorption, the turquoise lamp emission overlaps better with the action spectrum such that, for equal total irradiance, the turquoise may be more effective at driving the photochemistry of bilirubin in blood. *HSA,* Human serum albumin.

Table 98-3 Summary of Relative Risks of Mortality Associated with Phototherapy in Extremely Low-Birth-Weight Infants Reported from NICHD Trials

		Deaths/Subjects (g)		
NICHD Trial	**Study Cohort (g)**	**Phototherapy**	**No Phototherapy**	**RR (95% CI)**
Brown, 1985	<1000	23/39	15/38	1.49 (0.93-2.4)
		Aggressive Phototherapy	**Conservative Phototherapy**	
Oh, 2005 (Post-hoc analysis of Morris et al)	500-750	163/417	142/412	1.13 (0.96-1.34)
	500-650	106/214	80/212	1.27 (1.05-1.53)
	750-1000	67/529	76/532	0.93 (0.77-1.12)

Data from Brown AK, Kim MH, Wu PY, Bryla DA: Efficacy of phototherapy in prevention and management of neonatal hyperbilirubinemia. *Pediatrics* 75: 393–400, 1985; Oh W, Tyson JE, Fanaroff AA, et al: Association between peak serum bilirubin and neurodevelopmental outcomes in extremely low birth weight infants. *Pediatrics* 112: 773–779, 2003; Morris BH, Tyson JE, Stevenson DK, et al: Efficacy of phototherapy devices and outcomes among extremely low birth weight infants: multi-center observational study. *J Perinatol* 33: 126–133, 2013.
NICHD, National Institute of Child Health and Human Development; *RR,* relative risk.

lower-wavelength blue light by hemoglobin.[13] The "heat" or energy transfer is not due to radiant heat from the device, and it may not translate to increased core temperature. The effect of the deposition of the absorbed light energy has not been clinically determined. However, this energy load has to be dissipated and could be potentially deleterious for a sick preterm infant.

LEDs have several other advantages over fluorescent lamps besides their narrow emission spectra and the ability to pick the desired peak emission wavelength (color). Although their initial cost may be higher than that of fluorescent lamps, LEDs use much less power, last much longer, and maintain a much more constant light output over time. The intensity of light emission from LEDs can be electronically controlled. Using such control and the employment of light management films or lenses may allow design of LED arrays that can provide a relatively uniform distribution of intensities over a variety of distances and angles.

MEASURING EFFICACY

Many factors influence the efficacy of phototherapy. Clinical efficacy is associated with timely decrease of TB to an apparently safe level. Use of a change in TB as a marker for efficacy is complicated and depends upon various factors, such as the rates of bilirubin production and hepatic-mediated excretion, transport of bilirubin to or from the extravascular space, and phototherapy-mediated excretion. However, the TB level currently remains the only biomarker that can be tracked during phototherapy. The phototherapy-mediated excretion rate depends on the therapy light intensity or irradiance at the exposed skin, the area of skin irradiated, the spectrum of the light, the action spectrum, the quantum efficiency of conversion of bilirubin to photoproducts, and the excretion rates of the photoproducts.[5,6,8] Thus the independent operational elements that control phototherapy are the emission spectrum of the light source, the irradiance at the skin surface, and the exposed body surface area (BSA).

MEASURING IRRADIANCE

Clinical guidelines recommend irradiating as much BSA as possible (roughly 1500 cm^2 or approximately 80% of the BSA).[8] Using a lamp or LED light source from above and below an infant can easily achieve an even larger exposed BSA. The irradiance at the distance from the light source to the skin surface should be measured with an appropriate spectroradiometer. The irradiance should be uniform over the footprint of the light-exposed BSA (Figure 98-4). The measure of intensity is usually given in energy units as $\mu W/cm^2$. Integrating over the wavelength range of the light source and then multiplying the result by the exposed BSA (assuming uniform intensity over the area) and the time in seconds gives the total dose in joules. If desired, the dose measured in joules can be converted to photons, remembering that the conversion factor depends on the wavelength such that for the same energy there are more photons at higher wavelengths. Although this may be of interest to researchers, in clinical practice commercial radiometers measure the average irradiance over a wavelength range determined by the bandwidth filters in the device. The units are usually expressed as $\mu W/cm^2/nm$. Unfortunately, the various available radiometers have different wavelength ranges and can give different readings for the same light source.[8] Thus to predict the expected efficacy of a phototherapy device, one needs to consider concurrently manipulating three different spectral distributions: the sensitivity spectrum of the radiometer, the emission spectrum of the light source, and the bilirubin action spectrum. This has not generally been done in practice, so although intrastudy comparisons of efficacy can be made, comparisons of observations from one study to another may not be reliable.

