# Role of Phototherapy in Neonatal Hyperbilirubinemia

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## Abstract

Phototherapy is a simple treatment for neonatal hyperbilirubinemia. During phototherapy, the bilirubin in the neonatal body is changed into another form that can be easily excreted in the stool and urine. Phototherapy devices include halogen lamp, fluorescent, light emitting diode light sources. It is important that phototherapy is applied correctly to combat increased bilirubin production. Light in the wavelength range of 450–475 nm (blue) is the most effective because it overlaps the peak absorption spectrum of bilirubin. The effectiveness of phototherapy is dependent upon four major factors: Color of the light, Intensity of the light, Exposed body surface area and Duration of exposure. It is a safe and easily available treatment worldwide and the side effects of phototherapy are discussed.

**Keywords:** Phototherapy; Hyperbilirubinemia; Neonate; Irradiance.

## Introduction

Phototherapy is considered to be a safe and effective method for treatment of neonatal unconjugated hyperbilirubinemia [1]. Neonatal jaundice is a common condition in newborn babies, affecting about 50% of term and 80% of preterm babies in the first week of life. In physiological jaundice bilirubin levels do not increase to a level that requires treatment. However, in exaggerated physiological jaundice, and infants with pathological jaundice, bilirubin in the blood reaches very high levels that put the infant at risk for acute encephalopathy. The effective treatments to decrease serum bilirubin levels include phototherapy and exchange transfusion [2]. The effect and the ability of light to decrease serum bilirubin levels, was first described by Cremer et al. in 1958 [3]. This observation led to the development of phototherapy for use in the treatment of neonates with hyperbilirubinemia. The exchange transfusions are used as a rescue therapy to avoid kernicterus in newborns with severe jaundice when phototherapy is inadequate [4].

## Mechanism of Action

The basic mechanism of action of phototherapy is the use of phototherapy to transform bilirubin into more hydrosoluble products that can be excreted by the body. When bilirubin absorbs light, three types of photochemical reactions occur [3-5].

1. *Photoisomerization* occurs in the extravascular space of the skin. The natural isomer of unconjugated bilirubin (UCB) (4Z,15Z) is rapidly converted to a less toxic polar isomer (4Z,15E) that diffuses into the blood and is excreted into the bile without conjugation. However, excretion is slow, and the photoisomer is readily converted back to UCB, which is resorbed from the gut if the baby is not having stools. Configurational isomerization is reversible. The configurational isomers of bilirubin are less lipophilic than normal bilirubin and can be excreted into bile without undergoing glucuronidation in the liver. Some of the configurational isomers of bilirubin, however, revert back to the native form after excretion into bile and can be reabsorbed via enterohepatic circulation in the gut. After

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approximately 12 hours of phototherapy, the photoisomers make up approximately 20% of total bilirubin. Standard tests do not distinguish between naturally occurring bilirubin and the photoisomer, so bilirubin levels may not change much although the phototherapy has made the bilirubin present less toxic.

2. *Structural isomerization* is the intramolecular cyclization of bilirubin to lumirubin. Lumirubin makes up 2% to 6% of serum concentration of bilirubin during phototherapy and is rapidly excreted in the bile and urine without conjugation. Unlike photoisomerization, the conversion of bilirubin to lumirubin is irreversible, and it cannot be reabsorbed. Structural bilirubin isomers, like Z-lumirubin, can also be excreted in the urine.

3. The slow process of photo-oxidation converts bilirubin to small polar products that are excreted in the urine. The absorptions of light by bilirubin also results in the generation of excited-state bilirubin molecules that react with oxygen to produce colorless oxidation products, or photooxidation products. It is the least important reaction for lowering bilirubin levels. This process occurs more slowly than configurational or structural isomerization. Photooxidation products are primarily excreted in the urine.

