

# Dose-Response Relationship of Phototherapy for Hyperbilirubinemia



**WHAT'S KNOWN ON THIS SUBJECT:** A dose-response relationship exists between light irradiance and decrease of total serum bilirubin concentration (TsB) at relatively low irradiances. It has been questioned whether by increasing irradiance a "saturation point" exists, above which no further decrease of TsB is seen.



**WHAT THIS STUDY ADDS:** We found a linear relation between light irradiance in the range of 20 to 55  $\mu\text{W}/\text{cm}^2/\text{nm}$  and decrease in TsB after 24 hours of therapy, with no evidence of a saturation point.

## abstract

**BACKGROUND AND OBJECTIVE:** Using light-emitting diodes during conventional phototherapy, it is possible to reduce the distance from light source to infant, thus increasing light irradiance. The objective of this study was to search for a "saturation point" (ie, an irradiation level above which there is no further decrease in total serum bilirubin [TsB]). This was a prospective randomized study performed in the NICU of Aalborg Hospital, Denmark.

**METHODS:** One hundred fifty-one infants (gestational age  $\geq 33$  weeks) with uncomplicated hyperbilirubinemia were randomized to 1 of 4 distances from the phototherapy device to the mattress (20, 29, 38, and 47 cm). TsB was measured before and after 24 hours of phototherapy and irradiance every eighth hour. Main outcome was 24-hour decrease of TsB expressed in percent, ( $\Delta \text{TsB}_{0-24}$ , difference between  $\text{TsB}_0$  and  $\text{TsB}_{24}$  [%]).

**RESULTS:** A highly significant linear relation was seen between light irradiance and  $\Delta \text{TsB}_{0-24}$  (%) ( $P < .001$ ): when the irradiance increased from 20 to 55  $\mu\text{W}/\text{cm}^2/\text{nm}$ ,  $\Delta \text{TsB}_{0-24}$  (%) increased from approximately 30% to 50%. In addition, smooth regression showed no tendency for  $\Delta \text{TsB}_{0-24}$  (%) to level off as irradiance increased.  $\Delta \text{TsB}_{0-24}$  (%) was negatively correlated to birth weight and positively to formula volume. Average weight gain during phototherapy was 1%, independent of light irradiance.

**CONCLUSIONS:** By using light-emitting diodes, we found a linear relation between light irradiance in the range of 20 to 55  $\mu\text{W}/\text{cm}^2/\text{nm}$  and a decrease in TsB after 24 hours of therapy, with no evidence of a saturation point. *Pediatrics* 2012;130:e352–e357

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### KEY WORDS

neonates, hyperbilirubinemia, phototherapy, light irradiance, saturation point

### ABBREVIATIONS

$\Delta \text{TsB}_{0-24}$ —difference between  $\text{TsB}_0$  and  $\text{TsB}_{24}$

LED—light-emitting diodes

TsB—total serum bilirubin

$\text{TsB}_0$ —total serum bilirubin concentration before phototherapy

$\text{TsB}_{24}$ —total serum bilirubin concentration after 24 hours of phototherapy

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Phototherapy is one of the most frequently used therapeutic interventions in neonatal care, being the treatment of choice for jaundice. As phototherapy treatment has developed through the years, it has almost completely replaced exchange transfusion because of the efficacy and safety of the treatment.<sup>1</sup> The decrease of total serum bilirubin (TsB) during phototherapy is a result of formation of photoisomers. Light absorption in the skin transforms the toxic nonpolar Z,Z-bilirubin molecule into more excretable polar photoisomers: the configurational isomers Z,E-bilirubin and E,Z-bilirubin and the structural isomers Z-lumirubin and E-lumirubin.<sup>2</sup> In addition, a small amount of photooxidation products is formed. Generally photoisomers are induced shortly after phototherapy is initiated.<sup>3</sup> Presumably they are less toxic than bilirubin and less able to cross the blood-brain barrier.<sup>4</sup>

