www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2015;4(2):e040255
doi: 10.7363/040255
Received: 2015 Sept 09; revised: 2015 Oct 17; accepted: 2015 Oct 17; published online: 2015 Oct 27

Review

Phototherapy in the newborn: what's new?

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Proceedings

Proceedings of the 11th International Workshop on Neonatology and Satellite Meetings
Cagliari (Italy) · October 26th-31st, 2015
From the womb to the adult
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Abstract

When exposed to light, bilirubin undergoes photoisomerization which are water-soluble and can be excreted in bile and urine. Photoisomerization starts as soon as the lights turned on, and risk of bilirubin encephalopathy is lower in infants who receive phototherapy even in the same serum bilirubin levels. Blue light is absorbed most readily if bilirubin is in a tube, but skin penetration and albumin binding shift of the most effective light to blue-green region. However, there is no consensus on the most effective wavelength for phototherapy. The light sources used in conventional phototherapy are fluorescent bulbs, halogen lamps or light-emitting diodes (LED) with equally effective in reducing serum bilirubin levels. Fiberoptic devices are less effective. Despite higher irradiance in double or triple phototherapy, there is no superiority in clinical settings. Hyperthermia and skin rashes are higher when used super (high-intensity) LED devices. Watery loose stools may cause dehydration in preterm infants. Riboflavin loss and lipid peroxidation are prevented with using dark tubing or covering the line with aluminum foil. The consequences of light penetration into deep brain in newborn infants because of open wide fontanel and thin skull is unknown. Non-ocular light exposure and suppressed melatonin secretion may affect autonomic and behavioral disturbances. Phototherapy-induced hypocalcemia may be prevented by covering the head. Phototherapy does not effect ductal patency or reopening, its effect on the incidence of retinopathy of prematurity have yielded conflicting results. Neonatal phototherapy increases the risk of asthma and allergic disorders in older age groups. Aggressive (low-threshold) phototherapy increase mortality risk in small preterm infants less than 750 g at birth, which may be related to the reduced bilirubin with its

antioxidant effects. In conclusion, phototherapy is not a treatment without side effects and overtreatment should be reevaluated in small preterm infants.

Keywords

Phototherapy, newborn, preterm infants, side effects.

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How to cite

Yurdakök M. Phototherapy in the newborn: what's new? J Pediatr Neonat Individual Med. 2015;4(2):e040255. doi: 10.7363/040255.

Introduction

About 1 out of 2 of term and 8 out of 10 of preterm babies develop jaundice, which generally appears 2 to 4 days after birth, and resolves spontaneously after 7-14 days. In most infants with physiological jaundice bilirubin levels do not rise to a point that requires treatment. However, in some infants with exaggerated physiological jaundice, and in many infants with pathological jaundice, bilirubin in the blood reaches very high levels that put the infant at risk for acute and chronic encephalopathy (kernikterus). In these cases, treatment aimed at decreasing bilirubin level is required in order to avoid kernikterus. Effective treatments to decrease serum bilirubin levels with severe jaundice include phototherapy and exchange transfusion.

The decreasing effect of light on serum bilirubin levels in neonates with jaundice was first described by Cremer et al. in 1958 [1]. Since that time, phototherapy has been effectively used as a relatively inexpensive and noninvasive method of treating neonatal hyperbilirubinemia. Today exchange transfusions are rare and are only used as a rescue therapy to avoid kernikterus in newborns with severe jaundice when phototherapy is inadequate.

Mechanism of action

When exposed to light, a fraction of native bilirubin IXα (4Z,15Z) in skin undergoes photochemical conversion reactions occurring at different rates and resulting in several different products. Configurational isomerization (4Z,15E; 4E,15Z; 4E,15E; briefly Z,E; E,Z; E,E; respectively) is reversible; and is much faster than structural isomerization which is irreversible and results in lumirubin (Z-lumirubin; E-lumirubin). Lumirubin is quickly eliminated by the liver. Thus, the excretion of lumirubin is considered quantitatively to be more important during phototherapy than excretion of Z,E-bilirubin. Therefore, transformation to lumirubin is primarily responsible for the phototherapy effect. Photooxidation may also occur. But it occurs much more slowly, and is thought to be less important than than the others [2].

Metabolism of bilirubin photoisomers

The metabolism of the photoisomers is not known in detail. Due to increased polarity, these isomers are water-soluble and can be excreted in bile and urine, bypassing the need for conjugation. Thus, their formation facilitates the biliary elimination of bilirubin photoisomers when the normal pathway of hepatic glucuronidation is inadequate as in neonatal period.

E,E-bilirubin and E-lumirubin is completely excreted in bile in unchanged form without conjugation to glucuronides. Z,E- and E,Z-bilirubin, and Z-lumirubin are excreted rapidly in bile partly in unchanged form and partly as glucuronides, whose formation is catalyzed presumably by uridine-diphosphoglucuronate glucuronosyltransferase (UGT1A1). In contrast to the corresponding (Z,Z) parent isomers, the photoisomers formed only monoglucuronides.

Since Z,E-bilirubin and Z-lumirubin undergo glucuronidation by the same enzyme (UGT1A1) that catalyzes glucuronidation of the Z,Z-bilirubin it is likely that they will compete with bilirubin for glucuronidation. In this way, phototherapy might retard the normal excretion of bilirubin. However, this is unlikely to be a major effect because bilirubin is always in excess in the circulation, and the molecular structure of the native bilirubin has also advantage for glucuronidation. The pigment composition of bile of infants undergoing phototherapy is likely to be more complex than previously believed. Initially, the bile contain principally photoisomers of bilirubin along with relatively low concentrations of Z,Z-bilirubin formed by thermal reversion of its configurational isomers in bile. However, as the glucuronidating system in the liver becomes active these pigments will be accompanied, not only by mono- and diglucuronides of bilirubin, but by monoglucuronides of Z-lumirubin, E,Z- and Z,E-bilirubin [3].

Phototherapy and serum bilirubin levels

The effect of phototherapy is typically measured in reduction of serum total bilirubin (STB) level which depends on the rates of formation as well as the rates of clearance of the photoproducts. If phototherapy is initiated during the first 3-4 days of life when STB levels would normally be expected to increase, an absolute reduction of STB levels may not always be achievable. If phototherapy is started after this period, effective phototherapy should lead to a measurable reduction of STB within 4-6 hours, and a decline in STB levels of 40-50% in 24 hours can be achieved.

The commonly used laboratory methods for clinical bilirubin analysis do not distinguish between isomers [4], and changes in bilirubin photoisomers induced by light exposure during clinical practice do not influence the measured unbound bilirubin level [5]. The presence of photoisomers has also received much less attention in most clinical studies of phototherapy. Substantial amounts of photoisomers may be present in serum/plasma samples obtained from icteric infants even before they undergo phototherapy. These isomeric bilirubins are produced during exposure of infants to visible light or by incidental exposure of blood samples to light during collection and processing. In infants who receive phototherapy, photoisomer formation starts almost as soon as the lights are turned on, and long before significant changes in STB can be detected.

Phototherapy and bilirubin toxicity

Increase in serum Z,E-bilirubin earlier than then the other isomers, it is more slowly cleared. After 2 h of phototherapy STB is only minimally reduced, while significant formation of the Z,E photoisomer is detectable within 15 min, and the Z,E photoisomer alone constitutes between 20-25%, and other photoisomers, albeit present only in low concentrations, nevertheless add to that number. The change in STB is significant, although the Z,E bilirubin may not have peaked by 4 h of phototherapy [6].

Z,E-bilirubin is the most polar isomer of bilirubin and is relatively more soluble in water than the other isomers. Due to lower lipophilicity of the photoisomers compared with the Z,Z isomer, it could be expected to be less prone to cross the blood-brain barrier and enter the brain. Unfortunately, no studies investigating the transfer of bilirubin photoisomers to brain have been published. However even in the same STB levels, risk of bilirubin encephalopathy is lower in infants who receive phototherapy, and photoisomer formation might be directly neuroprotective, irrespective of the effect on excretion [7, 8].

The evidence regarding bilirubin photoisomer toxicity from *in vitro* studies is not definitive. In some studies, it seems to be evidence of increased cellular toxicity when cells are exposed to phototherapy in the presence of bilirubin. However, given the study conditions the results may not be relevant because of increased significant amounts of photooxidation products leading to oxidative cell damage [9].

Indications

To aid physicians in deciding when to initiate phototherapy, several guidelines has been developed as 'The American Academy of Pediatrics Subcommittee on Hyperbilirubinemia Guidelines on the Management of Hyperbilirubinemia in Newborns 35 or More Weeks Gestation' [10]. This guideline includes an algorithm for the management of jaundice in the newborn nursery as well as guidelines for the initiation of phototherapy based on STB levels, gestational age, age of the infant in hours, and individual risk factors.

There are not evidence-based guidelines on the indication for phototherapy in premature infants less than 35 weeks' gestation. However, commonly used reference books provide tables, although these are not evidence based but are primarily the result of expert opinion. A commonly used rule of thumb is to start phototherapy when the STB level is greater than 5 times the birth weight. Thus, in a 1-kg infant, phototherapy is started at a bilirubin level of 5 mg/dL; in a 2-kg infant, phototherapy is started at a bilirubin level of 10 mg/dL and so on.

Contraindications

There are few contraindications to phototherapy. These include congenital erythropoietic porphyria, or a family history of porphyria. Moreover, photosensitizing drugs such as nonsteroidal anti-inflammatory drugs (ibuprofen), diuretics (furosemide, hydrochlorothiazide), and certain antibiotics (ciprofloxacin, ofloxacin, levofloxacins) should be avoided while infants are receiving phototherapy. In general, however, photosensitivity from medications are most likely to occur after exposure to light in the ultraviolet spectrum. Because phototherapy does not produce significant ultraviolet,

phototoxic reactions in infants receiving these medications are a rare condition [11].