**Indications for Phototherapy**

The indication of phototherapy is only in the treatment of unconjugated hyperbilirubinemia although it has not reached levels requiring exchange transfusion. If indirect bilirubin level is high in the presence of conjugated hyperbilirubinemia, exchange transfusion is the indication. Prophylactic phototherapy may be indicated in special circumstances, such as with extremely low birth weight babies, when the TSB is anticipated to increase rapidly. A commonly used rule of thumb in the Special Neonatal Care Unit (SNCU) is to start phototherapy when the total serum bilirubin level is greater than 5 times the birth weight [3,6].
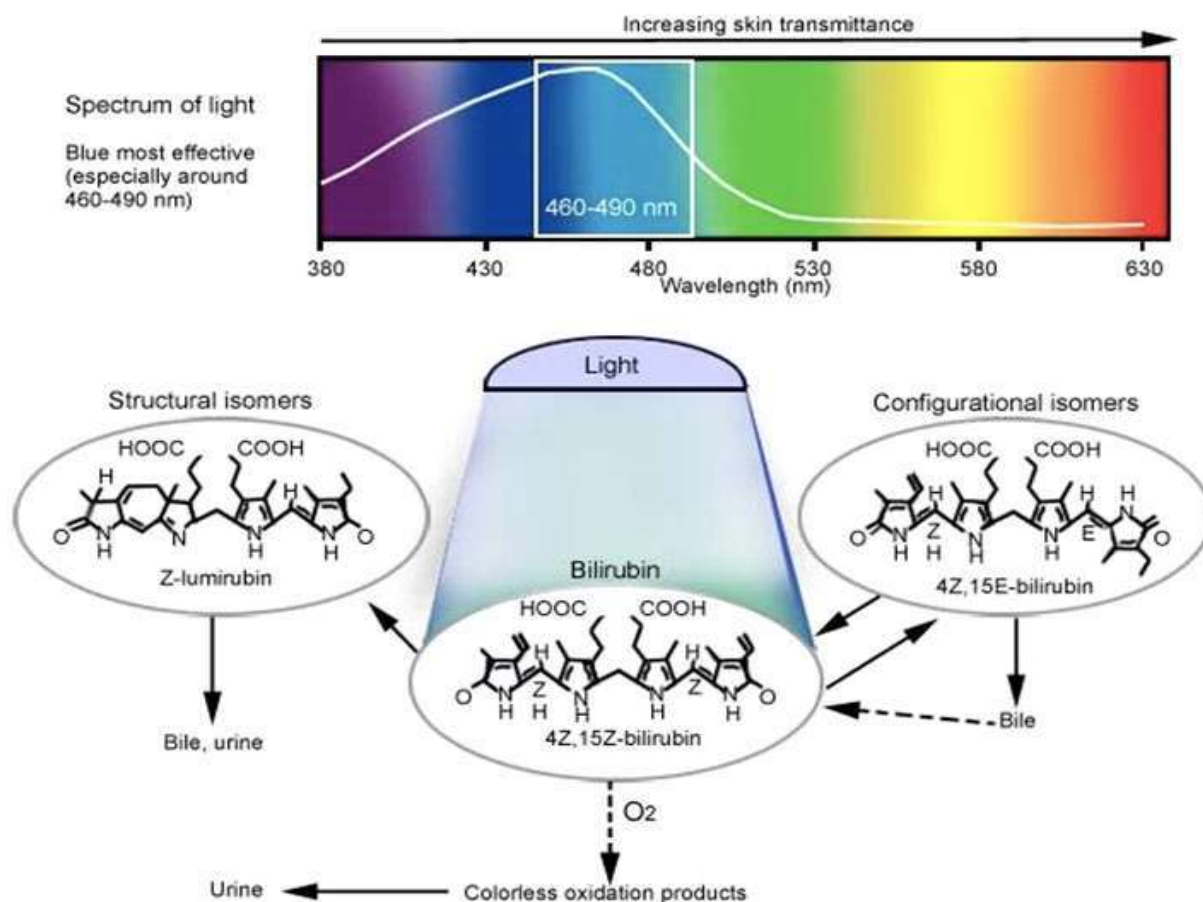


Fig. 1: Shows the Mechanism of phototherapy

**Contraindications for Phototherapy**

The concomitant use of photosensitizing medications, congenital erythropoietic porphyria, or a family history of porphyria are contraindications to phototherapy. It is usually contraindicated in infants with direct hyperbilirubinemia caused by liver disease or obstructive jaundice. Because it may lead to the "bronze baby" syndrome [7].