ASSESSING EFFICACY OF LIGHT SOURCES

For the clinician, it is important to know with certainty that sufficient irradiance is delivered to an infant, that harmful wavelengths are excluded, and that light of ineffective wavelengths

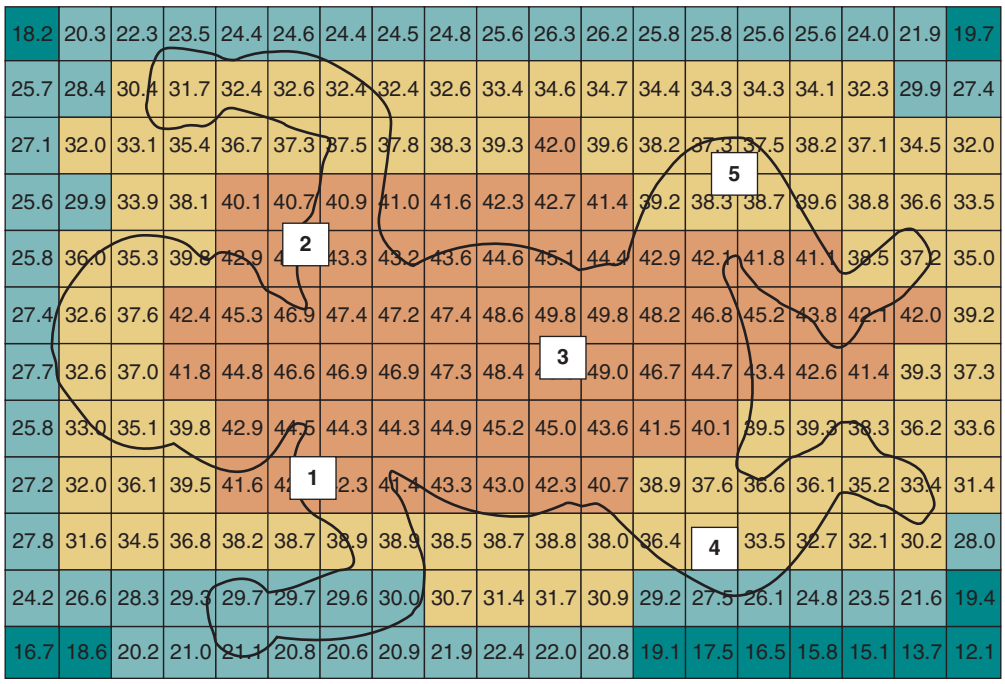

Figure 98-4 Light footprint. An acceptable distribution of irradiance levels within the footprint of the phototherapy light, showing a pattern of homogenous exposure. Numbered sites indicate clinical sites at which irradiance measures (by dosimeter) should be similar: *1,* right shoulder; *2,* left shoulder; *3,* umbilicus; *4,* right knee; and *5,* left knee. (From Bhutani VK, Wong RJ: Neonatal phototherapy: a choice of device and outcome. *Acta Paediatr* 101:441-443, 2012.)

is minimized. It is also important to remember that radiometers from different suppliers can have different ranges of sensitivity that are specific to their device. Furthermore, lamps and LEDs have different emission spectra. Appropriate practice demands that the TB levels be monitored at a frequency determined by the clinical status of the infant to ensure that the TB is being reduced to a "safe" level at a rate commensurate with clinical needs. Thus reliance on the irradiance level and dose (irradiance × time) alone may not be sufficient.

BILIRUBIN STRUCTURE, PHOTOCHEMISTRY, AND PHOTOTHERAPY MECHANISMS

An abridged description of the structure and photochemistry of bilirubin is presented here with the aim of addressing only salient features related to phototherapy. This brief description does not begin to honor the painstaking work required to uncover the complicated chemistry by many experts. Interested readers are directed to the recent, well-detailed historical and technical treatise by D.A. Lightner.[1] Although many investigators have made important contributions to the long saga, the current representation of the chemistry involved in phototherapy is based primarily on the works of A.F. McDonagh and D.A. Lightner and is reviewed by them.[4,28]

As produced from the degradation of heme, bilirubin exists in a particular geometric form, *4Z,15Z*-bilirubin, in which the groups attached to the two key carbon-carbon double bonds are in the so-called *Z* configuration. This is denoted, without the positional numbers, as the *Z,Z* structure in Figure 98-5. Upon absorption of light, bilirubin can undergo a variety of geometric and structural alterations with widely differing rates. Photooxidation to low-molecular-weight, colorless products is observed in vitro, and similar products have been observed in vivo.[4,28] However, this is a multistep process, and the rate (amount over time) at which it occurs is very low, by a factor one hundredth to one thousandth, compared to other alterations. These products are excretable. However, it has been concluded that this low efficiency photodegradation does not account for the therapeutic effect of phototherapy compared to more efficient isomerization processes.

