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REVIEW

The side effects of phototherapy for neonatal jaundice: what do we know? What should we do?

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Abstract Neonatal phototherapy (NNPT), a noninvasive, easily available therapy, has been widely used for the treatment of neonatal jaundice for more than half a century. Its efficiency in decreasing plasma bilirubin concentration is well documented, and NNPT leads to greatly reduced exchange transfusion rates for neonates with hyperbilirubinemia. It is generally accepted that the side effects of NNPT are not serious and seem to be well controlled. This review will focus on these possible side effects as well as the approaches to minimize them.

Keywords Jaundice · Newborn infant · Phototherapy · Side effect

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Introduction

Neonatal jaundice, the yellow coloration of the sclera and skin caused by hyperbilirubinemia, is one of the most common conditions confronting neonatologists daily. About 60% of term and 80% of preterm infants develop jaundice in the first week of life [74]. Bilirubin encephalopathy is a devastating brain injury, which can cause permanent neurodevelopmental handicaps [62]. Fortunately, a noninvasive and easily available treatment, neonatal phototherapy (NNPT), is effective in degrading unconjugated bilirubin. Following the discovery of NNPT in the 1950s, many clinical trials have addressed its application to neonatal jaundice [42]. In 1985, the National Institute of Child Health and Human Development reported that NNPT was as effective as exchange transfusion in preventing neurological sequelae [26]. Since then, NNPT has been widely adopted as the initial therapy of choice for hyperbilirubinemia. When comparing blue, blue-green, green, and white light, researchers found that blue light was the most effective in degrading bilirubin [94]. Therefore, NNPT with blue light is generally used in the clinical practice. The spectrum (380–550 nm) of blue light consists mainly of visible light with a peak at 450 nm and a minor component of ultraviolet (UV) light [18]. NNPT reduces serum bilirubin levels by converting bilirubin through structural photoisomerization and photo-oxidation into excretable products. The principal sites of NNPT action may localize not only in the skin but also in capillary circulation under the skin [42]. Recent studies have shown a possible relationship between NNPT and several complications. In a multicenter randomized controlled trial (RCT), aggressive phototherapy may have increased the mortality among infants weighing 501 to 750 g [69]. These

findings have drawn the attention of pediatricians to the potential side effects of NNPT.

Short-term side effects of NNPT

Interference with maternal–infant interaction

NNPT separates neonates from mothers, which might interfere with establishing parent–child bonding. For infants, NNPT affects neonatal behavior, including visual and auditory orientation and alertness [1, 45]. For parents, NNPT causes parental anxiety, excessive medical concerns, and increased outpatient visits in the first year [88]. Thus, unless jaundice is too severe, phototherapy can be safely interrupted at feeding time to allow breastfeeding, parental visits, and skin-to-skin contact to maintain parent–child bonding [84].

Imbalance of thermal environment and water loss

Conventional phototherapy changes the thermal environment of infants, which leads to insensible water loss, hypothermia/hyperthermia, and dehydration [24, 55, 60]. Also, infants might experience intestinal fluid losses from loose stools during NNPT. An RCT demonstrated that fluid supplementation in term neonates with severe hyperbilirubinemia could decrease the rate of exchange transfusion and the duration of NNPT [66]. Therefore, the core temperature of infants undergoing NNPT should be closely monitored and appropriate fluid supplementation should be given when necessary, especially in very low birth weight infants [24, 66, 97].

Electrolyte disturbance—hypocalcemia

NNPT can lead to decreased total and ionized calcium levels of neonates, especially in preterm neonates [38, 48]. This effect might be attributable to increased urinary calcium excretion [43]. In addition, light can affect calcium homeostasis by inhibiting pineal secretion of melatonin and consequently leading to hypocalcemia [38]. 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 NNPT [48]. Therefore, the benefits of prophylactic calcium to prevent hypocalcemia during NNPT need further study.

Disorder of circadian rhythms

Chen et al. [28] explored the effect of NNPT on the expression of circadian genes in peripheral blood mononuclear cells of jaundiced neonates. They found that NNPT significantly increased the expression of the Cry1 gene and decreased the plasma levels of melatonin, altering normal dark–light circadian rhythms and leading to abnormal behaviors such as frequent crying and jitteriness. These results suggest that NNPT should be better timed to accommodate normal circadian rhythms.

Bronze baby syndrome

Bronze baby syndrome (BBS) is a rare complication occurring in neonates with a raised conjugated bilirubin level (cholestasis) undergoing NNPT [33]. The pathogenesis of BBS is unclear. Cu–protoporphyrin metabolism disturbance and congenital biliary hypoplasia may be involved in its development [65, 77, 95]. The threshold of conjugated bilirubin for the syndrome has not yet been determined since not all babies with cholestasis develop BBS during NNPT. It is generally believed that BBS is harmless, and pigmentation returns slowly to normal if NNPT is discontinued [65]. However, BBS may constitute an additional risk for developing kernicterus [21]. Thus, neonates with a mixed (direct–indirect) hyperbilirubinemia undergoing NNPT should be closely investigated for underlying BBS.