**Ceasing Phototherapy**

Phototherapy should be given until serum bilirubin comes down to safe level i.e. below 10 mg/dl Rechecking the bilirubin level after cessation of phototherapy is not usually required unless increased risk of significant rebound is there as in haemolytic disease. In these circumstances, a bilirubin level is to be checked 12 hours after cessation of phototherapy [5-8].

The Effectiveness of Phototherapy is dependent upon four major factors: color of the light, intensity of the light, exposed body surface area and duration of exposure.

*a. Color & Wavelength of the Light*

*Color of the 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 (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.
- *Blue light* in the narrow wavelength band of 450-475 nm is the most closely matched and hence the most effective type of light in degrading bilirubin [6,7].
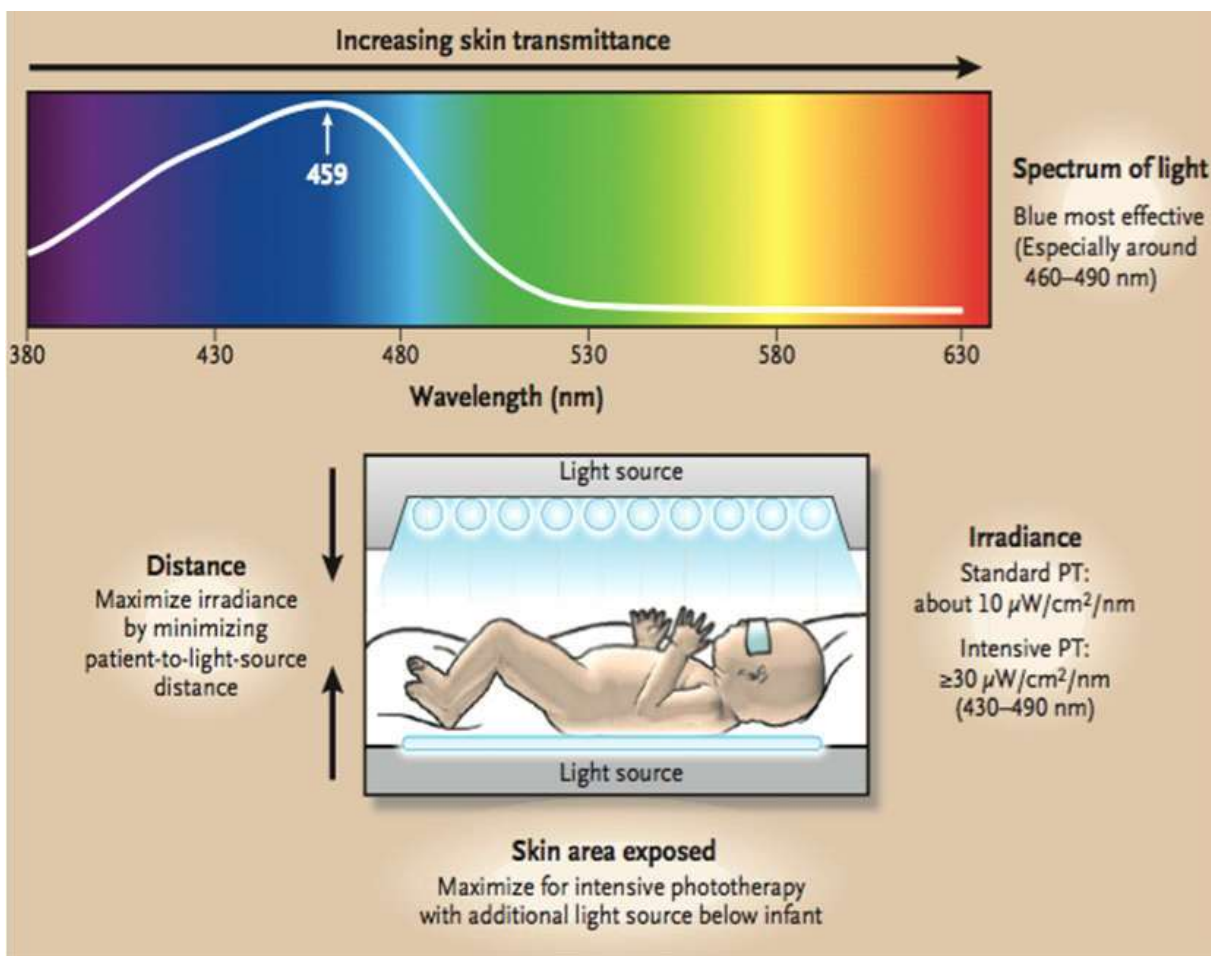