The efficacy of phototherapy in reducing TsB depends on several factors: the spectrum of the light emitted, spectral irradiance of the light, exposed body surface area, and duration of light exposure.<sup>5</sup> To ensure that the most optimal treatment is delivered to the infants regardless of design of phototherapy unit, the Committee on Fetus and Newborn of the American Academy of Pediatrics has made recommendations for phototherapy treatment.<sup>6</sup> They describe optimal phototherapy as blue light in the emission spectrum of 460 to 490 nm delivered at a light irradiance of  $\geq 30 \mu\text{W}/\text{cm}^2/\text{nm}$  to the largest possible body surface area. These recommendations are among others based on previous studies on the dose-response relationship between phototherapy with fluorescent tubes and the decrease of TsB.<sup>7–10</sup> Although few studies<sup>7–10</sup> have addressed the question of this correlation, they all showed a dose-response relationship between light irradiance and decrease of TsB. In one of

these a linear relationship was found by using relatively low light irradiances.<sup>7</sup> Contrary to this, Tan<sup>10</sup> has suggested a “saturation point” of  $30 \mu\text{W}/\text{cm}^2/\text{nm}$  above which no further decrease in TsB was seen with increasing irradiance.

In the above mentioned studies the distance from the light source to the infants was 40 to 50 cm because the heat formation from the fluorescent tubes risked overheating the infants at reduced distance. These studies were performed 30 years ago, and the phototherapy devices have improved since then. Today the most frequently used phototherapy is unidirectional (conventional) treatment with blue light from above in a narrow emission spectrum of  $\sim 460$  nm, which is the absorption peak of serum bilirubin. The newest phototherapy devices are light-emitting diodes (LEDs). Because the diodes generate a small amount of heat, it is now possible to reduce the distance from the light source to the infant and thus increase the light irradiance, but it has not been investigated whether this is followed by an increased decline in TsB.

The aim of this study was to use LEDs to investigate the relationship between light irradiance and decrease of TsB and to see if we could identify a saturation point.

## METHODS

Before initiation of the study, questionnaires about routine distance from the phototherapy apparatus to infants during conventional phototherapy from above were sent to all 17 Danish neonatal departments. From this survey, it was determined that the distance from the phototherapy apparatus to the mattress was a median 45 cm (range 20–65 cm). Four of the departments used neoBLUE LEDs.

The infants were enrolled in the study at the Aalborg Hospital NICU, Aarhus University Hospital, Denmark, between July

2009 and December 2010. Inclusion criteria were healthy neonates with gestational age  $\geq 33$  weeks and uncomplicated hyperbilirubinemia who could receive phototherapy in a bassinet. Thus, infants with hemolytic disease due to Rhesus or Kell blood group isoimmunization, or spherocytosis were not included. Furthermore, infants who needed double phototherapy or exchange transfusion due to a very high TsB or TsB increasing  $\geq 10 \mu\text{mol}/\text{L}/\text{h}$ , were not included. Most often a rapidly rising TsB is due to ABO blood group isoimmunization. Postnatal age was  $>24$  h and  $\leq 28$  days. Indication for phototherapy followed the guidelines of the Danish Pediatric Society, that is, the limit for phototherapy was a TsB ( $\mu\text{mol}/\text{L}$ ) corresponding to 10% of the infants' birth weight in grams with maximum TsB of  $300 \mu\text{mol}/\text{L}$ .

The authors established the allocation sequence. The neonatologist in charge enrolled patients and assigned them to their groups. After verbal and written informed consent was obtained from the parents, the infants were randomized using sealed, opaque envelopes to 1 of 4 phototherapy regimens. A distance from the phototherapy device to the mattress of 20, 29, 38, or 47 cm measured with a wooden measuring stick corresponded to an average distance between the device and each infant of 12, 21, 30, and 39 cm, respectively. An apparatus to mattress distance of 20 cm was the minimal distance that allowed nurses to routinely observe the infants sufficiently; a distance of 47 cm was about the average distance used in Denmark.

With reference to 24-hour decrease of TsB from a previous study,<sup>11</sup> sample size was calculated to demonstrate a 6% difference in decrease of TsB between groups after 24 hours of treatment with phototherapy. Setting a significance level of .05 and a power of .8, the required sample size was

determined to be 36 infants in each group.

The infants were placed in a bassinet with the phototherapy device placed above them. All infants were exposed naked (apart from eye pads and diaper) to continuous phototherapy for 24 hours, which is our routine treatment. Phototherapy was interrupted only for feeding and nursing for 30 minutes every 3 hours. Our previous studies have shown that with this practice, the infants are treated 85% of the time on average.<sup>12</sup>

TsB was determined on capillary blood drawn on heel prick before phototherapy (TsB<sub>0</sub>) and after 24 hours of treatment (TsB<sub>24</sub>) by reflection densitometry on Vitros 5.1 analyzer (Ortho-Clinical Diagnostic, Rochester, NY). TsB was calculated as the sum of measured unconjugated (Bu) and conjugated bilirubin (Vitros BuBc slide).<sup>13</sup> If the time interval between the first blood sample and initiation of phototherapy exceeded 4 hours, another blood sample was drawn.