Possible long-term side effects of NNPT

NNPT and allergic diseases

Mechanisms of NNPT for allergic diseases

With rates of allergic diseases such as asthma and allergic rhinitis increasing, much interest is currently focused on their immunologic mechanisms during early development. Immune competence is considered to be 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. Environmental stimuli easily affect immune regulation in early life [23], with a Th-2/Th-1 switch disorder caused by environmental factors contributing in many allergic diseases. The evidence that NNPT inhibits the immune system is supported by findings that NNPT affects the Th-2/Th-1 switch, ultimately causing allergic diseases during childhood and later in life. There are a few possible mechanisms for the Th-2/Th-1 switch disorder. First, NNPT can significantly increase the levels of cytokines, including TNF-alpha, IL-1 beta, and IL-8, but decrease the level of IL-6 in newborn infants [56, 73]. This change of cytokine levels is thought to be the principal cause of Th-2/Th-1 switch disorder (Fig. 1). Second, NNPT directly causes DNA damage to lymphocytes in jaundiced

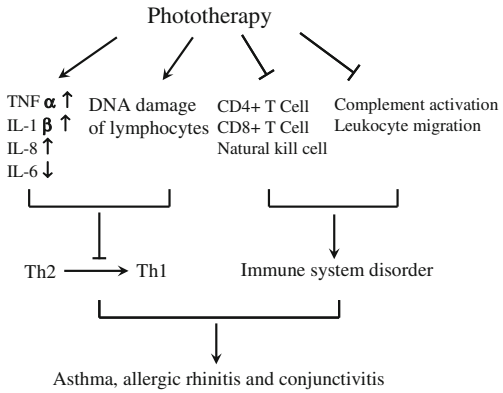

Fig. 1 Possible mechanisms of NNPT for allergic diseases

infants [12, 85] (Fig. 1). This injury could affect the genes regulating the Th-2/Th-1 switch and contribute to the disorder.

UV light, although a small component of NNPT, can activate the inflammatory pathways, leading to allergy or autoimmunity disorders [64]. UV light significantly decreases circulating $CD4^+$ T lymphocyte counts [86], interferes with $CD8^+$ cytotoxic T lymphocytes [6], and reduces natural killer cell activity [71]. Therefore, UV light in NNPT exposure may affect the immune system and lead to allergy and autoimmunity disorders (Fig. 1).

The effect of NNPT on immune regulation may partly be due to degrading bilirubin. Unconjugated bilirubin inhibits complement activation through the classical pathway [16] and prevents leukocyte migration [51]. A proper increase in bilirubin levels during the neonatal period protects infants from oxidative stress and promotes Th2/Th1 switching, which prevents allergic manifestations in later periods of life [40]. Thus, interfering with physiological bilirubin metabolism via NNPT may cause an immune system disorder (Fig. 1).

NNPT and asthma, allergic rhinitis, and conjunctivitis

NNPT degradation of bilirubin may increase oxidative stress, a possible risk factor for asthmatic manifestations in later life [40]. Thus, the decreased bilirubin level induced by NNPT and the resulting impaired antioxidant defense may contribute to the development of asthma.

Aspberg et al. [9, 10] explored whether NNPT is a risk factor for asthma. In their first study, 14,803 children hospitalized for asthma were compared with 1,386,029 children born at the same time in Sweden. They found that NNPT and jaundice are risk factors for asthma (OR 1.27; 95% CI, 1.08–1.50). These findings suggest an association between neonatal jaundice and/or NNPT and hospitalized childhood asthma. In their second study, 61,256 children, who were prescribed anti-asthmatic medication under 2 years of age with or without hospitalization, were compared with 1,338,319 children born at the same time. NNPT and/or jaundice were also found to be risk determinants (OR 1.30; 95% CI, 1.16–1.47) for children who developed asthma before the age of 12. Both studies indicated an association between NNPT and/or jaundice and childhood asthma. These findings are interesting and valuable because the data were obtained in a larger population and conclusions were drawn after minimizing the possibilities that there were secondary or other perinatal risk factors.

Interestingly, a recent study including patients with more than a 30-year follow-up period has shown that NNPT is associated with allergic rhinitis and conjunctivitis (P=0.046) [40]. Since this study group is small, further epidemiological research with larger groups and multi-center cooperation is needed to investigate the relationship between NNPT and allergic rhinitis and conjunctivitis.

The above research is all case–controlled studies with relatively small OR values, which cannot provide strong statistical evidence. Thus, final conclusions regarding the associations between phototherapy and asthma, allergic rhinitis, and conjunctivitis should be drawn after a well-designed RCT.

NNPT and melanocytic nevi, melanoma, skin cancer

It is estimated that the epidermis may absorb 60% of blue light irradiation. Melanocytic cells, localized to the epidermis, are easily affected by irradiation with blue light [63]. Neonatal skin has reduced enzymatic activity, low metabolic detoxification, and incomplete immunologic defense, which increase the sensitivity and vulnerability of neonates to NNPT [63].

Blue light is toxic to epithelial cells by inducing free radical production and mitochondrial and nuclear DNA damage, which facilitate the progress of skin cancer [47, 85]. In addition, the risk of skin cancer may partly be due to overlap between the spectrum of NNPT and UV radiation. Approximately 0.3% of the blue light comprises UV radiation [30]. NNPT with a total UV irradiance of 10.8 to 32.4 J/cm^2 was reported to cause ultraviolet burns [81]. Moreover, excessive exposure to UV significantly increases the risk of malignant melanoma [57]. Fortunately, UV light is not present in many modern phototherapy devices such as light-emitting diodes (LED) and fiber optic lights [61, 78, 79].