**Fig. 2:** Shows the effectiveness of phototherapy

*Turquoise (blue-green) 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.

*Light Wavelengths:* Bilirubin is a yellow pigment absorbs visible light with wavelengths of approximately 400 to 500 nm, the most effective lights for phototherapy are those with high energy output near the maximum absorption peak of bilirubin (450–460 nm).

*Special blue lamps* with a peak output at 425 to 475 nm are the most efficient for phototherapy. Blue fluorescent lamps have been used worldwide with peak emission at 452 nm providing more photoisomerization than green light or daylight

*Cool white lamps* with a principal peak at 550 to 600 nm and a range of 380 to 700 nm are usually adequate for treatment.

The most effective light in vivo is probably in the blue to green region (460-490nm). A turquoise fluorescent source with peak intensity near 490 nm is significantly more effective than blue or green fluorescent lamps in reducing the duration of phototherapy [7-13].

### b. Light Irradiance

Light intensity or energy output is defined by irradiance and refer to the number of photons (spectral energy) that are delivered per unit area (cm2) of exposed skin. The dose of phototherapy or "irradiance" which determines the effectiveness of treatment. It is reported in watts per square meter (irradiance) or in microwatts per square cm per nm (μW/cm2/nm) over a certain wavelength band (spectral irradiance). The higher the irradiance the larger the rate of serum total bilirubin (STB) decline. There may be a saturation point at 30 mW/cm2/nm where an increase in irradiance has no benefit in decreasing STB levels. Therefore phototherapy devices should be used to deliver at least 30 mW/cm2/nm. The flux or irradiance must be checked once a week with radiometer or spectroradiometer and tubes should be replaced when their flux falls below 15mW/cm2/nm. Conventional daylight phototherapy lamps deliver an irradiance of approximately 8-10 μW/cm2/nm. Special blue fluorescent lamps irradiance of 30-40 μW/cm2/nm. The irradiance of different phototherapy devices varies widely and is dependent on the number and distance of the light source from the neonate [14-15].

### c. Exposed Surface Area

Effective treatment for hyperbilirubinemia is dependent on exposing the infant's surface area to phototherapy as possible. The greater the area exposed, the greater the efficacy of phototherapy. When using spotlights, multiple devices may be necessary to ensure proper surface area coverage. When using banks of lights, caregivers must ensure that the intensity delivered to the entire surface area is within the effective intensity range.

### d. Duration

More effective phototherapy treatments will degrade bilirubin to safe levels faster resulting in shorter treatment times, especially with dangerously high bilirubin levels. During phototherapy, neonate's temperature will be monitored to ensure they are not getting too hot and they will be checked for signs of dehydration. Neonate's need to have intravenous fluids if they are becoming dehydrated and are not able to drink a sufficient amount. The bilirubin levels will be tested every four to six hours after phototherapy has started. Once levels start to fall, they will be checked every 6 to 12 hours. Phototherapy will be stopped when the bilirubin level falls to a safe level, which usually takes a day or two. The longer an infant is exposed to the phototherapy light, will increase the effectiveness of the treatment [14-18].