The phototherapy apparatus used was neoBLUE LED phototherapy device (Natus Medical, San Carlos, CA) emitting blue light with an emission peak at 460 nm and a bandwidth of 450 to 470 nm. The neoBLUE LED can be set to deliver phototherapy either with low or high intensity. In this setup, we used only the high-intensity regimen. We did not use turquoise light because this was not commercially available.<sup>12</sup> Irradiance was measured with the neoBLUE LED phototherapy radiometer (Natus Medical) every eighth hour at the infant's head, trunk, and knees, and the average was calculated. These measurements were performed by the attendant nurses. The radiometer measures spectral irradiance in the range of 420 to 500 nm with maximum sensitivity in the spectrum of 440 to 480 nm. It was calibrated before the study was initiated.

Infants' body weight was measured immediately before and after phototherapy.

## Ethics

The study was approved by The Regional Committee on Biomedical Research Ethics.

## Statistical Analysis

Total serum bilirubin concentrations and light irradiances are described as median (95% confidence interval). Comparisons between the randomization groups and the categorization groups were performed by using nonparametric tests: Kruskal-Wallis test when all groups were considered as a whole and Wilcoxon rank-sum test when they were compared pairwise.

The association between the percentage decrease of TsB during the 24 hours of treatment, or  $\Delta$  TsB<sub>0-24</sub> (%), difference between TsB<sub>0</sub> and TsB<sub>24</sub> expressed as a percent, and light irradiance was described by both linear regression and smooth regression by cubic spline with 3 knots.<sup>14</sup> A test for linearity was performed by testing if the cubic spline relationship could be reduced to a simple linear mean relationship.

A multiple linear regression analysis with adjustment for possible confounders of  $\Delta$  TsB<sub>0-24</sub> (%) was performed with  $\Delta$  TsB<sub>0-24</sub> (%) as dependent variable and light irradiance, TsB<sub>0</sub>, gestational age, birth weight, postnatal age, and volume of infant formula as independent variables.

Finally, the relation between change in body weight during the phototherapy and light irradiance was similarly studied by using linear regression analysis.

Statistical analysis was performed by using Stata 11. Statistic significance level was 5%.

## RESULTS

In all, 158 infants were included in the study. Seven infants dropped out: 5 infants because of compliance problems from the mother and 2 that could

not be kept warm (apparatus/mattress distance 47 cm). Thus, the study group consisted of 151 infants. Clinical and demographic data for the infants are shown in Table 1.

When considering all 4 randomization groups as a whole, there was a significant decline in TsB with decreasing distance from phototherapy device to the infant whereby the light irradiance increased. The same was observed when the groups were considered pairwise, except when comparing the distances of 29 versus 38 cm (Table 2). Similarly, when the light irradiance for all infants was categorized into 3 groups, <30, 30–45, and >45  $\mu$ W/cm<sup>2</sup>/nm, the decrease in TsB increased with increasing light irradiance, both when all 3 groups were considered as a whole and when 2 groups were considered pairwise (Table 3).

The relationship between light irradiance and TsB is shown graphically in Fig 1 both as a smooth curve and by simple linear regression. The smooth curve does not make assumption of the shape of the association between  $\Delta$  TsB<sub>0-24</sub> (%) and light irradiance, and contains the simple linear association as a special case. The association could be simplified from the general smooth curve to the linear association ( $p=0.27$ ), ie, the hypothesis of a simple linear association between  $\Delta$  TsB<sub>0-24</sub> (%) and light irradiance was accepted. Based on the linear presentation, there was a statistically significant association between the variables ( $P < .001$ ). By increasing the irradiance from 20 to 55  $\mu$ W/cm<sup>2</sup>/nm, the decrease in TsB<sub>0-24</sub> (%) increased from approximately 30% to 50%.