The most efficient processes involve isomerization between so-called *Z* and *E* forms and involve twists around the two key double bonds. The four possible configurational isomers are: *Z,Z*; *Z,E; E,Z;* and *E,E* (see Figure 98-5). These engender four distinct shapes of the bilirubin molecule. All three isomers that have an *E* component are more water soluble than the natural *Z,Z* isomer and are excretable without glucuronidation. Binding of bilirubin to human albumin restricts configurational photoisomerization, at least initially, to the *Z,E* isomer. All three *E* isomers have absorption spectra that are similar to that of the *Z,Z* isomer and can undergo the reverse photoisomerization to the respective *Z* isomer. *Z,Z* to *Z,E* isomerization is highly quantum efficient, with 10% to 20% of bilirubin molecules that absorb light converted to the *Z,E* isomer. Reverse photoisomerization from *Z,E* to *Z,Z* occurs with 40% to 80% quantum efficiency (quantum yield). The reversibility and high efficiencies of this interconversion lead to a rapid establishment of equilibrium at a mix of approximately 20% *Z,E*- and 80% *Z,Z*-bilirubin, which can be observed in vivo after less than an hour of therapy at the levels of irradiance commonly used. The *Z,E* isomer has a serum half-life of approximately 15 hours, indicating a relatively slow excretion rate. The *E* isomers are not thermally stable and can revert to *Z* isomers in the dark at rates dependent on their environment.

Structural isomerization, involving a cyclization with new bond formations within bilirubin, leads to a set of isomers collectively called *lumirubin*. This is less efficient than configurational isomerization. The photo-formation of lumirubin at steady state has quantum efficiency on the order of only 0.1%. Both structural considerations and experimental observations indicate that the lumirubins are formed from precursor *E* isomers. Their formation is irreversible. Lumirubin isomers are more water soluble than *Z,Z*-bilirubin and directly excretable at a relatively fast rate (serum half-life of approximately 2 hours). The relative contributions of the various photoproducts to the phototherapy-enabled excretion of bilirubin remain controversial. However, it is thought that, despite its low efficiency of production, the excretion pathway via lumirubin has greater importance. The difference in the photo-reversibility of lumirubin and the *Z,E* isomer has clinical implications. If formation of the *Z,E* isomer were essential to the light-induced excretion of bilirubin, the maximum fraction of *Z,E* isomer produced of approximately 20% to 25% (the photo-stationary fraction) would predict a limit to the useful light intensity. Once the stationary amount were reached, only enough light to maintain that amount against the excretion rate would be useful. Higher irradiance would not increase therapeutic efficacy and would only heat the infant. This suggests the possible benefit of using intermittent phototherapy, wherein sufficient irradiance to produce a photostationary mixture of *Z,Z* and *Z,E* isomers is employed, followed by a dark period, and then cycled again. However, if irreversible conversion to lumirubin substantially contributes to net bilirubin elimination, and given that lumirubin is formed from *E* isomers, then use of continuous, high-irradiance phototherapy would maximize the rate of reduction of TB. Greater doses of phototherapy are more effective in reducing the TB concentration, but it is uncertain whether there is a maximally effective dose.

OTHER EFFECTS OF PHOTOTHERAPY LIGHT

Despite the extensive use of phototherapy over the past 50 years, there have been limited long-term follow-up studies. Recent reports of presumed adverse effects are more likely associated with the use of early device designs that may not have effectively eliminated UV light. Unanticipated effects of phototherapy were an initial concern because of the potential for direct effect on structures at or near the body surface. UV light contamination was the most likely reason for cutaneous changes similar to sunburn. Other concerns, such as up-regulation of tyrosine kinase in melanocytes, alterations of vitamin D metabolism, disruption of circadian rhythms, effects on indole-O-methyltransferase (a pineal enzyme), and gonadal and retinal injury, have not been substantiated despite detailed inquiry.[6,8] It has been suggested that phototherapy may lead not only to alterations of various moieties that absorb blue light, such as riboflavin, but also to oxidative damage subsequent to free radical formation from photo-oxidation reactions.[29] The lower wavelength portion of the blue light region is the more relevant in this regard, providing further impetus to confine the phototherapy wavelength range to the higher blue and blue-green regions.