### Administering Phototherapy

The room temperature is optimum to prevent hypothermia or hyperthermia. Neonates should be nursed naked apart from a nappy under phototherapy. Place the neonate below the phototherapy unit. The distance from the phototherapy units to the infants is 30-45 cm because the heat formation from the fluorescent tubes risked overheating the infants at reduced distance. Expose as much of the skin surface as possible to the phototherapy light. Check flux with help of fluxmeter. Ideal 6-8 mw/cm2/nm.Cover the eyes with appropriate opaque eye covers. Phototherapy is switched on. Baby is turned every two hours or after each feed. Ensure optimum breasfeeding. Baby can be taken out for brestfeeding and the eye patch can be removed for better mother-infant interaction. Monitor vital signs and temperature at least 4 hourly, more often if needed. Ensure that phototherapy unit is turned off during collection of blood for TSB levels, as both conjugated and unconjugated bilirubin are photo-oxidized when exposed to white or

ultraviolet light. Observe for signs of potential side effects. Serum bilirubin is monitored at least every 12 hours. Phototherapy is discontinued if two serum bilirubin values are < 10 mg/dl. Rebound bilirubin is measured 6-8 hours after stopping phototherapy [2-7].

**Phototherapy Devices & Light Source**

In the management of neonatal jaundice, different phototherapy devices are being used worldwide. Two types of phototherapy devices are currently available: Conventional phototherapy device and Fiberoptic phototherapy device.

*A. Conventional phototherapy devices*

*The common light sources used in these devices are* conventional long Fluorescent-tube devices, halogen lamps with wide emission spectrum, Light-emitting diodes (LEDs) lights.

1. Conventional long Fluorescent-tube devices 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.

2. Halogen bulbs / Spotlight Spotlight phototherapy units generally use a 150 Watt, 21V halogen bulb with a specially coated reflector which absorbs infrared wave length. A fan continuously cools the hot bulb. Options for varying aperture diameter and different filters are available. Positioning of the light on the baby is critically important in maximizing the spotlight's effectiveness. They are most effective when located directly above the infant at a distance of 45-50cm. A few halogen spotlights incorporate a dosimeter which depicts how much dose of phototherapy the baby has received. It considers the total irradiance received by the baby and multiplies this by the duration in hours.

3. Compact Fluorescent Tubes These are short (approx. 5 to 7 inch) double folded tubes (9-18 Watts) that emit blue or white light. Several tubes [6-8] are housed in a panel with reflectors. As they do not produce much heat the distance to baby can be relatively short thus increasing the irradiance delivered. Most of them produce an irradiance of 20-30 $W/cm2/nm$ when placed close to the baby.

4. Light-emitting diodes (LEDs) 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. It does not appears to have a significant effect on transepidermal water loss. It has useful features such as light weight, compact size, non-fragile and an ability to be focused with a lens or through spatial orientation, in addition lasting durability without decreasing in intensity with age (at least 3,000 hours). 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 [15-19].

**B. Fiberoptic Phototherapy Devices / Fiber-Optic Pads**

In Fiberoptic phototherapy, 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. It 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. In recent models, the halogen light source has been replaced by high intensity high power LED bulbs. This increases the irradiance delivered by the pads [20].

*Filtered Sunlight*

Using direct sunlight for phototherapy has a number of clinical and practical drawbacks that could make its use undesirable. Sunlight contains 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 [21].

## 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 [22-23]. 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 [24].

### Reflecting lights

Aluminum foil or white cloth placed on either side of the infant to reflect light will increase irradiance. 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. Use of mirrors behind the bulbs in tunnel phototherapy units may lower STB levels earlier [25-26].

### Intermittent Vs Continuous Phototherapy

Phototherapy does not need to be continuous. Phototherapy may be interrupted during feeding or brief parental visits. If the infant's bilirubin level is approaching the exchange transfusion level, phototherapy should be administered continuously until a satisfactory decline in the serum bilirubin level occurs or exchange transfusion is initiated [2-8].