Counting melanocytic nevi has been used as the strongest factor to predict melanoma. Recent clinical trials have shown the potential impact of NNPT on increasing the melanocytic nevus count. A high correlation was found between NNPT and nevus count in 8–9-year-old children, especially for nevi from 2 to 5 mm (P=0.006). The mean nevus count was 3.17 per child in the NNPT group,

compared with 1.23 per child in the control group [63]. Csoma and colleagues [29] investigated 747 schoolchildren aged from 14 to 18 years who had received NNPT. They found that NNPT was associated with a significantly higher prevalence of clinically multiple common nevi and atypical nevi (OR, 1.43; 95% CI, 1.01–2.03), which is the most important independent phenotypic risk factor for the development of malignant melanoma. In a study on monozygotic twin pairs, twins exposed to NNPT had a statistically significantly higher number of common and atypical nevi than those who were not exposed to NNPT [31].

The relationship between NNPT and skin cancer has been studied. Berg et al. [20] studied 30 children with melanoma and 120 control children without melanoma. They found that all the children with melanoma had not received NNPT, which suggested that NNPT is not a risk factor for melanoma. Also, a retrospective cohort study recently reported that no case of squamous cell or basal cell carcinoma was observed in 5,868 NNPT-exposed persons. There is no statistical evidence to show that NNPT is an excess risk factor for melanoma at present [25].

To ascertain the relationship between NNPT and skin cancer, further delicate studies containing the following criteria should be considered. First, studies should be conducted in different genetic groups such as in non-White infants. The above studies were carried out in White populations who develop melanotic nevi and skin cancer easier than non-White populations. Second, the follow-up time needs to be extended. The follow-up time in the above 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 [25]. However, building a study with more than 30 years of follow-up is very difficult to be achieved because of the high proportion of lost to follow-up, unknown confounders in the different ages of the patients, and financial supports for such long-time trials. Third, studies should enroll preterm infants who have a relatively high risk of developing NNPT-related nevi. In the above studies, there is no independent study for preterm infants.

NNPT and patent ductus arteriosus

It is hypothesized that light can penetrate the thin chest wall of extremely preterm infants. This penetration is enhanced while neonates are being exposed to a higher spectral irradiance of NNPT [87]. The light photon causes the relaxation of aortic smooth muscle [91] through the activation of the nitric oxide–cyclic GMP pathway and Ca^{2+}-dependent K^+ ion channels [17]. Therefore, NNPT exerts a relaxing effect on the smooth muscles of the ductus arteriosus in neonates, thus reopening the ductus arteriosus [19].

In addition, abnormal blood flow change after NNPT is an important risk factor for patent ductus arteriosus (PDA). NNPT has been reported to alter heart function by increasing the heart rate and diminishing the variability of heart rate and cardiac output while affecting blood vessel function by diminishing the mean arterial blood pressure and increasing peripheral blood flow [14, 58, 98]. The alteration of cardiovascular function and the fluid homeostasis after NNPT treatment can affect the closure of PDA.

In 1986, a positive relationship between NNPT and PDA was firstly reported in premature infants with respiratory distress syndrome [76]. To determine the relationship of NNPT and PDA in extremely low birth weight (ELBW) infants, Barefield et al. [15] analyzed 295 infants with a birth weight of 501 to 999 g. Infants who received NNPT (n=128) had a significantly increased incidence of PDA compared to those not receiving NNPT (76% vs 53%). Benders et al. [19] designed a study with 27 preterm infants (gestational age ≤32 weeks, average birth weight <1,400 g), all of whom had a closed ductus arteriosus before NNPT. However, the ductus arteriosus were reopened in more than 50% of the infants during NNPT. Therefore, NNPT could be a risk factor for PDA, especially in the infants with a birth weight less than 1,500 g.

Further studies are necessary to verify if NNPT is truly linked to PDA or if some confounding factors may have biased this result. We should also consider that bilirubin levels >6 mg/dL are likely to be highly dangerous for most preterm infants already affected by several concurrent diseases. A careful balance must be performed in each case and this is likely to be very often in favor of NNPT [97].

NNPT and retinal damage

The wavelengths of light that are most efficient in decreasing bilirubin levels are also the wavelengths likely to produce retinal damage [36]. 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 [49, 50]. Because photon absorption is dramatically increased in the retina during blue light exposure, the susceptibility to light-induced cell death in the retina is significantly augmented, especially in premature infants [41].

Although some clinical evidence exists regarding the association between NNPT and retinopathy of prematurity (ROP), the basic mechanisms by which NNPT is thought to damage retina have nothing to do with ROP. ROP is a multifactorial disease, still not completely understood, in which free oxygen radicals seem to play a pivotal role [13]. Since bilirubin plays a role as an antioxidant [54], theoretically, ROP might be mitigated by bilirubin. By degrading bilirubin, blue light decreases the capacity of

oxidation resistance and increases the reactive oxygen species in both the retina and serum [11, 53]. In addition, premature infants have weaker intracellular defense mechanisms against oxygen radicals than term infants [90]. Therefore, by promoting bilirubin excretion, NNPT could decrease the oxidation resistance in preterm infants and facilitate the development of ROP.

In a retrospective study of 128 ELBW infants (birth weight ≤800 g and gestation age ≤27 weeks), 15 infants had severe visual loss due to ROP. This visual loss was significantly associated with a low-peak serum bilirubin concentration and a longer duration of NNPT (OR per 10 h, 1.17; 95 % CI, 1.02–1.33) than what was needed [101]. Also, infants (birth weight 1,000~2,000 g or gestational age <34 weeks) with ROP had a significantly longer duration of NNPT than infants without ROP, which suggests that NNPT may be involved in the occurrence of ROP [52]. Recently, Ebrahim et al. [37] studied the role of NNPT in ROP using 173 newborn infants with a mean birth weight of 1,680.6 g and a mean GA of 32.2 weeks. They found that NNPT was related to the occurrence of ROP (OR=2.405; 95 % CI, 1.04–5.59). However, if the neonates were between 32 and 36 weeks of gestational age, NNPT was not related to ROP [39]. Because ROP is an illness related to immaturity, we think that NNPT may be a risk factor for the development of ROP in preterm neonates. Therefore, further trials are required to assess the risk/benefit ratios of NNPT in different gestational ages. All of the side effects discussed above and the strength of research are summarized in Table 1.