EFFECT OF PHOTOTHERAPY ON DIRECT BILIRUBIN

Direct bilirubin is a mixture of mono-and di-glucuronides, with both having multiple variants. Together with delta-bilirubin, the proportions of these three (or more) species probably differs among babies, with delta-bilirubin increasing with time in chronic cases of cholestasis because it is covalently linked to albumin and is not excreted.[30] None of these forms of direct diazo-reacting bilirubin are easy to study because of their inherent instability. Consequently, there is no secure literature on the photochemistry of conjugated forms of bilirubin. The bronze baby syndrome is an uncommon condition associated with phototherapy in infants with cholestatic jaundice.[31] It is manifest as dark grayish discoloration of the skin, urine, and serum that resolves with time. It has been conjectured that these abnormal pigments arise because of impaired biliary excretion of bilirubin photoproducts that undergo polymerization. Bronze skin has not been reported in adults with elevated direct hyperbilirubinemia. Currently, there is no evidence that the bronze baby–associated cutaneous pigment is neurotoxic.

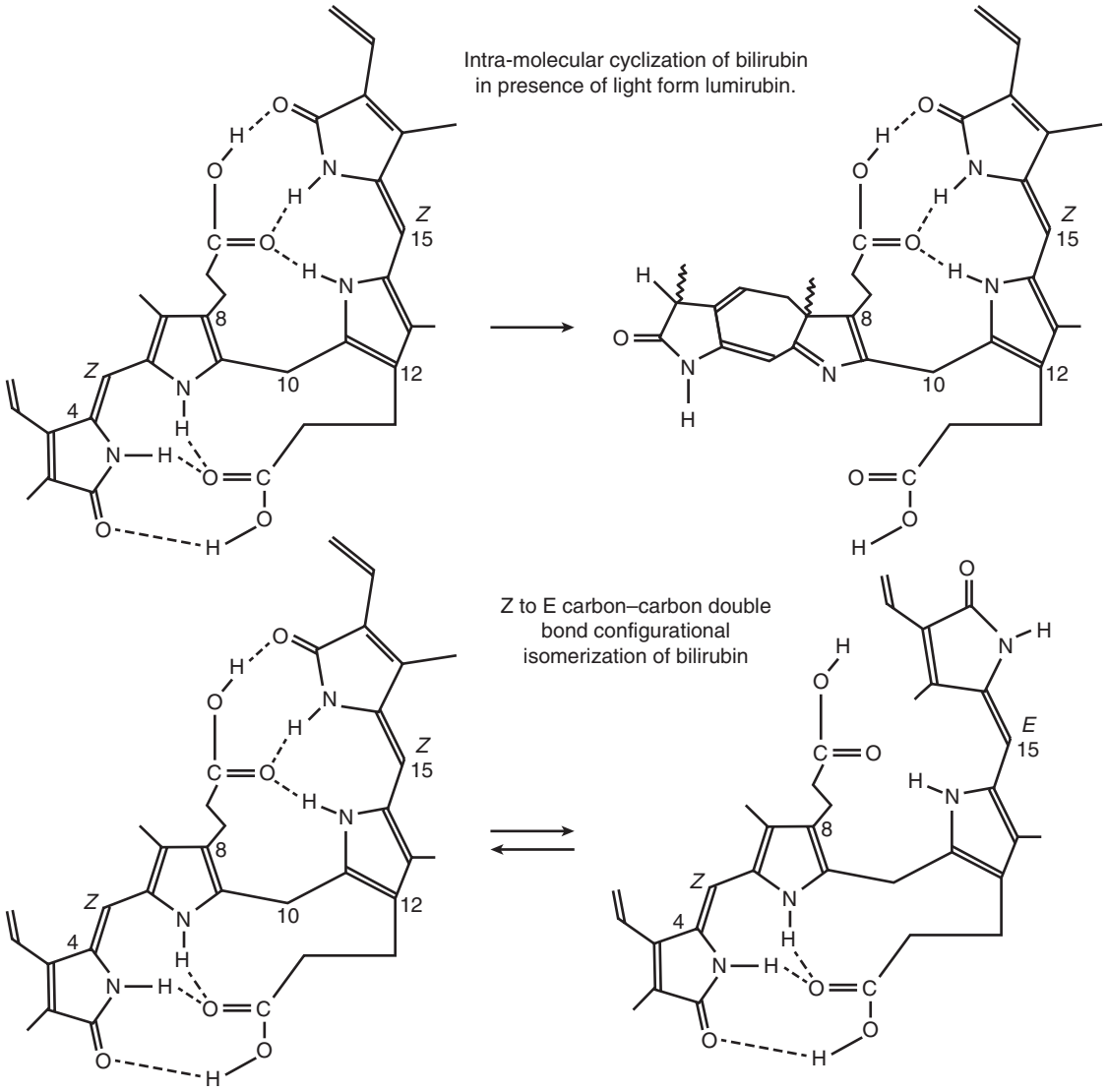

Figure 98-5 The four configurational isomers of bilirubin: *Z,Z; Z,E; E,Z; and E,E.* They represent the four possible structures with respect to configuration around the two double bonds at positions *4* and *15* in the drawings. Absorption of light by bilirubin weakens the double bonds and allows the rotations to interconvert these configurational isomers. The *E* isomers cannot adopt the folded structure of the *Z,Z* isomer and consequently are more polar and more water soluble. (From McDonagh AF, Lightner DA: 'Like a shrivelled blood orange'–bilirubin, jaundice, and phototherapy. *Pediatrics* 75:443–455, 1985.)

TRANSLATION TO CLINICAL PRACTICE

Optimization and standardization of phototherapy for the management of neonatal hyperbilirubinemia have been the subjects of several literature reviews and guidelines[6,8,32] (Table 98-4). Blue LED light sources are preferred, followed by compact fluorescent tubes, tungsten-halogen lamps, and fiberoptic blankets that help BSA exposure to light. Devices that meet dose specifications include blue Philips TL20W/52 and turquoise Osram L18W/860 tubes. The key *device* characteristics that contribute to effectiveness include (1) emission of light in the blue-to-green range that overlaps with the in vivo