Color of light

The human eye is sensitive to light which lies in a very small region of the electromagnetic spectrum labeled "visible light". This "visible light" corresponds to a wavelength range of 400-700 nanometers (nm) and the visible colors from shortest to longest wavelength are: violet, blue, green, yellow, orange, and red; e.g. blue and green lights have a wavelength of about 475 nm (450-495 nm) and 510 nm (495-570 nm). The white light is a mixture of the colors of the visible spectrum.

Bilirubin appears yellow because it strongly absorbs blue and green light. Blue light around 450 nm is absorbed most readily if bilirubin is in a tube. In a newborn infant other factors, including skin penetration and albumin binding, combine causing a color shift of the most effective light toward the blue-green region. A recent review recommends light in the wavelength range 400 to 520 nm and peaked at 450 ± 20 nm. The recommendation of the American Academy of Pediatrics is a more narrow range, 460 to 490 nm [10]. Presently phototherapy devices using light have peak intensity near 460 nm which is based on the absorption maximum of bilirubin bound to albumin *in vitro* [13].

Blue light has been investigated intensively, and has been shown to be effective. Blue fluorescent lamps have been used worldwide with peak emission at 452 nm and bandwidth of 55 nm with some studies showing that its more effectiveness, and providing more photoisomerization than green light or daylight [14, 15]. However, there appears to be no clear benefit in choosing either (daylight) fluorescent versus blue fluorescent lamps [16] or either blue fluorescent versus green fluorescent lamps [17, 18]. A recent study shows that broad-spectrum light phototherapy is more effective than blue LED phototherapy for the treatment of hyperbilirubinemia in late preterm and term infants. These findings are not due to the different irradiance of the two phototherapy systems, but probably depend on their different peak light emissions [19].

A turquoise (blue-green) fluorescent source with peak intensity near 490 nm is significantly more effective than blue [20] or green fluorescent lamps [21-24] in reducing the duration of phototherapy. Explanation of this finding could be made different capacity of photoisomerisation and skin penetrance. Both the configurational and structural bilirubin photoisomerizations are wavelength dependent [25]. Blue spectrum, near the bilirubin absorption maximum at 458 nm wavelength, may produce more of the Z,E isomer, and light at longer wavelengths, closer to the color turquoise, may produce more lumirubin [24]. Skin penetration is deeper at longer than shorter wavelengths [20, 24]. Turquoise light has longer wavelengths than blue light. Deeper penetration into the skin, and greater production of E,Z-bilirubin and lumirubin, in infants under turquoise light has a greater bilirubin reducing effect than blue light with equal irradiance. Furthermore, presumably the absorbance of bilirubin *in vivo* in the long-wavelength range is greater than that *in vitro*. This suggests, given equal irradiances, that light in the turquoise spectral range is preferable to the blue in treatment of newborn jaundiced infants [24]. There have been, however, continuous investigations and reports concerning the question of the most effective wavelength range for phototherapy with no apparent resolution [2].

Antibacterial effects of blue light

Blue light, particularly in the wavelength range of 405-470 nm, exhibits a broad-spectrum antimicrobial effect against bacteria (either gram-positive and gram-negative bacteria). Moreover, blue light therapy is a clinically accepted approach for *P. acnes* infections. Clinical trials have also been conducted to study the use of blue light which was delivered from a diode laser via a flexible optical fiber passed through the biopsy channel of the endoscope for *H. pylori* stomach infections and have shown promising results. Studies on blue light inactivation of important pathogenic bacteria, including *St. aureus* and *P. aeruginosa* have also been reported. The mechanism of blue light inactivation of bacteria is proved to be the photo-excitation of intracellular porphyrins and the subsequent production of cytotoxic reactive oxygen species. Certainly, further studies are required to optimize the optical parameters (e.g., wavelength, radiant exposure) and to ensure effective and safe blue light therapies for infectious disease [26].

Hemoglobin and melanin

There is a competition for phototherapy light by strongly absorbing substances in the skin, namely hemoglobin and melanin [27]. Higher hemoglobin level in the blood significantly reduce photoisomer formation, and phototherapy efficacy during the

early phase of phototerapy (15-60 min), which disappeared at the later time points [28]. Since hemoglobin is the main absorber of visible light in the skin, it is the major competitor with bilirubin for light absorption. Another possible explanation for this phenomenon is that the proportion of plasma to red cells is lower with high hemoglobin, so it takes longer for the circulating bilirubin to be exposed to phototherapy lights. Slower capillary circulation due to the higher viscosity of high hemoglobin blood may have the same effect, and as hemoglobin filters the light, more bilirubin molecules are exposed to less light. In addition, some light is back scattered out of the skin, and any melanin present would also present a significant competitive absorber of visible light [2, 29].

Different skin colors manifest different traits to light exposure. In fact skin color is primarily determined by melanin that is synthesized in the melanosome. Melanosomes in dark skin (African) are larger and more heavily pigmented than those in light skins (Asian and Caucasian). Since melanin can reduce the penetration of light, neonates with black skin may need more intensive phototherapy. Thus, truly individualized therapy, considering that the child's characteristic and risks are deemed acceptable, can obtain the most desired benefits [28, 29].

Light sources

In the management of neonatal jaundice, different phototherapy devices are being used worldwide. Two types of phototherapy devices are currently available: the conventional phototherapy light and the fiberoptic phototherapy device. The common light sources used in these devices are either fluorescent, or tungsten-halogen lamps with wide emission spectrum, or light-emitting diodes (LEDs) with narrow spectrum.

Conventional phototherapy devices

Conventional phototherapy devices use flurescent lamps, tungsten halogen bulbs, a metal halide gas discharge tubes or LEDs. Fluorescent tubes are the most common type of light source used. These tubes have the advantage of being inexpensive but their light intensity and irradiance reduces with time and needs to change after 1,000-1,500 hours. Quartz halogen bulbs have not been noted to reduce in intensity with age but they are quite fragile, especially when hot. Gas discharge bulb is not frequently used, and the lamb be changed after 1,000 hours. Today LED phototherapy is preferred in most of the neonatal units.

A LED is a special type of semiconductor diode which emits light when connected to an electrical circuit. The light produced is of narrower bandwidth, and the colour depends on the semiconductor utilized. LED devices usually contain indium or gallium nitrate or nitride as semiconductor element. Such light sources emit high-intensity light while generating little heat, and can be placed closer to the infant, increasing spectral irradiance. In addition LED phototherapy does not appear to have a significant effect on transepidermal water loss. Also, LEDs have useful features such as light weight, compact size, non-fragile because of the absence of glass parts and an ability to be focused with a lens or through spatial orientation, in addition to offering low energy consumption and lasting durability without decreasing in intensity with age (at least 3,000 hours). As LED devices utilize direct current power supply, they do not usually produce any flickering, a phenomenon that could be related to nausea and dizziness in healthcare professionals. These unique characteristics make LEDs convenient for phototherapy.

LED phototherapy might be clinically more effective than conventional phototherapy with blue-white or green fluorescent tubes as judged by the production of lumirubin *in vitro* studies [30].

However, there is no statistically significant difference in the effectiveness of phototherapy using blue-green LEDs, blue LEDs or conventional halogen-quartz bulbs. In a recent meta-analysis including six randomized controlled trials with five hundred and eleven term or late preterm neonates, no significant difference in STB rate of decrease was detected between LED and other types of phototherapy [31]. In a Cochrane review including 630 neonates in six randomised controlled trials (four studies compared LED and halogen light sources, two papers compared LED and compact fluorescent light sources, the duration of phototherapy, the rate of decline of STB, treatment failure (defined as the need of additional phototherapy or exchange blood transfusion), side effects of phototherapy such as hypothermia, hyperthermia, skin rash were all found similar to phototherapy with conventional (compact fluorescent lamp or halogen) light sources [32]. So LED and other phototherapy devices appeared to be equally effective in reducing STB. However, the variability of phototherapy units and the lack of a standard technique to measure spectral irradiance hamper the interpretation of patient treatments in these trials.

Fiberoptic phototherapy devices

Fiberoptic phototherapy, a new device using optical fibers, has been reported to be effective in reducing STB for neonates with jaundice. These devices use a standard light source, usually a quartz halogen bulb. The light from the bulb passes through a fiberoptic bundle into a pad of woven optic fibers. The pad can then be placed next to the neonate's skin. Thus, infants under fiberoptic phototherapy can be nursed close to their parents without mother-infant separation. Furtermore, retinal injury, or complications such as eye irritation, corneal abrasion, and conjunctivitis caused by eye shield can be avoided because light from optical fibers is directly delivered to the infant's trunk. Therefore, fiberoptic phototherapy is a safe alternative to conventional phototherapy although it has a low spectral irradiance and a lower spectral power, as it irradiates a minor body surface and it is not advised for intensive phototherapy in the most critical cases.

Although fiberoptic phototherapy is equally as effective as conventional phototherapy in preterm infants, these devices are less effective in decreasing the STB level than the conventional phototherapy. Combining a fiberoptic device with conventional phototherapy is more effective than conventional phototherapy alone. Infants should be nursed on the postnatal ward on a fiberoptic device, if the baby is over 48 hours old and there is no risk of rapidly rising STB levels or the need of exchange transfusion. Infants who have been initially treated with overhead phototherapy can receive phototherapy by the fiberoptic device as the bilirubin levels reduce. The overall aim is to treat the jaundice but also to minimise maternal and infant separation [33].