## Intensive Phototherapy

Intensive phototherapy is recommended for those with " higher risk" based on age specific nomograms. It implies the use of high levels of irradiance in the 430 to 490 nm band ( usually 30 microwatt/cm2/nm or more) with the aid of two or more light sources (combination of overheads, spots, biliblankets) delivered to as much of infant's surface area as possible. The overheads should be placed as close as to the baby as possible without causing hyperthermia or burn. Normally, bilirubin should decline by 1-2 mg/dl within 4-6 hours of intensive phototherapy and continue to decline and remain below the threshold level for exchange transfusion. Failure of intensive phototherapy is said to occur and hence an indication for exchange transfusion when this predicted normal fall in serum bilirubin does not occur.Thermal-neutral lights, such as LEDs, can be placedto provide intensive phototherapy while reducing the potential risk of thermal injury or fluid loss [5-7].

## Side Effects of Phototherapy [27-35]

1. *Insensible water loss* is increased in infants undergoing phototherapy, especially those under radiant warmers.

2. *Redistribution of blood flow.* In term neonates, left ventricular output and renal blood flow velocity decrease, whereas left pulmonary artery and cerebral blood flow velocity increase. After discontinuation of phototherapy, all velocities return to baseline. In pretermneonates, cerebral blood flow velocity also increases and renal vascular resistance increases with a reduction of renal blood flow velocity. In addition, in preterm neonates under conventional phototherapy, it has been shown that the usual postprandial increase in superior mesenteric blood flow is blunted. Although the changes in cerebral, renal, and superior mesenteric arteryblood flow with phototherapy treatment in preterm infants is of potential concern,no detrimental clinical effects due to these changes have been determined.

3. *Watery diarrhea and increased fecal water loss* may occur. The diarrhea may be caused by increased bile salts and unconjugated bilirubin in the bowel.

4. *Retinal damage* has been described in animals whose eyes have been exposed to phototherapy. The eyes should be shielded with eye patches.

5. *Tanning* of the skin of infants. During exposure to light, infants skin gets bleached. The clinical evalation of jaundice severity becomes unreliable in babies receiving phototherapy and hence serum bilirubin level should be monitered every 6-8 hourly. Erythema and increased skin blood flow may also be seen.

### Hyperthermia

LED phototherapy with low irradiances does not cause significant hyperthermia similar to conventional phototherapy with blue fluorescent light. LED phototherapy with high irradiances (60-120 μW/cm2/nm) significantly increases body temperature in hyperbilirubinemic newborns compared to infants who received conventional phototherapy with fluorescent lamps (10-15 μW/cm2/nm) or LED phototherapy (26-60 μW/cm2/nm). Thus the increase in body temperature is a function of increase of irradiance rather than the type of the light source. 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.

### Skin Rashes

Skin rash were noted in the super (high-intensity, or high-irradiant LED) group compared with the fluorescent tubes-treated group. Erythema and increased skin blood flow may also be seen.

*Bronze baby syndrome (BBS)* The bronze-baby syndrome (BBS) is a rare side-effect of phototherapy which causes the appearance of grey-brown discoloration of skin. It is harmless, and pigmentation returns slowly to normal if phototherapy is discontinued. Infant with parenchymal liver disease with biliary obstruction may develop peculiar bronz of skin due to excessive accumulation of one of the photoisomers designated as lumirubin retained and polymerized to Bilifuscin imparting brownish discoloration to skin.

### Hypocalcemia

Phototherapy can lead to decreased total and ionized calcium levels of neonates, especially in preterm neonates. This effect might be attributable to increased urinary calcium excretion. In addition, light can affect calcium homeostasis by inhibiting pineal secretion of melatonin and consequently leading to hypocalcemia.

## 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 Ca2+-dependent K+ ion channels. 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. Phototherapy has been reported to increase the heart rate, diminish the mean arterial blood pressure and increase peripheral blood flow. 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 VLBW infants.

Mutations, sister chromatid exchange, and DNA strand breaks have been described in cell culture.