plasma bilirubin absorption spectrum (460 to 490 nm); (2) irradiance of at least 30 μW/cm^2/nm at a suitable distance (confirmed with an appropriate irradiance meter calibrated over the appropriate wavelength range); and (3) minimization of light outside the therapeutically efficient wavelength range. Irradiance of more than 65 μW/cm^2/nm has not been adequately tested for safety. Due to reports of potentially increased mortality with phototherapy in infants weighing less than 1000 g, experts have recommended using less intensive levels of irradiance upon initiation of phototherapy, unless TB levels continue to rise.[33] Important *nondevice* factors include: (1) illumination of 35% to 80% of exposed BSA with multiple devices and (2) demonstration of a decrease in TB concentrations during the first 4 to 6 hours of exposure in the absence of excessive hemolysis. Standardization of irradiance meters, improvements in device design, and identification of lower and upper limits of light intensity for phototherapy devices merit further study. Comparing the clinical efficacy of phototherapy devices accurately is difficult with the present lack of an easily implemented standardized procedure.

BIOENGINEERING PERSPECTIVES

Barriers to effective phototherapy include use of unproven light sources, poor device maintenance, erratic or inconsistent power sources, and operational impediments.[34] To promote implementation of effective phototherapy at all birthing facilities, minimal

Table 98-4 Calculated Relative Photon Absorption Rates by Bilirubin (15 mg/dL; Hct = 50%) in Neonate Skin at Equal Irradiance for Various Light Sources*

Source	Peak Wavelength (nm)	Relative Photon Absorption Rate
LED†	450	0.62
LED	460	0.85
LED	470	0.96
LED	476	1.0‡
LED	480	0.98
LED	490	0.79
Philips TL20W/52 Blue lamp	450	0.61
OSRAM L18W/860	490	0.72

Data from Lamola AA, Bhutani VK, Wong RJ, et al: The effect of hematocrit on the efficacy of phototherapy for neonatal jaundice. *Pediatr Res* 74:54–60, 2013.
Hct, Hematocrit; *LED,* light-emitting diode.
*The photon absorption rate should predict the rate of bilirubin photochemistry.
†LED half-bandwidths ≈20 nm.
‡LED source with 476-nm peak wavelength taken as reference = 1.0.

technology criteria have been proposed to complement the safety and regulatory standards listed by the International Electrotechnical Commission.[35] Table 98-5 lists the minimum checklist to operationalize the use of phototherapy.