Filtered sunlight

Phototherapy may not be available in the less developed countries because of the lack of devices and/or of reliable electrical power. In these areas, modern phototherapy devices are not readily affordable, often break down because of electrical power surges, and are difficult to maintain due to the unavailability of replacement parts (which is recommended after 2,000 to 3,000 hours of use). Even where phototherapy devices are available, most hospitals lack the resources necessary to replace fluorescent lamps. Thus, it is not uncommon, especially in areas without access to phototherapy, for the parents/guardians of jaundiced infants to place their babies in direct sunlight unaware of the potential harm or safety risks.

Using direct sunlight for phototherapy has a number of clinical and practical drawbacks that could make its use undesirable. Sunlight contains altitude-, seasonal-, and time-of-day-dependent levels of harmful ultraviolet A, B, and C radiation, which can cause a serious and permanent damage to human skin. It also contains significant levels of warming infrared radiation, which, in the absence of sufficient cooling, could raise core body temperatures to unsafe levels.

It must be underlined that the use of sunlight, when filtered to exclude the harmful spectral radiation, is a novel, practical, and inexpensive method of phototherapy that potentially offers safe and efficacious treatment strategy for management of neonatal jaundice in tropical countries where conventional phototherapy treatment is not available [34].

The most practical and low-cost filters of sunlight are the commercially available window-tinting films, widely used in vehicles and residential and commercial structures in sunny climates. Window-tinting films can effectively reduce sunlight ultraviolet and infrared radiation, and offer a range of significant attenuations of therapeutic blue light. Although window-tinting films are traditionally affixed to a glass surface, these films can also be stretched over a support frame, under which an infant basket, bassinet, or crib can be placed [35].

Irradiance

Irradiance is reported in watts per square meter (irradiance) or in microwatts per square cm per nm ($\mu W/cm^2/nm$) over a certain wavelength band (spectral irradiance). The higher the irradiance the larger the rate of STB decline [36]. There may be a saturation point at 30 $mW/cm^2/nm$ where an increase in irradiance has no increased benefit in decreasing STB levels. Therefore phototherapy devices should be used to deliver at least 30 $mW/cm^2/nm$ [10]. Conventional daylight phototherapy lamps can be expected to deliver an irradiance of approximately 8-10 $\mu W/cm^2/nm$, and with special blue fluorescent lamps irradiance levels may reach 30-40 $\mu W/cm^2/nm$. The irradiance of different phototherapy devices varies widely and is dependent on a number of factors, including the number of light sources, and distance of the light source from the neonate.

Double or triple phototherapy

Despite significantly higher irradiance in the double (fiberoptic plus conventional, or both

conventional) or triple phototherapy, there is no statistically significant differences in the treatment [37-41]. Although STB values decrease significantly more slowly in infants who received single phototherapy than the double or triple phototherapy, the actual difference in 0-4 h decrease is small [42, 43]. More studies are needed to evaluate the double or triple phototherapy with high-energy phototherapy units.

Super (high-intensity) phototherapy

Recently, significantly higher STB decline rates were reported in newborns treated with the super (high-intensity) [44]. However, another study shows that the rate and level of photoisomerisation is not influenced by irradiance and light source [19].

Distance of the light source

The irradiance decreases exponentially as the distance from the baby increases. Irradiance is maximized by bringing the light source lights as close to the infant as possible. The distance from the light source to the infants is 40 to 50 cm because the heat formation from the fluorescent tubes risked overheating the infants at reduced distance. For LED lights this distance is 20 cm [36].

Reflecting lights

Aluminum foil or white cloth placed on either side of the infant to reflect light will increase irradiance [45]. Though hanging of white reflective sling on sides of fluorescent phototherapy equipment results in marginal increase in irradiance, it does not decrease the duration of phototherapy [46]. Use of mirrors behind the bulbs in tunnel phototherapy units may lower STB levels earlier [47].

Overhead versus underneath phototherapy

A planar (horizontally flat) overhead phototherapy lamp illuminates up to one third of a baby's skin surface area. For the treatment of neonatal jaundice, commercially available LED devices provide light from either above or underneath the baby. The efficacy of these different directions of application has not been thoroughly investigated. Probably overhead is superior to underneath LED phototherapy in the treatment of neonatal jaundice because of the increased body surface exposed to light [48].

Intermittent versus continuous phototherapy

Intermittent phototherapy (on for 1 hour then off 1 hour; 12 hours on, 12 hours off; 1 hour on, 3 hours off) is as effective as the continuous phototherapy [49, 50].

Nursing during phototherapy

Skin care

To increase the speed of STB decrease, as much of the neonate's skin surface as possible should be exposed to the light. Spectral power is optimized by exposing the wider skin surface as possible, exceptions being the need for protective covering of the eyes and, if absolutely necessary, diapers should be minimal; small or transparent nappies are sometimes used. There is no difference in STB reducing rate in partially clotted (dispossible nappy only) versus naked infants [51].

Infants in isolettes who are less than 1,200 g are generally nursed without a nappy on an absorbent sheet protector. Infants in isolettes who are more than 1,200 g may be nursed with a nappy on if STB level is not rising rapidly. If intensive phototherapy is required then the nappy should be removed.

Infant should be clean and dry. Only water is used for cleaning. Oils or creams should not be used to the exposed skin. Infants nursed in nappies where the buttocks are not exposed may have zinc and castor oil applied to areas of skin excoriation. However application of clear topical ointment on the skin of jaundiced small preterm infants receiving conventional phototherapy in incubators reduces transepidermal water loss significantly without effect on STB level which may be related to the skin thickness [52].

Care in incubator

Light bulbs should be as fresh as possible, and any optical filters in the unit should be cleaned regularly. In comparison with the measurement taken outside an incubator, the mean spectral irradiance detected within a single-walled incubator is significantly decreased, and the reduction of spectral irradiance within an incubator correlated with the degree of incubator wall with a maximal loss of 15 percent [53].

The irradiance under the overhead daylight fluorescent lamp phototherapy dose not change with the increasing humidity (60-80%) in a double-wall incubator which is kept at 36°C. However, above 90%

humidity, when water vapour inside the incubator is so saturated to the point of totally condensing in the incubator walls, the measured irradiance decreases 15% of the initial values with the blue LED phototherapy and 45% with the halogen spotlight phototherapy. Therefore health professionals should be aware that mist and water condensation inside an incubator may significantly reduce the efficacy of photoherapy [54].

A clear perspex plastic headbox is used to increase oxygen concentration of air for mild respiratory distress, and a thin plastic sheet or a transparent thermal blankets (plastic bubble blanket designed for industrial packing) are widely used as heat shields to reduce heat and evaporative losses in the very low birthweight infant. Use of transparent plastic insulation substantially decreases the transmission of phototherapy light. A reduction in irradiance by 5% was recorded with a perspex heat shield, 7% with a single plastic sheet, and 11% with a thermal blanket. Where difficulty in maintaining body temperature is encountered there is a tendency to increase the number of plastic layers. This reduces the irradiance further. A perspex heat shield in addition to a double layer of plastic or bubble sheet is used, reduces irradiance 17% and 25%, respectively. Reflection of light from the surface of the plastic is also a problem. This increases if the surface is irregular. Thickness and the type of plastic used have no effect [55, 56].

Changing position or massage

Turning newborns two to three hourly during phototherapy, as is common practice, does not increase the effect of phototherapy [57, 58]. The principal sites of phototherapy action may localize not only in the skin but also in capillary circulation under the skin. Increase in capillary circulation in skin with massage in preterm newborns with jaundice, may delay a need for phototherapy [59].

Monitoring during phototherapy

Pulse oximetry monitoring

Infants under the blue lights need at least saturation monitoring as it is difficult to assess the infants colour under these lights. Well babies who receiving white light phototherapy do not require monitoring. It is important to underline that bilirubin, due to a different spectrum of light absorption, has no effect on pulse oximetry. Therefore, pulse oxymetry can be used reliably for monitoring jaundiced patients, including neonates. But oxygen saturation monitor probes must be shielded from broad-spectrum phototherapy lights because light interferes with the accuracy of pulse oximetry measurements. Patients with severe hemolytic jaundice might also have increased carboxyhemoglobin (COHb) levels, which could potentially lead to erroneous pulse-oximetry readings [60].

Transcutaneous bilirubin monitoring

Phototherapy units should be turn off during phlebotomy for bilirubin levels. Obtaining venous or heel stick blood samples is an invasive and painful procedure. Transcutaneous bilirubin (TcB) is an easy, time-saving, and painless alternative to decrease the need for STB. Before phototherapy, there is a good association between bilirubin concentrations in the blood and the skin, as assessed through TcB optical spectroscopy. With the initiation of phototherapy, a rapid decrement in dermal bilirubin. Therefore, the validity of TcB has been questioned during and after phototherapy. Currently, TcB assessment is used before initiating phototherapy only. According to the findings of a prospective observational study of term and preterm neonates TcB levels of were −7.3 mg/dL below the STB levels. After 8 hours, this value was reduced to approximately −5.0 mg/dL. Therefore TcB measurements remain a valuable tool after phototherapy when time-dependent underestimation of TcB is being accounted for [61]. Another study also demonstrates a good correlation between TcB and TsB by 8 hours even after phototherapy [62].

Another practical method is measuring TcB on a patched area of the skin. It is well known that blanching effect the light exposure occurs only exposed areas, while shaded sites remain icteric. A photo-opaque patch 2.5 cm in diameter was positioned on the skin of forehead over the measurement site prior to the start phototherapy, and TcB was measured on an unpatched area of the forehead skin and on the nearby site covered by the photo-opaque patch by lifting the patch. This study confirms that only patched (unexposed) skin of the forehead can be safely used for the evaluation of bilirubin levels in newborn infants under phototherapy [63].