Minimize the side effects of NNPT

NNPT has been in clinical use for over half of a century. Its efficacy in decreasing plasma bilirubin concentrations has been demonstrated by the significantly reduced exchange transfusion rates. Nevertheless, the exact mechanisms of NNPT are not yet completely understood. Furthermore, it is not yet fully known whether NNPT during the first 2–3 weeks of life will produce long-term toxicity since only a few clinical studies have been performed. Thus, we cannot completely exclude the possibility that long-term side effects could be confirmed in future clinical studies. On the other hand, since the side effects of hyperbilirubinemia are known to be toxic, NNPT remains a cornerstone for treatment.

Because there is no consensus on the level of total serum bilirubin (TSB) for which therapy should be initiated, the use of NNPT currently varies widely, especially for preterm infants [75, 89, 97]. As it is hard to quantify the risk of bilirubin-associated brain damage, prophylactic NNPT to prevent infants from bilirubin encephalopathy has been over-used by neonatologists in clinical practice, possibly resulting in many unnecessarily irradiated babies in the neonatal intensive care unit [82]. The best current strategy

Table 1 The side effects of phototherapy and strength of research

Side effect	References	Type of research	Strength[a]
Interference with maternal–infant interaction	[1, 88]	Cohort study	2b
	[45]	RCT	1b
Imbalance of thermal environment and water loss	[60]	Before–after study	2c
	[24, 55, 66]	RCT	1b
Electrolyte disturbance—hypocalcemia	[38, 48]	Before–after study	2c
	[43]	Cohort study	4
Disorder of circadian rhythms	[28]	RCT	1b
Bronze baby syndrome	[33, 95]	Case report	4
	[21, 77]	Case series	4
Asthma	[9, 10]	Case–control study	3b
Allergic rhinitis and conjunctivitis	[40]	Case–control study	3b
Melanotic nevus and skin cancers	[81]	Case report	4
	[20, 29, 31, 63]	Case–control study	3b
	[25]	Cohort study	2b
Patent ductus arteriosus	[14, 19, 98]	Before–after study	2c
	[15, 58]	Cohort study	2b
	[76]	RCT	1b
Retinopathy of prematurity	[101]	Case–control study	3b
	[37, 52]	Cohort study	2b
	[39]	Cross-sectional study	4

[a] From Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=1025; version current at February 19, 2011)

for NNPT is to use it only when really needed, considering risks and benefits, and following the officially available guidelines.

Current guidelines for NNPT issued by the American Academy of Pediatrics (AAP) are widely accepted in clinical practice. The AAP guidelines are based on an extensive review of available evidence. They describe in detail the mechanism of action, risks and benefits, type of device, and tips and tricks for NNPT as well as future research directions [7]. Other guidelines, such as those issued by the Dutch Pediatric Association [35], European Society for Pediatric Research [22], Canadian Pediatric Society [27], the Spanish National Society of Neonatology [59], and South Africa medical faculties [44] are based on AAP guidelines. All of these guidelines recommend a safe approach, with a careful consideration of the risks and benefits of NNPT, and are largely in favor of NNPT. In 2010, UK's National Institute for Health and Clinical Excellence (NICE) published new guidelines for the assessment and treatment of neonatal jaundice. The guidelines recommend substantial changes to the current practice for term and preterm infants. The NICE guidelines are accused of being overly concerned with parental anxiety and less concerned with medical issues. Since inappropriate restrictions on exchange transfusion could increase the risk of kernicterus [32], AAP guidelines are recommended over NICE guidelines.

Some experts still believe that hyperbilirubinemia in "healthy" infants without other complications is overtreated [96], while other experts doubt that the recommended NNPT guidelines are strong enough to prevent ELBW infants from developing kernicterus [68]. Kernicterus is not simply related to TSB levels. An interaction between free unconjugated bilirubin (UB) and the blood–brain barrier plays an important role in kernicterus. UB has been used to predict bilirubin neurotoxicity because UB levels are closely associated with bilirubin concentrations in the central nervous system [3, 4]. The neurotoxicity of bilirubin is more closely related to UB levels than TSB levels [5, 102]. Since the current guidelines for NNPT are based primarily on TSB levels but not UB levels, predicting the risk of kernicterus with TSB has a high sensitivity but a low specificity [99]. Thus, new evidence-based guidelines integrating UB and TSB measurements would better determine whether NNPT is necessary for jaundiced patients [2, 5, 31].

Theoretically, the side effects of NNPT could partly depend on its irradiance dose. Unfortunately, no single standardized method is used for reporting NNPT dosages in clinical literature, which makes it hard to compare the dose in published clinical studies [62, 92]. Thus, the irradiance dose of NNPT should be carefully checked using a standard radiometer and using an irradiance mapping technique, taking into account the surface area irradiated [93].