REVIEW OF EFFICACY OF PHOTOTHERAPY DEVICES

Several commercial and indigenous device adaptations of current (or available devices) have been performed without rigor of scientific inquiry regarding the safety, efficacy, and actual performance of these devices prior to their clinical use. Of these, homogenous exposure to a light source has been the most challenging (see Figure 98-4). In 1998, Vreman and colleagues pioneered the use of LEDs as phototherapy light sources.[10] Systematic analyses of the efficacy of both LED and non-LED sources were published independently by Kumar and colleagues and by Tridente and De Luca.[12,36] (Table 98-6 shows the similarities and the diverse perspectives of both systematic reviews.) The Cochrane Library review[12] concluded that use of LEDs can decrease TB at rates similar to non-LED sources. They added that further randomized controlled trials are needed to determine the efficacy indices of phototherapy in neonates with severe hyperbilirubinemia associated with hemolysis.

GUIDELINES FOR PHOTOTHERAPY

The initial provisional recommendation guidelines[2] have generally withstood the test of time. These are briefly listed here:

1. The cause of hyperbilirubinemia should always be investigated. Categorizing the cause as increased bilirubin production, decreased elimination, or increased enterohepatic circulation may allow for targeted intervention and/or follow up.
2. Phototherapy should be used for infants with unconjugated hyperbilirubinemia and not prior to onset of an elevated TB level. Phototherapy should be administered continuously, but may be interrupted for breast-feeding. Use of cycled (intermittent) phototherapy is still being investigated.[37]

Table 98-5 Minimum Specifications for an Effective Phototherapy Device

Technical Requirement	Clinical Specifications
Regulatory approval	FDA, 510K, and/or CE mark
Emission spectrum	Blue or blue-green (range 430-490 nm); preferably narrow band and peaked at 470 ± 10 nm
Spectral irradiance	25 to <45 μW/cm²/nm at body surface
Light source	LED (preferred), 20,000 hours lifetime with irradiance ≥30 μW/cm²/nm
Light footprint	5-point measure; 30 by 50 cm area with minimum to maximum ratio >0.4
Device energy source(s)	Compatible with 90-240 V and 48-60 Hz power input, built-in circuit-breaker
Device structure (and stand)	UV protection; topple-resistant, portable (castors with brakes); height adjustable; base allows stand to fit under radiant warmers, bassinets, or isolettes

Data from Bhutani VK, Cline BK, Donaldson KM, Vreman HJ: The need to implement effective phototherapy in resource-constrained settings. *Semin Perinatol* 35:192–197, 2011.
CE, Conformité Européenne; *FDA,* Food and Drug Administration; *LED,* light-emitting diode; *UV,* ultraviolet.

Table 98-6 Recent Systematic Reviews of Phototherapy in Infants at Least 35 Weeks' Gestational Age

Systematic Review	Cochrane Review	Meta-analysis
Publications identified	1215	103
Selected manuscripts	630	81
Comprehensive review	6	6
Studies of infants with gestational age ≥35 wk	4	4
Total number of infants	511	511
Randomized Controlled Trials: LED vs. non-LED light sources		
Weightage of single study	–	61.4%
Heterogeneity	NS	$\chi^2 = 3.44$; p = .488
Forrest plot test	NS	I^2 value = 0%
Funnel plot test	NS	NS; $p = .149$
TB decline	0.01 (95% CI, -0.02-0.04)	–
Duration of phototherapy	0.43 (95% CI, -1.91-1.05)	–
Treatment failure	1.83 (95% CI, 0.47-7.17)	

Data from Kumar P, Chawla D, Deorari A: Light-emitting diode phototherapy for unconjugated hyperbilirubinaemia in neonates. *Cochrane Database Syst Rev* (12):CD007969, 2011; Tridente A, De Luca D: Efficacy of light-emitting diode versus other light sources for treatment of neonatal hyperbilirubinemia: a systematic review and meta-analysis. *Acta Paediatr* 101:458–465, 2012.
LED, Light-emitting diode; *TB,* total serum/plasma bilirubin.

3. Phototherapy should be used for infants in whom adverse hyperbilirubinemia-related neurologic risks outweigh the therapy-related risks. Phototherapy should be used for infants with TB levels that do not yet meet the threshold for exchange transfusion when there is a reasonable chance of exceeding that threshold based on the rate of TB rise.