Tryptophan is reduced in amino acid solutions exposed to phototherapy

Maternal-infant separation – this can interfere with bonding and breastfeeding but can be minimised by utilising Bilibeds on the postnatal wards when appropriate.

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. Changes in peripheral blood flow and cardiac output during conventional phototherapy may also contribute to ileus during conventional phototherapy in preterm neonates.

In some infant, platelet turnover may be increased resulting in lower mean platelet count but bleeding does not occur.

Recent studies have suggested that phototherapy is associated with an increased risk for childhood bronchial asthma. Allergic rhinitis are also more common in children who have history of jaundice and/or phototherapy during neonatal period.

## Conclusion

Phototherapy is the use of visible light which is safe and easy to use for the treatment of hyperbilirubinemia in the newborn.

## References

1.  Singh M. Jaundice. In Care of the Newborn. Eds: Singh M. 8 th edn; Sagar Publications, New Delhi 2004.

2.  Maisels MJ, Baltz RD, Bhutani V, et al. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114:297–316.

3.  American Academy of Pediatrics, Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of Pediatrics. 2004;114(1):297–316.

4.  Cremer RJ, Perryman PW, Richards DH. Influence of light on the hyperbilirubinaemia of infants. Lancet. 1958;1(7030):1094-7.

5.  Maisel MJ, McDonagh AD. Phototherapy for Neonatal Jaundice. N Engl J Med. 2008;358:920-928.

6.  Muchowski KE. Evaluation and treatment of neonatal hyperbilirubinemia. Am Fam Physician. 2014 Jun 1; 89(11):873-8.

7.  Martin CR, Cloherty JP. Neonatal hyperbilirubinemia. In Manual of Neonatal Care. In Cloherty JP, Eichenwald EC, Stark AR. (eds) 8 th edn; Philadelphia, Lippincott Williams & Wilkins.2004 .

8.  Ennever JF, Sobel M, McDonagh AF, Speck WT. Phototherapy for neonatal jaundice: in vitro comparison of light sources. Pediatr Res. 1984;18(7):667-70.

9.  Costarino AT Jr, Ennever JF, Baumgart S, Speck WT, Polin RA. Effect of spectral distribution on isomerization of bilirubin in vivo. J Pediatr. 1985;107(1):125-8.

10. Ebbesen F, Madsen P, Stovring S, Hundborg H, Agati G. Therapeutic effect of turquoise versus blue light with equal irradiance in preterm infants with jaundice. Acta Paediatr. 2007;96(6):837-41.

11. Donzelli GP, Pratesi S, Rapisardi G, Agati G, Fusi F, Pratesi R. 1-Day phototherapy of neonatal jaundice with blue-green lamp. Lancet. 1995;346(8968):184-5.

12. Seidman DS, Moise J, Ergaz Z, Laor A, Vreman HJ, Stevenson DK, Gale R. A prospective randomized controlled study of phototherapy using blue and blue-green light-emitting devices, and conventional halogen-quartz phototherapy. J Perinatol. 2003;23(2):123-7.

13. Ebbesen F, Madsen P, Støvring S, Hundborg H, Agati G. Therapeutic effect of turquoise versus blue light with equal irradiance in preterm infants with jaundice. Acta Paediatr. 2007;96(6):837-41.

14. Vandborg PK, Hansen BM, Greisen G, Ebbesen F. Dose-response relationship of phototherapy for hyperbilirubinemia. Pediatrics. 2012;130(2):e352-7.

15. 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. 2011;128(4):e1046-52.

16. Agati G, Fusi F, Pratesi R, McDonagh AF. Wavelength dependent quantum yield for Z'!E isomerizarion of bilirubin complexed with human serum albumin. Photochem Photobiol. 1992;55(2):185-90.

17. Zonios G, Bykowski J, Kollias N. Skin melanin, hemoglobin and light scattering properties can be quantitatively assessed in vivo using diffuse reflectance spectroscopy. J Invest Derm. 2001;117(6):1452-57.