Fiberoptic phototherapy, a new device using optical fibers, has been reported to be effective in reducing serum bilirubin for neonates with jaundice [67]. Infants under fiberoptic phototherapy can be nursed close to their parents without mother–infant separation. In addition, because light from optical fibers is directly delivered to the infant's trunk, it can avoid retinal injury, ROP, or complications such as eye irritation, corneal abrasion, and conjunctivitis caused by eye shield. Therefore, fiberoptic phototherapy is a safe alternative to conventional phototherapy. Nonetheless, fiberoptic phototherapy has a low spectral irradiance and a lower spectral power, as it irradiates a minor body surface. Therefore, it is not advised for intensive phototherapy in the most severe cases [7]. LED, as a new light source for phototherapy, have recently been utilized in phototherapy units [55]. With a relatively low heat output, LED lights could avoid the imbalance of thermal environment and water loss [62]. Furthermore, blue LED lights have a narrow spectral band that avoids overlap with UV radiation [55]. Therefore, these unique characteristics of LED can also reduce the side effect from UV radiation.

Alternative to NNPT

Several agents, such as metalloporphyrins and clofibrate, have been demonstrated to decrease the need for NNPT [80, 83]. Metalloporphyrins are competitive inhibitors of the rate-limiting enzyme, heme oxygenase, in bilirubin production and can thus prevent the production of excess bilirubin [83]. Nevertheless, the safety of metalloporphyrins in clinical practice needs more investigation as only a few small clinical studies are available at present. Clofibrate, a hypolipidemic drug, is a glucuronosyltransferase inducer which accelerates bilirubin elimination. Its effect on reducing serum bilirubin has been demonstrated in preterm and term neonates [80]. Since the follow-up time and sample sizes are limited in these trials, more research with larger sample sizes and longer follow-up time will be required. Phenobarbitone, another glucuronosyltransferase inducer, is thought to decrease jaundice by promoting the excretion of bilirubin and producing more receptor protein for bilirubin uptake [8]. Phenobarbitone is administered as a treatment for neonatal jaundice in Asia. Prophylactic oral phenobarbitone has been shown to decrease TSB but not the use of NNPT [8, 70]. Unfortunately, phenobarbitone has some side effects such as somnolence and an increased need for mechanical ventilation in preterm infants [34, 100]. Therefore, the efficacy and safety of phenobarbitone needs further investigation.

Ideally, the use of new agents including metalloporphyrins and clofibrate may be proposed as an alternative choice for preventing or treating severe hyperbilirubinemia so as to reduce the need for NNPT.

Individual treatment

It is generally accepted that gene–environment interaction plays an important role in the development of many diseases. This is also the case in neonatal jaundice. On the one hand, for individual neonates, the susceptibility to hyperbilirubinemia and the risk for kernicterus are variable [40, 99]. On the other hand, different skin colors manifest different traits to light exposure. This is because skin color is primarily determined by melanin that is synthesized in the melanosome [72]. Melanosomes in dark (African) skin are larger and more heavily pigmented than those in light (Asian and Caucasian) skins [46]. Since melanin can reduce the penetration of light, neonates with black skin may need more intensive NNPT. Thus, truly individualized therapy, considering that the child's characteristic and risks are deemed acceptable, can obtain the most desired benefits. Based on this indication, genetic and phenotypic targeting would finally bring rationality to the management of neonatal jaundice and maximally avoid the overuse of NNPT.

Therefore, individual dosing of NNPT such as intermittent/continuous NNPT, high/low dose NNPT, and different types of light sources could be considered in clinical practice. Hereditary characteristics of infants, severity of jaundice, and maturity of neonates also need to be analyzed. To get a truly individual NNPT treatment, continued pre-clinical exploration and subsequently multicenter randomized control trials are required in the future.