4. Even when infants meet thresholds for exchange transfusion, an immediate "crash-cart" approach should be implemented and may avert the need for the exchange procedure. In some infants, such as those with Rh hemolytic disease and rapidly increasing TB levels, the exchange transfusion should not be delayed.
5. Phototherapy is prescribed when an abnormal rate of bilirubin production has been demonstrated (>0.2 mg/dL/hour).
6. Response to phototherapy, measured by TB (not transcutaneous bilirubin), is generally noted within 4 hours and continues to be observed in 24 to 36 hours. With 8 to 12 hours of effective phototherapy, there is an average decrease in TB of 3 to 4 mg/dL in those infants who do not have active hemolysis.
7. Serial TB measurements should be obtained during the course of phototherapy. By eliminating visible jaundice, phototherapy may mask mild hemolysis due to ABO incompatibility, hereditary spherocytosis, or glucose 6-phosphate dehydrogenase (G6PD) deficiency.
8. The use of phototherapy in infants with concurrent conjugated hyperbilirubinemia remains controversial.
9. Infants who complete successful phototherapy do not require follow-up unless there is a need to determine the underlying cause of jaundice or the infant is at risk for the sequelae of extreme hyperbilirubinemia.
10. Currently, phototherapy has not been associated with either short- or long-term consequences. Eye patches are important for eye protection from bright lights; diapers serve as aids for comfort and hygiene.

INNOVATION AND FUTURE DIRECTIONS

TB levels remain an imprecise indicator of both bilirubin exposure and neurotoxicity. A specific threshold-based relationship between TB and subtle or moderate diverse-domain neurotoxicity (such as the syndrome of bilirubin-induced neurologic dysfunction) has been elusive, indicating that additional critical factors contribute to a phenotype that could be either transient or irreversible. Novel and translational neonatal functional biomarkers of increased bilirubin load due to increased bilirubin production, disordered albumin binding, and ensuing reduced BBC are the subject of ongoing studies.[13,22] The ratios of UB to TB (which is inversely related to the reserve binding capacity) and TB to BBC (the extent of saturation of the BBC) present two different views of bilirubin-binding status. Considering them together, as a plot of UB/TB versus percent of saturation, may provide an improved assessment of risk. These extrapolations also suggest a potential role for individually measured BBC and TB.[22]

SUMMARY

Neonatal phototherapy is the current standard of care for treatment of significant hyperbilirubinemia, which can result in bilirubin neurotoxicity including kernicterus. Much of the current knowledge of the mechanisms underlying this therapy is represented in Figure 98-6. Modulation of irradiance or dose based on