Adjustment for possible confounding variables of the association between  $\Delta$  TsB<sub>0-24</sub> (%) and light irradiance is shown in Table 4. The association remains highly significant after the adjustment ( $P < .001$ ). In addition,  $\Delta$  TsB<sub>0-24</sub> (%) was significantly negatively

**TABLE 1** Clinical and Demographic Data of the Patients (*N* = 151)

Characteristic	<i>n</i>
Gender, female/male	65/86
Gestational age, days, median (range)	254 (231, 292)
Birth wt, g, median (range)	2780 (1410, 4500)
Apgar score $\leq 7$ at 5 min, <i>n</i> (%)	4 (3)
Maternal/gestational diabetes, <i>n</i> (%)	6 (4)
Transient tachypnea of the newborn, <sup>a</sup> <i>n</i> (%)	2 (1)
Hypoglycemia, <sup>b</sup> <i>n</i> (%)	8 (5)
Nonwhite, <i>n</i> (%)	8 (5)
Wt change from birth to phototherapy, %, median (range)	-5 (-15, 28)
Age at phototherapy, h, median (range)	81 (36, 486)
Wt change from start to end of phototherapy, %, median (range)	1 (-4, 8)
TsB <sub>0</sub> , $\mu\text{mol/L}$ , median (range)	295 (148,402)
Feeding during phototherapy	
Breast feeding, <i>n</i> (%)	53 (35)
Formula, <i>n</i> (%)	4 (3)
Mixed, <i>n</i> (%)	94 (62)
Infant formula mL/kg, median (range)	21 (0, 157)

<sup>a</sup> Less than 48 h.

<sup>b</sup> Blood glucose  $<1.8 \mu\text{mol/L}$ .

**TABLE 2** Changes in TsB in Relation to the Distance From the Phototherapy Apparatus to the Mattress

	Distance (cm)				<i>P</i> value
	47	38	29	20	
Infants ( <i>n</i> )	37	38	38	38	
TsB <sub>0</sub> ( $\mu\text{mol/L}$ ) <sup>a</sup>	302 (273–347)	288 (274–347)	301 (282–335)	274 (241–301)	.31
TsB <sub>24</sub> ( $\mu\text{mol/L}$ ) <sup>a</sup>	210 (172–235)	167 (154–184)	186 (168–196)	139 (119–159)	$<.001$
$\Delta$ TsB <sub>0–24</sub> ( $\mu\text{mol/L}$ ) <sup>a</sup>	101 (94–115)	117 (105–125)	120 (99–135)	134 (116–142)	.001
$\Delta$ TsB <sub>0–24</sub> (%) <sup>a</sup>	34 (31–38)	41 <sup>b</sup> (38–44)	40 <sup>c</sup> (36–45)	49 <sup>d</sup> (46–53)	$<.001$
Light irradiance ( $\mu\text{W/cm}^2/\text{nm}$ ) <sup>a</sup>	25 (23–26)	31 (29–33)	39 (36–40)	44 (42–48)	$<.001$

<sup>a</sup> Median (95% confidence interval).

<sup>b</sup> 47 cm vs 38 cm: *P* = .004.

<sup>c</sup> 38 cm vs 29 cm: *P* = .98.

<sup>d</sup> 29 cm vs 20 cm: *P* = .001.

**TABLE 3** Changes in TsB in Relation to Light Irradiance Categorized Into 3 Groups

	Light Irradiance ( $\mu\text{W/cm}^2/\text{nm}$ )			<i>P</i> value
	$< 30$	30–45	$> 45$	
Infants ( <i>n</i> )	52	78	21	
TsB <sub>0</sub> ( $\mu\text{mol/L}$ ) <sup>a</sup>	305 (279–343)	286 (266–300)	297 (254–333)	.12
TsB <sub>24</sub> ( $\mu\text{mol/L}$ ) <sup>a</sup>	195 (170–234)	166 (144–178)	157 (124–186)	$<.001$
$\Delta$ TsB <sub>0–24</sub> ( $\mu\text{mol/L}$ ) <sup>a</sup>	108 (99–119)	117 (108–126)	139 (122–148)	$<.001$
$\Delta$ TsB <sub>0–24</sub> (%) <sup>a</sup>	36 (32–39)	42 <sup>b</sup> (40–46)	47 <sup>c</sup> (44–52)	$<.001$
Light irradiance ( $\mu\text{W/cm}^2/\text{nm}$ ) <sup>a</sup>	26 (24–27)	36 (36–39)	49 (47–51)	$<.001$

<sup>a</sup> Median (95% confidence interval).

<sup>b</sup>  $<30$  vs 30–45  $\mu\text{W/cm}^2/\text{nm}$ : *P*  $<.001$ .