Transport and home phototherapy

Phototherapy during neonatal transport is feasible and safe and may result in a decreased requirement for subsequent exchange transfusion

[64]. Home phototherapy in full-term infants with non-hemolytic moderate hyperbilirubinemia, is a potential option that avoids separation of mother and infant, facilitating and maintening breast-feeding, and is cheaper than hospitalization. It can be used safely, provided that the total serum bilirubin level is monitored regularly. This can be considered either as a continuation of phototherapy commenced in hospital or as a new treatment in babies whose gone home on early discharge. However all these infants should have full blood count, baby blood group and direct Coombs test, and G6PD in male infants. Home phototherapy cannot be offered for babies living in remote areas, and the parents must be educated about the use device prior discharge or at home. Newer home fiberoptic phototherapy devices should be more effective [2]. However, no high-quality evidence is currently available to support or refute the practice of home-based phototherapy for non-haemolytic jaundice in infants at more than 37 weeks' gestation [65].

Discontinuation of phototherapy

Intensive phototherapy can result in a decrement of bilirubin values of 30 to 40% in the first 24 hours, with the most pronounced decline occurring in the first 4 to 6 hours; phototherapy can be discontinued when the STB level has fallen below 13 to 14 mg/dL. Although there are no established guidelines for discontinuation of phototherapy, phototherapy can be safely stopped in infants treated during the birth hospitalization when the STB falls below the level at which phototherapy was initiated [2].

Rebound bilirubin levels

A rebound in the STB level of 1-2 mg/dL (and occasionally more) can occur after phototherapy is discontinued. It is usually unnecessary to keep a baby in the hospital to check for rebound.

Term babies who are readmitted for phototherapy (usually between day 3-6) for jaundice do not require a routine rebound STB level after lights are stopped. Reasons to check a rebound bilirubin 24 hours after stopping phototherapy may include positive Coombs test, prematurity, bruising and early use of phototherapy (started in 72 hours of life) [66, 67]. Children with bilirubin levels lowered to ≤ 14 mg/dL with phototherapy are also unlikely to receive repeat phototherapy [68]. Consider using the TcB use to assess the need for further bilirubin levels to prevent unnecessary blood tests.

Side effects

Although phototherapy has been used for more than 60 years it has some complications which are outlined below [69].

Short-term side effects

Interference with maternal-infant interaction

Neonatal phototherapy separates neonates from mothers, which might interfere with establishing parent-child bonding. Thus, unless jaundice is too severe, fiberoptic devices could be used [33], or phototherapy can be safely interrupted at feeding time to allow breastfeeding, parental visits, and skin-to-skin contact to maintain parent-child bonding [49, 50]. 'Family-centered phototherapy' strongly support the rooming-in, skin-to-skin contact, and breastfeeding [70].

Hipo- or hyperthermia

LED phototherapy with low irradiances does not cause significant hyperthermia similar to conventional phototherapy with blue fluorescent light. A randomised and controlled unicentric clinical trial in Brasil showed that blue LED phototherapy with heterogeneous irradiance (which may be explained by the concentration of nine bulbs in the centre of device providing a higher small illuminated area) exhibited a similar efficacy as daylight fluorescent lamp phototherapy from below with uniform irradiance in decreasing bilirubinemia in newborns with a gestational age of ≥ 35 weeks. However, patients who received LED phototherapy exhibited more hypothermia (35-36.0°C) than patients treated with fluorescent phototherapy (23% vs. 9%; $p = 0.02$), so there is a greater need for more rigorous control of the room temperature [71].

LED phototherapy with high irradiances (60-120 μW/cm^2/nm) significantly increases body temperature in hyperbilirubinemic newborns compared to infants who received conventional phototherapy with fluorescent lamps (10-15 μW/cm^2/nm) or LED phototherapy (26-60 μW/cm^2/nm). Thus the increase in body temperature is a function of increase of irradiance rather than the type of the light source [72]. Hyperthermia might be related to release of pyrogenic cytokines, although effects of light with different wave-lenghts and irradiances on serum cytokine levels are not known [73].

Benign skin rashes

Although benign skin rashes are reported as less than 3% in studies conducted different aims, until recently, there has not been single systematic study of the putative association between phototherapy and the development of benign newborn rashes [74]. In a recent study from Turkey reported that dramatic increased incidence with the frequency of skin eruptions was 36% in the conventional phototherapy group and 33% in the LED group (p = 0.83). The skin eruptions were macules in 22.4%, papules in 8.6%, and maculopapular rashes in 3.4% infants. There were no differences in the incidence and extent of skin eruptions in preterm infants who received conventional fluorescent phototherapy group or LED group [75]. However, higher rates of skin rash (39% vs 1%, P=0.002) were reported in the super (high-intensity, or high-irradiant LED) group compared with the fluorescent tubes-treated group [44].

Purpuric and bullous eruptions

Neonates with cholestatic jaundice who are receiving phototherapy may develop purpuric (probably circulating porphyrins are the causative factors) and bullous eruptions. The cause of the elevated serum (copro- and proto-) porphyrins is uncertain. Hepatic cholestasis may have been a contributing factor to the increase in serum porphyrins. Origin of circulating porphyrins may also be through the hemolysis of young erythrocyte precursors, such as reticulocytes which harbor a tenfold higher concentration of porphyrins than do mature erythrocytes. Photoactivated porphyrins stimulate photodamage via reactive oxygen species and free radicals. Clinically, the majority of the cutaneous porphyrias demonstrate blistering, which occurs by accumulation of water-soluble porphyrins. Purpuric patches develops at sites of maximal exposure to the phototherapy lights, with dramatic sparing at shielded sites within 24 hours after initiation of the phototherapy. On discontinuation of phototherapy, all eruptions disappear within one week [76].

Bronze baby syndrome

The bronze-baby syndrome (BBS) is a rare side-effect of phototherapy which causes the appearance of grey-brown discoloration of skin, serum, and urine. BBS is harmless, and pigmentation returns slowly to normal if phototherapy is discontinued. BBS occurs only in newborns with cholestasis and with elevated plasma levels of both unconjugated and conjugated bilirubin. It is important to underline that not all babies with cholestasis develop the BBS during phototherapy, but all babies who do should be investigated for underlying liver disease. The presence of direct hyperbilirubinemia is not considered a contraindication for phototherapy. When phototherapy is stopped and cholestasis resolves, the coloration disappears [2].

The mechanisms responsible for the onset of BBS, and the chemical nature of the abnormal pigment(s) have not been identified. The abnormally high serum levels of porphyrins present in these newborns are likely to be due to cholestasis, which also determines an enhanced copper level in the serum and in the liver. The coincidence of the two events induces the formation of copper-porphyrins. The presence of copper partially prevents enzymatic conversion of the porphyrin molecule along the sequence of uro-, copro- and protoporphyrin. Copper-porphyrin undergo photodestruction sensitized probably by bilirubin yielding uncharacterized photoproducts causing brown-discoloration [77].

Despite the copper-porphyrin theory has gained acceptance in the literature, copper-porphyrins are chemically robust molecules, and bilirubin photosensitize degradation of copper-porphyrins seems unlikely. Moreover, bilirubin is a poor photosensitizer, and does not photosensitize degradation of copper-porphyrin. Thus the basic premise of the copper-porphyrin hypothesis, that it stems from degradation of copper-porphyrins photosensitized by bilirubin, is incorrect. That is not to say that copper-porphyrins do not accumulate in serum during cholestasis. However, there is no evidence that they cause the hallmark hyperpigmentation of the BBS; despite the well-known metallic association between copper and bronze-colored pigmentation [78].

A post-mortem report suggests that the photodecomposed pigmented products of bilirubin are unable to pass the blood-brain barrier [79]. Although it is generally believed that BBS is harmless, and pigmentation generally returns slowly to normal if phototherapy is stopped, BBS may constitute an additional risk for developing kernicterus. Management of hyperbilirubinemia (especially the hemolytic kind) in the presence of BBS may include an exchange transfusion carried out at lower TSB concentration than previously recommended [80].

Ileus

Jaundice appears to inhibit gastric emptying, and phototherapy influences emptying indirectly by lowering STB level. This effect is likely to be of clinical significance in a small minority of jaundiced infants [81].

Phototherapy may be an independent risk factor for ileus in small preterm neonates. A significantly higher proportion of neonates under phototherapy developed ileus than those without phototherapy (63% vs. 9%) [82]. Ileus in such a situation occurred frequently in the absence of associated risk factors like enteral feeds, electrolyte imbalance, medications like morphine, and sepsis.

Ileus during conventional phototherapy due to photorelaxation of gut smooth muscle as in vascular smooth vessels possibly either by nitric oxide-cyclic guanosine monophosphate pathway or direct photorelaxation is thus biologically plausible [83]. Changes in peripheral blood flow and cardiac output during conventional phototherapy may also contribute to ileus during conventional phototherapy in preterm neonates [84]. However, superior mesenteric artery blood flow does not change significantly during phototherapy. Therefore mesenteric ischemia is unlikely to be a contributing factor towards ileus during phototherapy [85].

Loose watery stools

Phototherapy-associated diarrhea (possibly due to an increased intestinal secretion) and altered transepithelial electric potential difference have been well-documented in neonates under conventional phototherapy [86, 87]. Intestinal absorption of water, sodium chloride, and potassium is significantly impaired in the patients receiving phototherapy. Such impairment is transient, as it is not apparent when phototherapy is stopped [86].