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References

1. Abrol P, Sankarasubramanian R (1998) Effect of phototherapy on behaviour of jaundiced neonates. Indian J Pediatr 65:603–607
2. Ahlfors CE (2010) Predicting bilirubin neurotoxicity in jaundiced newborns. Curr Opin Pediatr 22:129–133
3. Ahlfors CE, Amin SB, Parker AE (2009) Unbound bilirubin predicts abnormal automated auditory brainstem response in a diverse newborn population. J Perinatol 29:305–309
4. Ahlfors CE, Parker AE (2008) Unbound bilirubin concentration is associated with abnormal automated auditory brainstem response for jaundiced newborns. Pediatrics 121:976–978
5. Ahlfors CE, Wennberg RP, Ostrow JD, Tiribelli C (2009) Unbound (free) bilirubin: improving the paradigm for evaluating neonatal jaundice. Clin Chem 55:1288–1299
6. Ambach A, Bonnekoh B, Gollnick H (2006) UVA1 radiation (340–400 nm) interferes with the perforin-granule system of CD8hi + cytotoxic T lymphocytes in vitro. J Photochem Photobiol B 82:236–243
7. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (2004) Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 114:297–316
8. Arya VB, Agarwal R, Paul VK, Deorari AK (2004) Efficacy of oral phenobarbitone in term "at risk" neonates in decreasing neonatal hyperbilirubinemia: a randomized double-blinded, placebo controlled trial. Indian Pediatr 41:327–332
9. Aspberg S, Dahlquist G, Kahan T, Kallen B (2007) Is neonatal phototherapy associated with an increased risk for hospitalized childhood bronchial asthma? Pediatr Allergy Immunol 18:313–319
10. Aspberg S, Dahlquist G, Kahan T, Kallen B (2010) Confirmed association between neonatal phototherapy or neonatal icterus and risk of childhood asthma. Pediatr Allergy Immunol 21:e733–e739
11. Aycicek A, Erel O (2007) Total oxidant/antioxidant status in jaundiced newborns before and after phototherapy. J Pediatr (Rio J) 83:319–322
12. Aycicek A, Kocyigit A, Erel O, Senturk H (2008) Phototherapy causes DNA damage in peripheral mononuclear leukocytes in term infants. J Pediatr (Rio J) 84:141–146
13. Baba L, McGrath JM (2008) Oxygen free radicals: effects in the newborn period. Adv Neonatal Care 8:256–264
14. Bader D, Kugelman A, Blum DE et al (2006) Effect of phototherapy on cardiorespiratory activity during sleep in neonates with physiologic jaundice. Isr Med Assoc J 8:12–16
15. Barefield ES, Dwyer MD, Cassady G (1993) Association of patent ductus arteriosus and phototherapy in infants weighing less than 1000 grams. J Perinatol 13:376–380
16. Basiglio CL, Arriaga SM, Pelusa F et al (2010) Complement activation and disease: protective effects of hyperbilirubinaemia. Clin Sci (Lond) 118:99–113
17. Batenburg WW, Kappers MH, Eikmann MJ et al (2009) Light-induced vs. bradykinin-induced relaxation of coronary arteries: do *S*-nitrosothiols act as endothelium-derived hyperpolarizing factors? J Hypertens 27:1631–1640
18. Bauer J, Buttner P, Luther H et al (2004) Blue light phototherapy of neonatal jaundice does not increase the risk for melanocytic nevus development. Arch Dermatol 140:493–494
19. Benders MJ, Van Bel F, Van de Bor M (1999) Cardiac output and ductal reopening during phototherapy in preterm infants. Acta Paediatr 88:1014–1019
20. Berg P, Lindelof B (1997) Is phototherapy in neonates a risk factor for malignant melanoma development? Arch Pediatr Adolesc Med 151:1185–1187
21. Bertini G, Dani C, Fonda C et al (2005) Bronze baby syndrome and the risk of kernicterus. Acta Paediatr 94:968–971
22. Bhutani VK, Maisels MJ, Stark AR, Buonocore G (2008) Management of jaundice and prevention of severe neonatal hyperbilirubinemia in infants>or=35 weeks gestation. Neonatology 94:63–67
23. Bjorksten B (2008) Environmental influences on the development of the immune system: consequences for disease outcome. Nestle Nutr Workshop Ser Pediatr Program 61:243–254
24. Boo NY, Chew EL (2006) A randomised control trial of clingfilm for prevention of hypothermia in term infants during phototherapy. Singapore Med J 47:757–762
25. Brewster DH, Tucker JS, Fleming M et al (2010) Risk of skin cancer after neonatal phototherapy: retrospective cohort study. Arch Dis Child 95:826–831
26. Bryla DA (1985) Randomized, controlled trial of phototherapy for neonatal hyperbilirubinemia. Development, design, and sample composition. Pediatrics 75:387–392