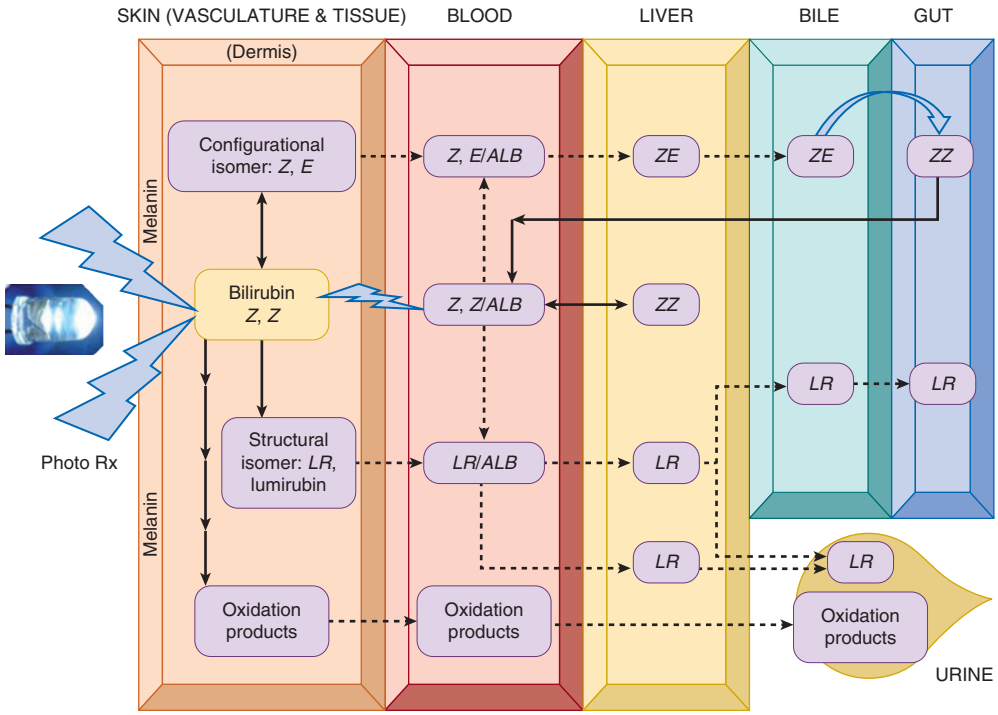

Figure 98-6 Schematic of the salient features of phototherapy of unconjugated hyperbilirubinemia. The light must first pass through the epidermis, where it is weakly diminished by any melanin (does not affect the action spectrum). Entering the dermis, the light is quickly rendered diffuse and is absorbed by the hemoglobin and bilirubin present there. The competition for light absorption by hemoglobin essentially dictates the wavelength range where bilirubin most effectively absorbs the light. The bilirubin that absorbs light undergoes efficient conversion to the *Z,E* isomer until a steady-state level of approximately 20% of the bilirubin is reached. The bilirubin also undergoes a less efficient conversion to lumirubin in a process that is not photo-reversible. Much less efficient, requiring multiple chemical reactions, is the conversion of bilirubin to low-molecular-weight oxidation products. All of these products are transported (the *E* isomers and lumirubin are probably mostly bound to albumin) by the circulating blood to the liver and other sites and excreted. *E* isomers can be reverted to their *Z* counterparts by mechanisms not requiring light. (Adapted from McDonagh AF, Lightner DA: 'Like a shrivelled blood orange'–bilirubin, jaundice, and phototherapy. *Pediatrics* 75:443–455, 1985.)

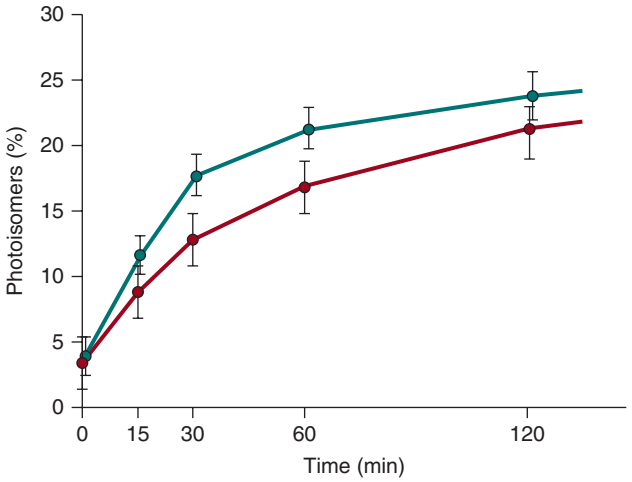

Figure 98-7 The rise of the *Z,E* isomer of bilirubin with light dose. Study for 12 infants with average hemoglobin (Hb) <14.5 g/dL *(green)* and 12 infants with average Hb ≥14.5 *(red),* as reported in a preliminary study. (Reprinted with permission from Mreihil K, Madsen P, Nakstad B, et al: Early formation of bilirubin isomers during phototherapy for neonatal jaundice: effects of single vs. double fluorescent lamps vs. photodiodes. *Pediatr Res* 78:56–62, 2015.)

hematocrit, now observed clinically[26] (Figure 98-7), may be a developing guideline. Drug effective absorbed dose of blue-green light (458 to 490 nm) depends on its wavelength-specific irradiance and an infant's skin tissue characteristics. Infants with thin, translucent skin with almost no subcutaneous tissue may be more vulnerable to the oxidants generated by light exposure. The mechanism of action of phototherapy on the native unconjugated bilirubin (bilirubin 1Xα; *Z,Z*) proceeds via efficient photochemical reactions providing configurational isomers (*4Z,15E; 4E,15Z; 4E,15E*) and structural isomers (*Z*- and *E*-lumirubins) that are more soluble than the native isomer. These polar isomers are eliminated through bile and urine and bypass the need for UGT conjugation. Because of their polarity, these isomers should be less able to cross the BBB, and therefore their formation could be beneficial. Though suggestive, this lowered neurotoxic potential of photoisomers has yet to be validated. Oxidants formed through photochemical reactions, perhaps especially at the lower wavelengths of blue light, could have adverse consequences for extremely low-birth-weight neonates and possibly those who are extremely small for gestational age. Further optimization of the therapy's benefits and risks based on the relative efficacy of continuous versus cycled light delivery[37] awaits further clinical investigation.

ACKNOWLEDGEMENTS

This chapter was supported in part by the Ahlfors Center for Unbound Bilirubin Research & Development and the Kaplan-Goldstein Family Foundation. No commercial financial assistance was received in support of this chapter. The authors thank Martin E. Castillo Cuadrado and Ronald J. Wong for their assistance in the preparation of this manuscript.

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