The high concentration of bilirubin and bile salts found in the colonic contents of neonates during phototherapy would appear to be a factor in the pathogenesis of phototherapy-associated diarrhea in the jaundiced neonate [88]. Unconjugated bilirubin significantly increases the permeability of intestinal epithelium with triggering a reversible redistribution of tight junctional occluding, without affecting nutrient digestion or absorption in an *in vitro* study. This effect is maximal at 6 h and tended to be reversed at 48 h [89].

Dehydration

Conventional phototherapy changes the thermal environment of infants, which leads to increased insensible water loss, and dehydration. Phototherapy-induced loose stools also increase the intestinal fluid losses. Therefore, newborn infants undergoing phototherapy should be closely monitored and appropriate fluid supplementation should be given when necessary, especially in very low birth weight infants. Preterm infants have about a 20% increase in transepidermal water loss when they receive phototherapy despite being nursed in humidity and a double walled crib. The daily fluid rate may need to be increased by 10-15 ml/kg per day to prevent dehydration [90].

It has been demonstrated that intravenous fluid supplementation 70 mL/kg (50 mL/kg equivalent to mild dehydration plus 20 mL/kg) of N/5 (2%) saline in 5% dextrose for a period of 8 hours, and, in addition, breast/formula feed *ad libitum* as they were taking before in term neonates with nonhemolytic severe hyperbilirubinemia could decrease the rate of exchange transfusion and the duration of phototherapy [91]. The findings of this trial reevaluated by using isotonic versus hypotonic fluid supplementation. Hypotonic fluid supplementation (0.2% saline in 5% dextrose) increases the incidence of hyponatremia, whereas isotonic fluid (0.9% in 5% dextrose) decreases the incidence of hyponatremia but increases the risk of hypernatremia. Both equally decrease the rate of blood exchange transfusion and phototherapy duration. *Post hoc* calculations suggest that N/3 (0.3%) saline in 5% dextrose may have the least risk of hyponatremia as well as hypernatremia [92].

However, according to the findings of two studies, intravenous fluid therapy has no effect on the rate of decrease in STB and decrease in duration of phototherapy compared the breastfeeding in healthy term newborns with no dehydratation [93, 94]. Insensible fluid loss is increased during phototherapy, so oral feeding is important for protection of hydration status of newborns. Using the oral route avoids the need for intravenous cannulae and their attendant complications. No need any intravenous fluid supplementation unless the presence of severe dehydration.

Riboflavin deficiency

Riboflavin is highly sensitive to light. It is because of its photoreactivity and its presence in almost

all body fluids and tissues that riboflavin assumes importance in phototherapy of neonatal jaundice. The absorption maxima of both bilirubin and riboflavin in the body are nearly identical. In consequence, blue visible light will cause photoisomerization of bilirubin accompanied by photodegradation of riboflavin. This results in diminished erythrocyte glutathione reductase, which indicates generalized tissue riboflavin deficiency and red cell lysis. Riboflavin deficiency is progressive with the duration of phototherapy. Many newborns, especially if premature, have low stores of riboflavin at birth. The absorptive capacity of premature infants for enteral riboflavin is likewise reduced. Consequently, inherently low stores and low intake of riboflavin plus phototherapy for neonatal jaundice will cause a deficiency of riboflavin at a critical period for the newborn. Supplementation to those infants most likely to develop riboflavin deficiency is useful [95]. But riboflavin deficiency induced by phototherapy in full-term neonates is not of sufficient severity to metabolic disorders [96].

Lipid peroxidation

Parenteral lipids are susceptible to light-induced peroxidation, particularly under phototherapy. Because lipid hydroperoxides are cytotoxic and can cause adverse effects in preterm neonates. Phototherapy light-induced formation of triglyceride hydroperoxides is prevented with using dark tubing or covering the intravenous lipid line with aluminum foil. This method also prevents loss of riboflavin in intravenous multivitamin solution [97]. If the infant is receiving breast milk via a tube feed, keep this away from the phototherapy lights to prevent lipid peroxidation in the milk [98].

Enlightening the brain, and its consequences

In mammals, light – mostly long wavelengths – penetrate the skull in several species investigated, including human [99]. While unfixed human cadaver studies do not reflect all the conditions seen in the living condition, transcranial application of 808 nm wavelength light penetrated the scalp, skull, meninges, and brain to a depth of approximately 40 mm [100]. Significant amount of light penetrate into deep brain is more probable in newborn infants because of open wide fontanel and thin skull.

Light can effect mammalian brain physiology independent of retinal function, and cerebral cortical tissue responds even to low-intensity visible light [101]. Low levels of visible light which is approximately equal to the amount of light that can penetrate the rat head through fur, scalp, skull, and dura mater, enhances neurotransmitter release [102]. More interestingly, the extracranial light stimulus consisted of a 3-hour pulse of light by using a fiberoptic phototherapy device presented to the popliteal region, the area directly behind the knee joint, can change circadian body temperature changes probably via 'humoral phototransduction' [103].

Extra-retinal tissues provide non-image-forming photoreception [104]. Nonvisual photoreceptors present in the deep brain (septal and hypothalamic), pineal gland and retina play a role in the circadian and circannual regulation of periodic functions. Various opsins and other members of the phototransduction cascade have been demonstrated in telencephalic and hypothalamic groups of the periventricular cerebrospinal fluid (CSF)-contacting neurons sitting in the wall of the brain ventricles that send a ciliated dendritic process into the CSF [101].

Circadian rhythm refers to an endogenous biologic clock with a period of approximately 24 hours. In mammals, the circadian pacemaker is located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. There is some evidence that circadian rhythms develop prenatally. At least 12 genes have been reported to be involved in regulating the circadian rhythm; e.g. *Cry1* is a negative regulator, whereas *Bmal1* is a positive regulator. These genes oscillate not only in the SCN, but also at the peripheral tissues, such as liver, kidney, skin, oral mucosa, fibroblast cells, and peripheral blood mononuclear cells. In a recent study it has been shown that 24 hour blue light phototherapy significantly increases the expression of the circadian gene *Cry1* and decreases *Bmal1* and plasma melatonin levels. During phototherapy, the infant's eyes are routinely covered to avoid retinal damage. Consequently, nonocular light exposure can alter the expression of circadian genes in the peripheral tissues of human beings. Whether such subtle changes in circadian gene expression during phototherapy may translate into neonatal behavior disturbances, e.g. increased crying, jitteriness, alterations in normal heart rate or blood pressure circadian pattern or sleep patterns, needs further study [105].

The role of melatonin in the control of circadian rhythm has been extensively investigated. Circulating melatonin is largely derived from the pineal gland, although other organs producing melatonin include gastrointestinal tract, epithelial hair follicles, skin, retina, salivary glands platelets, lymphocytes and

developing brain. Its synthesis and secretion is controlled by light and dark conditions, whereby light decreases and darkness increases its production. Thus, melatonin is also known as the 'hormone of darkness'. It performs a clock and calendar function in body. Along with antioxidant actions, melatonin is a biological modulator of mood, sleep, sexual behavior and circadian rhythm. Decrased melatonin production and altered nocturnal melatonin secretion have been linked to various central nervous system disorders. Low levels of melatonin have also been shown in obesity, diabetes, ocular diseases, immune disorders, cardiovascular diseases reproductive system disorders, cancer [106]. Short- and long-term effects of prolonged whole body illumination in newborn infants are unknown.

Hypocalcemia

Phototherapy can lead to decreased total and ionized calcium levels of neonates, especially in preterm neonates [107]. This effect might be attributable to increased urinary calcium excretion [108]. In addition, light can affect calcium homeostasis by inhibiting pineal secretion of melatonin and consequently leading to hypocalcemia. Melatonin seems to promote bone formation and prevent bone resorption via several mechanisms which include the increase in the osteoblastic activity and differentiation, as well as the reduction in osteoclastic differentiation and activity, and by increasing osteoprotegerin expression and scavenging the free radicals responsible of bone resorption [109]. Fortunately, only a few hypocalcemic neonates present clinically, and in almost all hypocalcemic neonates serum levels of calcium return to normal 24 h after ending phototherapy [110]. Therefore, no need prophylactic calcium during phototherapy.

Phototherapy caused hypocalcemia can be prevented by covering the head (wearing a hat) during phototherapy [111, 112]. Although these studies was conducted on full-term neonates, it seems logical to apply the hat on preterm neonates as well as the incidence of the phototherapy-induced hypocalcemia is higher in the latter than in full-term neonates. This may due to the higher penetration of light in preterm neonates.

Patent ductus arteriosus

It is hypothesized that light can penetrate the thin chest wall of extremely preterm infants, and causes the relaxation of aortic smooth muscle through the activation of the nitric oxide-cyclic GMP pathway and Ca^{2+}-dependent K^{+} ion channels [113, 114]. Therefore, neonatal phototherapy may exert a relaxing effect on the smooth muscles of the ductus arteriosus in neonates, thus prevents the closure of patent ductus arteriosusu (PDA) and may cause the reopening the ductus arteriosus [115]. In addition, phototherapy has been reported to increase the heart rate, diminish the mean arterial blood pressure and increase peripheral blood flow [116-118]. These alterations may also affect the closure of PDA, and it has been speculated that phototherapy may be a risk factor for PDA, especially in the infants with a birth weight less than 1,500 g.

In 1986, a positive relationship between phototherapy and PDA was firstly reported in premature infants with respiratory distress syndrome [119]. This observation was supported by a study in which infants with a birth weight of 501 to 999 g who received neonatal phototherapy had a significantly increased incidence of PDA compared to those not receiving phototherapy (76% vs. 53%) [120]. It has also been reported that the ductus arteriosus were reopened during phototherapy in more than 50% of the small preterm infants (gestational age ≤ 32 weeks, average birth weight < 1,400 g), all of whom had a closed ductus arteriosus before phototherapy [121].