27. Canadian Paediatric Society (2007) Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants (35 or more weeks' gestation)—summary. Paediatr Child Health 12:401–418
28. Chen A, Du L, Xu Y et al (2005) The effect of blue light exposure on the expression of circadian genes: bmal1 and cryptochrome 1 in peripheral blood mononuclear cells of jaundiced neonates. Pediatr Res 58:1180–1184
29. Csoma Z, Hencz P, Orvos H et al (2007) Neonatal blue-light phototherapy could increase the risk of dysplastic nevus development. Pediatrics 119:1036–1037, author reply 1037–1038
30. Csoma Z, Hencz P, Orvos H et al (2007) Neonatal blue-light phototherapy could increase the risk of dysplastic nevus development. Pediatrics 119:1269
31. Csoma Z, Kemeny L, Olah J (2008) Phototherapy for neonatal jaundice. N Engl J Med 358:2523–2524, author reply 2524–2525
32. De Luca D (2010) NICE guidelines on neonatal jaundice: at risk of being too nice. Lancet 376:771
33. De Luca D, Picone S, Fabiano A, Paolillo P (2010) Images in neonatal medicine. Bronze baby syndrome: pictorial description of a rare condition. Arch Dis Child Fetal Neonatal Ed 95:F325
34. Dennery PA (2002) Pharmacological interventions for the treatment of neonatal jaundice. Semin Neonatol 7:111–119
35. Dijk PH, de Vries TW, de Beer JJ (2009) Guideline 'Prevention, diagnosis and treatment of hyperbilirubinemia in the neonate with a gestational age of 35 or more weeks'. Ned Tijdschr Geneeskd 153:A93
36. Dobson V (1976) Editorial: phototherapy and retinal damage. Invest Ophthalmol 15:595–598
37. Ebrahim M, Ahmad RS, Mohammad M (2010) Incidence and risk factors of retinopathy of prematurity in Babol, north of Iran. Ophthalmic Epidemiol 17:166–170
38. Eghbalian F, Monsef A (2002) Phototherapy-induced hypocalcemia in icteric newborns. Iran J Med Sci 27:169–171
39. Gleissner MW, Spantzel T, Bucker-Nott HJ, Jorch G (2003) Risk factors of retinopathy of prematurity in infants 32 to 36 weeks gestational age. Z Geburtshilfe Neonatol 207:24–28
40. Gloria-Bottini F, Bottini E (2010) Is there a role of early neonatal events in susceptibility to allergy? Int J Biomed Sci 6:8–12
41. Grimm C, Wenzel A, Williams T et al (2001) Rhodopsin-mediated blue-light damage to the rat retina: effect of photoreversal of bleaching. Invest Ophthalmol Vis Sci 42:497–505
42. Hansen TW (2010) Twists and turns in phototherapy for neonatal jaundice. Acta Paediatr 99:1117–1118
43. Hooman N, Honarpisheh A (2005) The effect of phototherapy on urinary calcium excretion in newborns. Pediatr Nephrol 20:1363–1364
44. Horn AR, Kirsten GF, Kroon SM et al (2006) Phototherapy and exchange transfusion for neonatal hyperbilirubinaemia: neonatal academic hospitals' consensus guidelines for South African hospitals and primary care facilities. S Afr Med J 96:819–824
45. Ju SH, Lin CH (1991) The effect of moderate non-hemolytic jaundice and phototherapy on newborn behavior. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 32:31–41
46. Juzeniene A, Setlow R, Porojnicu A et al (2009) Development of different human skin colors: a review highlighting photobiological and photobiophysical aspects. J Photochem Photobiol B 96:93–100
47. Karadag A, Yesilyurt A, Unal S et al (2009) A chromosomal-effect study of intensive phototherapy versus conventional phototherapy in newborns with jaundice. Mutat Res 676:17–20
48. Karamifar H, Pishva N (2002) Prevalence of phototherapy-induced hypocalcemia. Iran J Med Sci 27:166–168
49. Kernt M, Hirneiss C, Neubauer AS et al (2010) Protective effect of blue light-absorbing IOLs on the human retinal pigment epithelium. Ophthalmologe 107:150–157
50. Kernt M, Neubauer AS, Liegl R et al (2009) Cytoprotective effects of a blue light-filtering intraocular lens on human retinal pigment epithelium by reducing phototoxic effects on vascular endothelial growth factor-alpha, Bax, and Bcl-2 expression. J Cataract Refract Surg 35:354–362
51. Keshavan P, Deem TL, Schwemberger SJ et al (2005) Unconjugated bilirubin inhibits VCAM-1-mediated transendothelial leukocyte migration. J Immunol 174:3709–3718
52. Khatami SF, Yousefi A, Bayat GF, Mamuri G (2008) Retinopathy of prematurity among 1000–2000 gram birth weight newborn infants. Iran J Pediatr 18:137–142
53. King A, Gottlieb E, Brooks DG et al (2004) Mitochondria-derived reactive oxygen species mediate blue light-induced death of retinal pigment epithelial cells. Photochem Photobiol 79:470–475
54. Kumar A, Pant P, Basu S et al (2007) Oxidative stress in neonatal hyperbilirubinemia. J Trop Pediatr 53:69–71
55. Kumar P, Murki S, Malik GK et al (2010) Light emitting diodes versus compact fluorescent tubes for phototherapy in neonatal jaundice: a multi center randomized controlled trial. Indian Pediatr 47:131–137
56. Kurt A, Aygun AD, Kurt AN et al (2009) Use of phototherapy for neonatal hyperbilirubinemia affects cytokine production and lymphocyte subsets. Neonatology 95:262–266
57. Leiter U, Garbe C (2008) Epidemiology of melanoma and nonmelanoma skin cancer—the role of sunlight. Adv Exp Med Biol 624:89–103
58. Liu GS, Wu H, Wu BQ et al (2008) Effect of phototherapy on blood endothelin and nitric oxide levels: clinical significance in preterm infants. World J Pediatr 4:31–35
59. Luna MS, Alonso CR, Mussons FB et al (2009) Recommendations for the care of the healthy normal newborn at delivery and during the first postnatal hours. An Pediatr (Barc) 71:349–361
60. Maayan-Metzger A, Yosipovitch G, Hadad E, Sirota L (2001) Transepidermal water loss and skin hydration in preterm infants during phototherapy. Am J Perinatol 18:393–396
61. Maisels MJ, Kring EA, DeRidder J (2007) Randomized controlled trial of light-emitting diode phototherapy. J Perinatol 27:565–567
62. Maisels MJ, McDonagh AF (2008) Phototherapy for neonatal jaundice. N Engl J Med 358:920–928
63. Matichard E, Le Henanff A, Sanders A et al (2006) Effect of neonatal phototherapy on melanocytic nevus count in children. Arch Dermatol 142:1599–1604
64. Maverakis E, Miyamura Y, Bowen MP et al (2010) Light, including ultraviolet. J Autoimmun 34:J247–J257
65. McDonagh AF (2011) Bilirubin, copper-porphyrins, and the bronze-baby syndrome. J Pediatr 158:160–164
66. Mehta S, Kumar P, Narang A (2005) A randomized controlled trial of fluid supplementation in term neonates with severe hyperbilirubinemia. J Pediatr 147:781–785
67. Mills JF, Tudehope D (2001) Fibreoptic phototherapy for neonatal jaundice. Cochrane Database Syst Rev CD002060
68. Moll M, Goelz R, Naegele T et al (2010) Are recommended phototherapy thresholds safe enough for extremely low birth weight (ELBW) infants? A report on 2 ELBW infants with kernicterus despite only moderate hyperbilirubinemia. Neonatology 99:90–94
69. Morris BH, Oh W, Tyson JE et al (2008) Aggressive vs. conservative phototherapy for infants with extremely low birth weight. N Engl J Med 359:1885–1896
70. Murki S, Dutta S, Narang A et al (2005) A randomized, triple-blind, placebo-controlled trial of prophylactic oral phenobarbital to reduce the need for phototherapy in G6PD-deficient neonates. J Perinatol 25:325–330