18. Lamola AA, Bhutani VK, Wong RJ, Stevenson DK, McDonagh AF. The effect of hematocrit on the efficacy of phototherapy for neonatal jaundice. Pediatr Res. 2013;74(1):54-60.

19. Okada H, Abe T, Etoh Y, Yoshino S, Kato I, Iwaki T, Okubo K, Yasuda S, Kawada K, Kusaka T, Namba M, Nishida T, Imai T, Isobe K, Itoh S. In vitro production of bilirubin photoisomers by light irradiation using neoBLUE. Pediatr Int. 2007;49(3):318-21.

20. Mills JF, Tudehope D. Fibreoptic phototherapy for neonatal jaundice. Cochrane Database Syst Rev. 2001;(1):CD002060.

21. Slusher TM, Vreman HJ, Olusanya BO, Wong RJ, Brearley AM, Vaucher YE, Stevenson DK. Safety and efficacy of filtered sunlight in treatment of jaundice in African neonates. Pediatrics. 2014;133(6):e1568-74.

22. Nuntnarumit P, Naka C. Comparison of the effectiveness between the adapted-double phototherapy versus conventional-single phototherapy. J Med Assoc Thai. 2002;85(Suppl 4):S1159-66.

23. Romagnoli C, Zecca E, Papacci P, Vento G, Girlando P, Latella C. Which phototherapy system is most effective in lowering serum bilirubin in very preterm infants? Fetal Diagn Ther. 2006;21(2):204-9.

24. Boonyarittipong P, Kriangburapa W, Booranavanich K. Effectiveness of double-surface intensive phototherapy versus single-surface intensive phototherapy for neonatal hyperbilirubinemia. J Med Assoc Thai. 2008;91(1):50-5.

25. Hansen TW. The role of phototherapy in the crash-cart approach to extreme neonatal jaundice. Semin Perinatol. 2011;35(3):171-4.

26. Sivanandan S, Chawla D, Misra S, Agarwal R, Deorari AK. Effect of sling application on efficacy of phototherapy in healthy term neonates with nonhemolytic jaundice: a randomized conrolled trial. Indian Pediatr. 2009;46(1):23-8.

27. Aydemir O, Soysaldý E, Kale Y, Kavurt S, Bas AY, Demirel N. Body temperature changes of newborns under fluorescent versus LED phototherapy. Indian J Pediatr. 2014;81(8):751-4.

28. Kurt A, Aygun AD, Kurt AN, Godekmerdan A, Akarsu S, Yilmaz E. Use of phototherapy for neonatal hyperbilirubinemia affects cytokine production and lymphocyte subsets. Neonatology. 2009;95(3):262-6.

29. Clark CF, Torii S, Hamamoto Y, Kaito H. The "bronze baby" syndrome: postmortem data. J Pediatr. 1976;88(3):461-4.

30. Eghbalian F, Monsef A. Phototherapy-induced hypocalcemia in icteric newborns. Iran J Med Sci. 2002;27(4):169-71.

31. Hooman N, Honarpisheh A. The effect of phototherapy on urinary calcium excretion in newborns. Pediatr Nephrol. 2005;20(9):1363-4.

32. Venturini CM, Palmer RM, Moncada S. Vascular smooth muscle contains a depletable store of a vasodilator which is light-activated and restored by donors of nitric oxide. J Pharmacol Exp Ther. 1993;266(3):1497-500.

33. Benders MJ, Van Bel F, Van de Bor M. Cardiac output and ductal reopening during phototherapy in preterm infants. Acta Paediatr. 1999;88:1014-9.

34. Bader D, Kugelman A, Blum DE, Riskin A, Tirosh E. Effect of phototherapy on cardiorespiratory activity during sleep in neonates with physiologic jaundice. Isr Med Assoc J. 2006;8(1):12-6.

35. Liu GS, Wu H, Wu BQ, Huang RZ, Zhao LH, Wen Y. Effect of phototherapy on blood endothelin and nitric oxide levels: clinical significance in preterm infants. World J Pediatr. 2008;4(1):31-5.