Infants treated with fiberoptic blankets are at lower risk for PDA compared with those treated with the other PT devices. Although it is speculated with different physiological effects for a small preterm infant lying on their back on a fiberoptic blanket vs. an overhead phototherapy light [122]. However the recent NICHD phototherapy trial did not show a difference in the relative risk of PDA between the aggressive and conservative groups despite a very significant difference in the duration of phototherapy treatment [123].

Rosenfeld et al. [119] have been reported that chest shielding during phototherapy reduced the incidence and severity of PDA by 50% in small preterm infants, and have speculated that if shielding reduces the occurence of PDA, then phototherapy may have a role in ductal patency. However in this study, the evaluation of ductal patency was based on presence of murmur. Echocardiographic evaluation was performed only in those with a murmur consistent with PDA. So, the real incidence of PDA was not definite in this randomized, non-blinded study. Another study on chest shielding in extremely preterm infants revealed that chest shielding did not have any effect on the incidence or severity of PDA, ductal diameter and LA/Ao

ratio. The limitation of this prospective study was the usage of indomethacin which has lead to interference while evaluating the data [124]. In a recent study, similarly, no statistical difference was detected in ductal patency, ductal diameter, LA/Ao ratio before and after phototherapy [125].

After birth, the balance between vasoconstricting and vasodilating forces regulates ductus contractility. Prostaglandins (PGs) and nitric oxide which are locally produced in endothelial cells of the ductus contribute to ductal patency. Among vasodilator prostaglandins (PGE_2, PGI_2), particularly PGE_2 plays an important role in maintaining the patency of the ductus during fetal and neonatal life [126]. Since blood vessels have been shown to be capable of prostaglandin synthesis, the superficial vessels underlying the skin surface which exposed to phototherapy might affect the synthesis and plasma levels of prostaglandins. Therefore it has been hypothesized that, during phototherapy, PG levels will be increased in parallel with the patency of ductus after phototherapy. However, the findings showed that phototherapy did not effect ductal patency and did not have any enhancing effect on PGE_2 and PGI_2 levels [125]. Therefore, further studies are necessary to verify if phototherapy is truly linked to PDA or if some confounding factors present in small preterm infants already affected by several concurrent diseases.

Retinal damage

The plastic cover of the lamp and the incubator wall filter out ultraviolet light. But excessive exposure to visible light causes photochemical lesions in the retina. The damaging light is absorbed by rhodopsin, a visual pigment which triggers several reactions causing lipid peroxidation and apoptosis. Therefore retina has greater susceptibility to blue light than green light. Short time exposure to blue light has deleterious effects on retinal morphology in rat models [127]. Recent studies have shown a protective role of blue light-filtering lenses in human retinal pigment epithelium exposed to light, illustrating the toxic effect of blue light [128]. These findings show the importance of accidental removal of eye coverings during neonatal blue light phototherapy especially in premature infants.

The infant's eyes should be protected from the light with eye pads or the head shields. Before applying the eye pads ensure that they are the correct size for the infant, that the infant's eyes are closed and that the eye pads are secured comfortably. The pads should be removed every four hours to check for irritation and relieve pressure, which could occlude the nostrils or put the infant at risk of suffocation. Removal of pads should be coordinated with parental visits, as lack of eye contact with the infant can interfere with bonding. Eye cares attended with normal saline.

A modified oxygen (orange) headbox has been described to prevent the complications of eye patches including eye infection, suffocation with displaced eye-patches, accidental exposure of the eyes to light, periorbital skin irritation and eye infection, and provide a convenient and inexpensive means of eye protection especially in busy and understaffed neonatal units where continual vigilant eye-care of infants receiving phototherapy may not be possible. The perspex head shields can be used if the serum bilirubin level is not too high. Position the shield over the infant's head but ensure that it is not too low down so as to prevent the phototherapy light from reaching the upper part of the body. The neonatal head has a much larger surface area ratio to their body, so use of a tinted shield risks covering a lot of area that could be exposed to the treatment lights [129].

Retinopathy of prematurity

Retinopathy of prematurity (ROP) is a multi-factorial disease, still not completely understood, in which free oxygen radicals seem to play a pivotal role. Since small premature infants have weaker intracellular defence mechanisms against oxygen radicals than term infants, theoretically, by promoting bilirubin, a potent *in vitro* antioxidant excretion, phototherapy could decrease the oxidation resistance in preterm infants and facilitate the development of ROP. However, the effects of neonatal bilirubin levels on the incidence of ROP, have yielded conflicting results. Whereas some authors [130-133] have found a marginally beneficial role for elevated bilirubin levels, others [134-137] have shown there is little significance to the levels, and some others [138-140] have found elevated bilirubin levels may be a risk factor for ROP.

In a recent a case-control study to examine the independent and combined effects of serum bilirubin and breast milk feeding on ROP risk in infants less than 32 weeks gestation or with birth weight less than 1,500 g has been shown that the peak bilirubin levels were lower in ROP cases than in controls (mean 7.2 vs. 7.9 mg/dL; $p = 0.045$) with a negative association between highest serum bilirubin level and risk of ROP (OR = 0.82 per 1-mg/dL change in bilirubin; $p = 0.06$) [141]. Therefore, further trials are required

to assess the risk of neonatal phototherapy on the development of ROP in with small preterm infants.

Hematological effects

The exposure of red cells to phototherapy light in the presence of bilirubin resulted in oxidative injury to the cellular membrane as manifested by a significant increase in the concentration of the products of lipid peroxidation in the membrane and hemolysis [142]. Increase in the mean end-tidal carbon monoxide (ETCO) provides a direct index of heme turnover, hemolysis and bilirubin production. Although in one study of preterm neonates standard phototherapy produced a modest, but statistically significant increase in the mean ETCO [143], a recent study no increased ETCO levels were determined in newborn infants ≥ 35 weeks gestation receiving intensive phototherapy [144]. Therefore phototherapy does not produce hemolysis in newborn infants. If phototherapy increases hemolysis in some newborns, this effect is generally small although there is a subgroup of infants who, for unknown reasons, (e.g. genetic) tend to hemolyze when exposed to phototherapy. An *in vitro* study shows that bilirubin may make the plasma membrane of normal erythrocytes more fragile, therefore newborns with hereditary spherocytosis may be sensitive to phototherapy [145]. However, the measurement of blood viscosity and erythrocyte aggregation and filtration do not show significant alterations during the overall time of phototherapy [146].

Mild or moderate, but usually asymptomatic and transient thrombocytopenia (platelet count below 150,000/cm^3) may be seen in 79% or newborn infants after 48 hours of phototherapy [147]. In the presence of bilirubin the *in vitro* irradiation of platelets with visible light induces significant lysis. The extent of platelet lysis is a function of irradiation time, being about 20% after 2 h of irradiation [148]. If pre-phototherapy the platelet count is low, it may fall after phototherapy. When bone marrow compensation is adequate, no platelet count difference is detected before and after phototherapy [149].

Transient DNA damage

Phototherapy may lead to oxidative injury to the cell membrane and, as a result, increases the levels of lipid peroxidation products [150]. Free oxygen radicals in excess may give rise to injury to host cells and may induce DNA strand breaks. Accumulation of DNA damage with time can lead to gene modifications in cells that may be mutagenic or carcinogenic. This is of particular concern for newborns, as they have a lower antioxidant activity if compared with adults. Single- and double-strand DNA breaks and oxidative modifications to DNA can lead to oxidative stress-related diseases such as necrotizing enterocolitis in newborn infants and even increase the risk for cancer development in their future life. An experimental study has demonstrated that apoptosis in the small intestine of neonatal rats that expose the abdomen to 72 h phototherapy light placed under 4-7 cm under wire netting flour [151].

Peripheral blood lymphocytes are commonly used to monitor environmentally induced genetic damage. DNA damage in lymphocytes is usually determined by use of the alkaline comet assay or sister chromatid exchange. Phototherapy causes DNA damage and induces apoptosis in peripheral blood lymphocytes of full-term infants [152-155]. Recently, both hyperbilirubinemia and phototherapy were found to enhance apoptosis of peripheral blood lymphocytes (increased the frequency of micronuclei and DNA fragmentation), probably through downregulation of *BCL2* gene (an anti-apoptotic oncogene) expression and upregulation of *BAX* gene (a promoter gene of apoptosis) expression [156].

Intensive and conventional phototherapies similarly increase DNA damage in newborns [157], and the DNA damage increased significantly with the duration of phototherapy [153, 155]. Although it has been demonstrated a strong correlation between admission STB levels and DNA damage frequency [158] and a significant increase in DNA fragmentation and micronuclei in lymphocytes of hyperbilirubinemic compared to non-hyperbilirubinemic neonates [156], hyperbilirubinemia does not probably induce DNA damage and apoptosis in peripheral blood lymphocytes of full-term infants [154, 155]. Before making a conclusion as hyperbilirubinemia does not influence DNA damage and apoptosis, more studies are needed.

Although DNA damage is induced in human cells through exposure to phototherapy light, these alterations do not result in immediate or widespread harmful consequences: in fact, no serious side effects have been reported in thousands of babies who had received phototherapy for management of hyperbilirubinemia for a long time. Furtermore, genotoxic effect of phototherapy is restricted within the phototherapy period only; after, DNA damage disappears [159]. This shows that human cells have

some capacity for the repair of phototherapy-induced DNA damage.