71. Neill WA, Halliday KE, Norval M (1998) Differential effect of phototherapy on the activities of human natural killer cells and cytotoxic T cells. J Photochem Photobiol B 47:129–135
72. Parra EJ (2007) Human pigmentation variation: evolution, genetic basis, and implications for public health. Am J Phys Anthropol 45:85–105
73. Procianoy RS, Silveira RC, Fonseca LT et al (2010) The influence of phototherapy on serum cytokine concentrations in newborn infants. Am J Perinatol 27:375–379
74. Rennie J, Burman-Roy S, Murphy MS (2010) Neonatal jaundice: summary of NICE guidance. BMJ 340:c2409
75. Rennie JM, Sehgal A, De A et al (2009) Range of UK practice regarding thresholds for phototherapy and exchange transfusion in neonatal hyperbilirubinaemia. Arch Dis Child Fetal Neonatal Ed 94:F323–F327
76. Rosenfeld W, Sadhev S, Brunot V et al (1986) Phototherapy effect on the incidence of patent ductus arteriosus in premature infants: prevention with chest shielding. Pediatrics 78:10–14
77. Rubaltelli FF, Jori G, Reddi E (1983) Bronze baby syndrome: a new porphyrin-related disorder. Pediatr Res 17:327–330
78. Seidman DS, Moise J, Ergaz Z et al (2000) A new blue light-emitting phototherapy device: a prospective randomized controlled study. J Pediatr 136:771–774
79. Seidman DS, Moise J, Ergaz Z et al (2003) A prospective randomized controlled study of phototherapy using blue and blue-green light-emitting devices, and conventional halogen-quartz phototherapy. J Perinatol 23:123–127
80. Sharafi R, Mortazavi Z, Sharafi S, Parashkouh R (2010) The effect of clofibrate on decreasing serum bilirubin in healthy term neonates under home phototherapy. Iran J Pediatr 20:48–52
81. Siegfried EC, Stone MS, Madison KC (1992) Ultraviolet light burn: a cutaneous complication of visible light phototherapy of neonatal jaundice. Pediatr Dermatol 9:278–282
82. Sola A (2007) Turn off the lights and the oxygen, when not needed: phototherapy and oxidative stress in the neonate. J Pediatr (Rio J) 83:293–296
83. Stevenson DK, Wong RJ (2010) Metalloporphyrins in the management of neonatal hyperbilirubinemia. Semin Fetal Neonatal Med 15:164–168
84. Stokowski LA (2006) Fundamentals of phototherapy for neonatal jaundice. Adv Neonatal Care 6:303–312
85. Tatli MM, Minnet C, Kocyigit A, Karadag A (2008) Phototherapy increases DNA damage in lymphocytes of hyperbilirubinemic neonates. Mutat Res 654:93–95
86. Tobin AM, Maguire B, Enright H, Kirby B (2009) The effects of phototherapy on the numbers of circulating natural killer cells and T lymphocytes in psoriasis. Photodermatol Photoimmunol Photomed 25:109–110
87. Travadi J, Simmer K, Ramsay J et al (2006) Patent ductus arteriosus in extremely preterm infants receiving phototherapy: does shielding the chest make a difference? A randomized, controlled trial. Acta Paediatr 95:1418–1423
88. Usatin D, Liljestrand P, Kuzniewicz MW et al (2010) Effect of neonatal jaundice and phototherapy on the frequency of first-year outpatient visits. Pediatrics 125:729–734
89. van Imhoff DE, Dijk PH, Hulzebos CV (2009) Uniform intervention criteria for jaundice in hyperbilirubinemia in preterm infants. Ned Tijdschr Geneeskd 153:A94
90. Varsila E, Pitkanen O, Hallman M, Andersson S (1994) Immaturity-dependent free radical activity in premature infants. Pediatr Res 36:55–59
91. Venturini CM, Palmer RM, Moncada S (1993) 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 266:1497–1500
92. Vreman HJ (2010) Phototherapy: the challenge to accurately measure irradiance. Indian Pediatr 47:127–128
93. Vreman HJ, Wong RJ, Murdock JR, Stevenson DK (2008) Standardized bench method for evaluating the efficacy of phototherapy devices. Acta Paediatr 97:308–316
94. Vreman HJ, Wong RJ, Stevenson DK et al (1998) Light-emitting diodes: a novel light source for phototherapy. Pediatr Res 44:804–809
95. Wales JK, Walker V, Moore IE, Clayton PT (1986) Bronze baby syndrome, biliary hypoplasia, incomplete Beckwith–Wiedemann syndrome and partial trisomy 11. Eur J Pediatr 145:141–143
96. Walsh SA, Murphy JF (2010) Neonatal jaundice—are we over-treating? Ir Med J 103:28–29
97. Watchko JF, Jeffrey Maisels M (2010) Enduring controversies in the management of hyperbilirubinemia in preterm neonates. Semin Fetal Neonatal Med 15:136–140
98. Weissman A, Berkowitz E, Smolkin T, Blazer S (2009) Effect of phototherapy on neonatal heart rate variability and complexity. Neonatology 95:41–46
99. Wennberg RP, Ahlfors CE, Aravkin AY (2009) Intervention guidelines for neonatal hyperbilirubinemia: an evidence based quagmire. Curr Pharm Des 15:2939–2945
100. Whitelaw A, Odd D (2007) Postnatal phenobarbital for the prevention of intraventricular hemorrhage in preterm infants. Cochrane Database Syst Rev CD001691
101. Yeo KL, Perlman M, Hao Y, Mullaney P (1998) Outcomes of extremely premature infants related to their peak serum bilirubin concentrations and exposure to phototherapy. Pediatrics 102:1426–1431
102. Zecca E, Romagnoli C, De Carolis MP et al (2009) Does ibuprofen increase neonatal hyperbilirubinemia? Pediatrics 124:480–484