Testicular effects

Continuous phototherapy for 72 h on the newborn rat testicle decreases spermatogonia numbers per tubule, tubular fertilization index and sperm sertoli cell index which are the most reliable methods in estimating future fertility potential, without significant difference in DNA index [160, 161]. But these results have not been confirmed with human studies. Although damage of the gonads during phototherapy is unlikely because the period of exposure is relatively short and gonads are shielded by the skin over the subcutaneous tissue, in most of the neonatal wards infant's gonads keep covered during phototherapy with a small nappy or with the nappy tucked down as far as possible, to protect gonads from potentially harmful exposure to light. Diapers may be used for hygiene but are not essential for testicular protection [162].

Possible long-term side effects

Allergic diseases

Aspberg et al. [163] first found the association between neonatal phototherapy and an increased risk for childhood bronchial asthma in 2007. Allergic rhinitis are also more common in children who have history of jaundice and/or phototherapy during neonatal period [164]. Then several studies have found a link between neonatal hyperbilirubinemia and/or neonatal phototherapy and childhood allergic diseases. Since the number of patients in reported studies is small, further epidemiological research with larger groups is needed to evaluate this relationship [165-168].

In a recent systematic review a total of seven good quality studies including 101,499 children up to 12 yr of age, there is a significant increase in the odds of asthma and allergic rhinitis after neonatal hyperbilirubinemia [asthma, OR 4.26 (95% CI 4.04-4.5); allergic rhinitis, OR 5.37 (95% CI 4.16-6.92)] and after neonatal phototherapy [asthma, OR 3.81 (95% CI 3.53-4.11); allergic rhinitis, OR 3.04(95% CI 2.13-4.32)] [169]. Another large study (27,693 neonates with neonatal jaundice and 55,367 matched non neonatal jaundice cohorts) which was not evaluated in this systematic review, also found similar association between neonatal jaundice and the development of allergic diseases in early childhood. The incidence density and hazard ratios (HRs) of the five allergic diseases, namely allergic conjunctivitis, allergic rhinitis, atopic dermatitis, asthma, and urticaria are greater in the neonatal jaundice cohort than in the non neonatal jaundice cohort, and the HRs declined modestly with age. The HRs for allergic rhinitis (HR = 2.51, 95% confidence interval [CI] = 2.43-2.59) and atopic dermatitis (HR = 2.51, 95% CI = 2.40-2.62) are the highest, and that for urticaria was the lowest (HR = 2.06, 95% CI = 1.94-2.19). The HRs of allergic diseases are substantially greater for boys and those requiring phototherapy. The HRs of the allergic diseases, except urticaria (HR = 2.49, 95% CI = 1.57-3.97), were not significantly different between the neonatal jaundice regardless of whether the patients received exchange transfusion [168]. Such an association is also found between neonatal phototherapy and insulin-dependent diabetes mellitus (OR 1.95; 1.19-3.20) [170].

There are some speculations to explain the association between neonatal phototherapy and childhood allergic diseases. Immune competence is in a state of equilibrium between humoral immunity (Th-2 cells) and cellular immunity (Th-1 cells). Normally, the immune system shifts from mainly Th-2 immune responses towards more Th-1 responses after birth. Abnormalities in Th-2/Th-1 switch caused by environmental factors including phototherapy contribute in many allergic diseases during childhood and later in life. Phototherapy can cause changes in cytokine levels. Although there are no differences in serum IL-8, IL-10, IL-1beta, and TNF-alpha levels, but decreased IL-6 levels after 24 hours on phototherapy [171], at 72 h of exposure to phototherapy serum TNF-alpha, IL-1beta and IL-8 levels are increased, while the serum IL-6 level at the same time is not changed [172]. In addition the percentage of $CD3^+$ lymphocyte subset is significantly lower in newborns at 72 h of exposure to phototherapy [172]. Phototherapy also causes direct DNA damage to lymphocytes in jaundiced infants [154], and the DNA damage increases with the duration of phototherapy, at 24, 48, and 72 h ($p < 0.001$) [153]. These changes of cytokine levels, and DNA damage to lymphocytes may contribute to the Th-2/Th-1 switch disorder. Th-2/Th-1 switching disorder due to phototherapy may partly be due to decreased bilirubin levels, because bilirubin inhibits complement activation through the classical pathway [173] and prevents leukocyte migration [174]. The decreased bilirubin level induced by phototherapy may result in impaired antioxidant defense and airway damage, and contribute to later

development of asthma [164]. Eosinophilic cationic protein (ECP) is one of several highly basic proteins present in the secretory granule of the eosinophils and its increase reflects eosinophilic activation. Phototherapy increases ECP levels that may play a role in developing allergic diseases later in life [175].

Melanocytic nevi, melanoma, skin cancer, and café-au-lait macules

Increased numbers of common melanocytic nevi or clinically atypical melanocytic nevi are risk factors for the development of cutaneous melanoma [176]. In previous years, several studies have been made to investigate a possible association between neonatal blue light phototherapy and the development of common melanocytic nevi and clinically atypical melanocytic nevi in childhood. While some studies could show an increasing incidence of common melanocytic nevi or clinically atypical melanocytic nevi after neonatal blue light phototherapy [177-180], others could not confirm these results and did not find higher numbers of melanocytic nevi or melanoma after neonatal blue light phototherapy [181-183].

Twin studies showed increased numbers of common and atypical melanocytic nevi in association with neonatal blue light phototherapy [178, 179]. Environmental factors are usually similar in twins, and genetic traits are the same in monozygotic twins; hence, this type of study population seems to be ideal for comparison. However, the age of the twin pairs at the time of examination ranged from 3 to 30 years [179] and from 6 to 30 years [178], respectively. This finding was not supported later which was confined to an age group of 5 to 6 years [184]. These different results could be explained with the time of skin examination, since the development of nevi is generally increasing with age [185].

Differences in results could also be due to the ultraviolet A portion in the lamps used used for neonatal phototherapy. Unfortunately, information related to the type of light sources, information on devices and safety standards used for neonatal phototherapy is missing in most of the studies [177-181, 183]. In some earlier studies, the information on neonatal phototherapy was taken from the parents via questionnaires, making it difficult to provide exact details on the type of phototherapy, such as light source and intensity [177, 181, 183].

In the twin study conducted Csoma et al. [179], the emission spectrum of lamps ranged from 370 to 600 nm with approximately 0.3% ultraviolet A radiation. In the other twin study, the emission spectrum was blue light (460 to 490 nm) in accordance with safety standards and thus did not contain significant ultraviolet radiation [184]. Although it is postulated that the immature skin of preterm children could be more sensitive to blue light and may thus result in increased numbers of nevi [183], this is not confirmed later [184]. However, there is no independent study for preterm infants.

The relationship between neonatal phototherapy and skin cancer has also been studied. It seems that neonatal phototherapy is not a risk factor for melanoma [186] and squamous cell or basal cell carcinoma [187]. However, the follow-up time in these studies is within 30 years, which is not long enough for an observation of the development of skin cancer because the risk of skin cancer is relatively low in persons under the age of 30 years.

Although there is no reported risk of melanoma development from café-au-lait macules, a significantly higher prevalence of these macules was found in 5- to 6-year old children with neonatal blue light phototherapy. The association between café-au-lait macules and blue light is not known [184].

Uveal melanoma

Uveal melanoma is considered the second most common primary malignancy of the eye worldwide after childhood retinoblastoma. Moreover it is the principal fatal intraocular disease in adults. Uveal melanoma can be diagnosed at any age but it is more common in middle to later life. Although it is a relatively rare neoplasm, uveal melanoma is associated with particularly high mortality, primarily due to its association to a high level of metastatic liver disease. Ultraviolet exposure, coupled with specific skin pigment gene polymorphisms, is a prominent factor in the development of cutaneous melanoma. A link between ultraviolet exposure and uveal melanoma, as observed with cutaneous melanoma, has been suggested, but the evidence for this is not conclusive. These findings are consistent with the properties of the adult crystalline lens and cornea, which collectively filter out all wavelengths below 400 nm. Unlike ultraviolet radiation, blue light (400-500 nm) can reach the posterior uveal tract while retaining sufficient energy to be deleterious to biological structures. This damage can generally result in cell dysfunction or death, the main causes of cellular aging and age-related macular degeneration, but may also contribute to tumorigenesis, including uveal melanoma [188].

Blue light phototherapy has been reported to increase the risk of dysplastic nevus development in eye. A very interesting follow-up study of monozygotic and heterozygotic twins aged 3 to 30 years (in which one of each pair had received and one had not neonatal blue light therapy), found an increase in benign ocular pigmented lesions of the iris in the cohort who had received blue light therapy. Although broad-spectral emission bulbs are frequently used in this therapy (370-600 nm, maximal emission 450 nm), ultraviolet A contamination remains negligible at approximately 0.3% of output. These finding is surprising because eye protection is worn in neonatal blue light therapy; however, accidental removal of eye coverings may occur and the neonatal eye allows greater transmission of lower frequency blue light relative to the adult eye [179].

During neonatal phototherapy the nurses monitor babies periodically for around 10 minutes in every hour with most of them working within 30 cm of the phototherapy source from the direct or reflected radiation beam. Some of the equipment may present relevant spectral emission also in the ultraviolet A region. Taking into account that the exposure to ultraviolet in childhood has been established as an important contributing factor for melanoma risk in adults, it is recommended that special safety training be provided for the affected employees, in particular protective eyewear can be necessary during newborn assistance activities carried out in proximity of light sources [189].

Is phototherapy absolutely safe for small preterm infants?

Low bilirubin kernicterus in preterm neonates, though rare, remains an unpredictable and refractory form of brain injury. Despite compulsive attention to STB levels, hypoalbuminemia, co-morbid CNS insult(s), infection, and inflammation are contributing causes that, in many cases, appear to interact in potentiating bilirubin neurotoxicity. However, we have also to take into account the risks and benefits of any intervention, including phototherapy [190].

Prophylactic versus threshold phototherapy

A multi-center observational study shows that blue LEDs performed better than conventional fluorescent lights and fiberoptic blankets but similar to halogen spotlights in the treatment of preterm infants with hyperbilirubinemia [191]. This information could be important for starting phototherapy on ELBW infants with a high serum bilirubin level where a rapid response is desired to minimize the possibility of bilirubin encephalopathy, need for an exchange transfusion and exposure to phototherapy.

The efficacy and safety of prophylactic phototherapy in preventing jaundice in preterm infants were evaluated in a meta-analysis covering a total of nine clinical trials representing 3,449 infants. Based on the available data there is evidence that prophylactic phototherapy initiated soon after birth (within 36 hours) prevents a significant rise in unconjugated hyperbilirubinaemia, reduces the need for exchange transfusion and may reduce long-term neurodevelopmental impairment. Although a recent study shows that prophylactic phototherapy is not associated with any improvement in neonatal outcomes [192], further well-designed studies are needed to determine the efficacy and safety of prophylactic phototherapy on long-term outcomes including neurodevelopmental outcomes [191].

Lower (aggressive) versus high (conservative) threshold phototherapy

In infants weighing less than 1,000 g at birth who received conservative phototherapy (if serum bilirubin levels exceeded 8.8 mg/dL) has a tendency for poor neurodevelopmental outcome compared to in infants who received aggressive phototherapy (12 h of age) [193]. It has also been shown that among newborn infant who weighed less than 2,000 g at birth whether less than 1,000 g or not, there were no statistically significant differences in mortality between those infants who treated with phototherapy as compared with the control group [194]. To revaluate these findings, a multicenter, National Institute of Child Health and Human Development Neonatal Research Network randomized trial was conducted to compare the effects of aggressive-phototherapy with conservative-phototherapy on the incidence of death or neurodevelopmental impairment in 1,974 infants with extremely low birth weight (ELBW) at 18 to 22 months after the expected date of delivery (the corrected age). For infants with a birth weight of 501 to 750 g, the aggressive phototherapy was continued or restarted whenever the bilirubin level was found to be 5 mg/dL or higher. For infants with a birth weight of 751 to 1,000 g, the aggressive phototherapy was continued or restarted whenever the bilirubin level was found to be 5 mg/dL or higher during the first 7 days after birth and 7 mg/dL or higher during the next 7 days. Conservative phototherapy was initiated, continued, or restarted whenever the bilirubin level

was 8 mg/dL or higher for infants weighing 501 to 750 g at birth and 10 mg/dL or higher for infants weighing 751 to 1,000 g at birth [123].

Aggressive phototherapy, as compared with conservative phototherapy, significantly reduced the mean peak serum bilirubin level but not the rate of death. The rate of neurodevelopmental impairment at 18 to 22 months was lower with aggressive phototherapy than with conservative therapy (26% vs. 30%; relative risk, 0.86; 95% CI, 0.74 to 0.99). In subgroup analyses, the rates of death were 39% with aggressive phototherapy and 34% with conservative phototherapy for infants with a birth weight of 501 to 750 g (relative risk, 1.13; 95% CI, 0.96 to 1.34), although the rates of death were similar in both groups in infants with a birth weight of 751 to 1,000 g. However, aggressive phototherapy did reduce neurodevelopmental impairment at 18-22 months corrected age (after term) (RR = 0.86; [0.74-0.99]), a reduction due almost entirely to a reduction in profound impairment (RR = 0.68; [0.52-0.89]) [123]. The possibility that aggressive phototherapy increases mortality of ventilated infants ≤ 750 g BW treated is supported by our Bayesian analyses performed to complement the frequentist analyses [195].

Therefore, aggressive phototherapy may be preferred for infants with birth weights of 751 to 1,000 g, because of significant neurodevelopmental benefits in this subgroup and no evidence that the therapy increased the rate of death or other adverse outcomes at 18 to 22 months. However, for infants with a birth weight of 501 to 750 g, the possibility that increased mortality may offset any potential benefits of aggessive phototherapy must be considered [123].

Increased mortality after neonatal phototherapy in infants less than 750 may be explained with reduced tissue bilirubin levels. It is controversial whether modest elevations of serum bilirubin cause brain damage in preterm infants. Some observational studies of preterm infants have suggested that bilirubin levels as low as 5 mg/dL or even lower may cause neurodevelopmental deficits [131, 196]. However, other observational studies have suggested that moderately higher bilirubin levels have no neurotoxic effects [146, 197] or might even benefit these infants [198], because bilirubin is a powerful antioxidant. The reduction in bilirubin with phototherapy might increase the susceptibility of extremely low birth weight (1,000 g or less) infants whose skin readily transmits light and who would be most vulnerable to oxidative injury.

Bilirubin is a non-enzymatic endogenous anti-oxidant. Low concentrations of bilirubin scavenge reactive oxygen species (ROS), reduce oxidant-induced cellular injury and attenuate oxidant stress. Physiologic jaundice is accepted as a protective mechanism for the newborn infant against ROS in the first days of life [195, 199, 200]. Furthermore in term neonates total bilirubin up to 20 mg/dL has a positive correlation with total antioxidant capacity (TAC) and negative correlation with malondialdehyde (MDA), an important marker of lipid peroxidation [201].

However, in preterm infants, STB level does not exert a meaningful antioxidant effect *in vivo*; heme oxygenase does not exert a pro-oxidant effect involving an non-transferrin-bound iron increase and that, on the contrary, it could exert an antioxidant effect; and the concurrent heme oxygenase and erythrocyte CuZn superoxide dismutase activity increase could indicate a synergic antioxidant effect of the two enzymes [202].

In addition to STB lowering effect, phototherapy induces the release of cutaneous reactive nitrogen species and reactive oxygen species, and photolysis products that are cytotoxic and are associated with the production of free oxygen radicals. In term and late-preterm infants phototherapy leads to lower TAC levels, and increase oxidative stress index (OSI) regardless of the type of the light source and intensity with a weak but significant correlation between the decline in STB and decrease in TAC. Serum total oxidant status (TOS) increases after conventional phototherapy with blue fluorescent lights and intensive LED phototherapy with high irradiances and to a lesser extent after intensive LED phototherapy with low irradiances [203].

Nevertheless, decrease in TAC cannot be attributed to decrease in antioxidant bilirubin alone which has only a small contribution (2.4%) to TAC. Other components of TAC are probably affected by phototherapy as well. Serum vitamin C and uric acid which are non-enzymatic antioxidants decrease, whereas serum TAC does not change significantly 48 h after phototherapy in term neonates although serum TOS, lipid hydroperoxide and finally OSI are higher after phototherapy [204]. In term neonates after phototherapy reduced TAC and glutathione significantly decrease whereas MDA, superoxide dismutase and catalase increase [142]. All these results show that phototherapy disturb oxidant/antioxidant balance in favor of oxidants.

Vigintiphobia: use or abuse of phototherapy

Current recommendations for evaluating and treating jaundice in term babies include a strict

monitoring of all babies closely for jaundice, obtaining several laboratory tests in those with early jaundice or bilirubin levels more than 12 to 13 mg/dL, using phototherapy to try to keep bilirubin levels below 20 mg/dL, and doing exchange transfusions if phototherapy fails, regardless of the cause of the jaundice. This is called "vigintiphobia" (fear of 20). Most of the experts believe that hyperbilirubinemia in "healthy" infants without other complications is overtreated, and the recommendations are likely to lead to unnecessary testing and treatment of jaundiced term infants [205]. Bilirubin toxicity is rare in term babies without hemolysis, most jaundiced infants have no underlying illness, and jaundice subsided spontaneously in most of these mature infants. In this low-risk group, the risks and cost of identifying and treating high bilirubin levels may exceed the benefits. New treatment recommendations that are less aggressive than those recommended previously were set forth.

New treatment recommendations that are less aggressive than those recommended previously were set forth, including a goal of keeping STB levels below 23.4-29.2 mg/dL among healthy term infants without hemolytic disease, with either phototherapy (treatment threshold 17.5-22 mg/dL) or exchange transfusion (treatment threshold: 25-29 mg/dL) [206]. In contrast to many previous jaundice management recommendations, serum bilirubin treatment thresholds were given as ranges rather than as single numbers. However, newborns with hemolytic disease should be followed more closely, and their bilirubin levels kept below 20 mg/dL [207]. These recommendations should be reevaluated continuously [208].

Because there is no consensus on the level of STB for which therapy should be initiated, the use of neonatal phototherapy currently varies widely, especially for preterm infants. As it is to difficult to quantify the risk of bilirubin-associated brain damage, prophylactic phototherapy to prevent infants from bilirubin encephalopathy has been over-used in clinical practice, possibly resulting in many unnecessarily irradiated babies in the neonatal intensive care unit. Although phototherapy is assumed to be both effective and safe for ELBW infants, as mentioned above phototherapy has some potential side effects in these infants. The best current strategy for phototherapy is to use it only when really needed, considering risks and benefits, and following the officially available guidelines. Therefore strategies to optimize the risk/benefit ratio in achieving low STB, e.g., use of lowered irradiance levels, LED phototherapy units, and cycled (intermittent) phototherapy, deserve rigorous evaluation [209].

Declaration of interest

The Author declares that there is no conflict of interest.

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