<sup>c</sup> 30–45 vs  $>45 \mu\text{W/cm}^2/\text{nm}$ : *P* = .03.

correlated to birth weight and positively to formula volume. The body weight gain during phototherapy was 1% (Table 1), and it was not significantly related to light irradiance (*P* = .26).

The only side effects observed were loose stools; no rash was seen.

## DISCUSSION

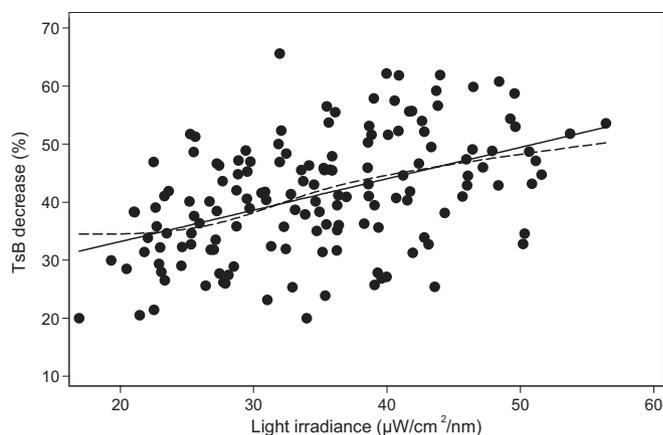
The purpose of this study was to examine the relationship between light irradiance and decrease in TsB and also to see if we could demonstrate a saturation point of the decrease in TsB.

The overall result showed a highly significant positive correlation between light irradiance and  $\Delta$  TsB<sub>0–24</sub> (%). Because the test for linearity was significant and the smooth curve did not level off, we found no evidence of a saturation point. When the irradiance increased from 20 to 55  $\mu\text{W/cm}^2/\text{nm}$ ,  $\Delta$  TsB<sub>0–24</sub> (%) increased from 30% to 50%.

A linear dose-response relationship has previously been proved by Mims et al<sup>7</sup> using unidirectional phototherapy from above with blue fluorescent tubes, although at relatively low light irradiances. In contrast, Tan<sup>9,10</sup> described the relation as an asymptotic regression of bilirubin response to increasing irradiance and demonstrated a saturation point of the rate of TsB decrease: first, in 1977, a saturation point at an irradiance level of  $\sim 10$  to  $12 \mu\text{W/cm}^2/\text{nm}$  and then in 1982 at an irradiance level of  $\sim 30 \mu\text{W/cm}^2/\text{nm}$ .  $\Delta$  TsB<sub>0–24</sub> (%) were 37 and 50, respectively. The improved decrease in TsB was a result of using lamps with a more effective spectral emission curve.

Solana et al<sup>15</sup> showed a significantly greater decrease of TsB at  $40 \mu\text{W/cm}^2/\text{nm}$  than at  $30 \mu\text{W/cm}^2/\text{nm}$ , which is in accordance with our results. The difference between Tan's<sup>10</sup> and ours as well as Solana et al's<sup>15</sup> results may be partly due to differences of the light measurements because data on light irradiance are dependent on the emission spectrum of the applied light and the radiometers.

In this study, we used unidirectional phototherapy with blue LEDs from above. Tan<sup>9,10</sup> used a phototherapy unit containing either both blue and daylight fluorescent tubes<sup>9</sup> or only blue tubes<sup>10</sup> in a multidirectional setup. In this setup, he had a system of switches to differentiate the light irradiances, that is, the highest irradiances were provided by bi- or multidirectional phototherapy. The total light irradiance



**FIGURE 1**

$\Delta$  TsB<sub>0-24</sub> (%) in relation to light irradiance ( $\mu\text{W}/\text{cm}^2/\text{nm}$ ). Solid line indicates linear regression, dashed line indicates smooth regression. Equation:  $\Delta$  TsB<sub>0-24</sub> (%) = 22.41 + 0.55 \* light irradiance ( $\mu\text{W}/\text{cm}^2/\text{nm}$ ).

**TABLE 4** Multiple Linear Regression Analysis With  $\Delta$  TsB<sub>0-24</sub> (%) as Dependent Variable and Light Irradiance, TsB<sub>0</sub>, Gestational Age, Birth Wt, Postnatal Age, and Infant Formula as Independent Variables

Variable	Coefficient (95% CI)	P value
Light irradiance ( $\mu\text{W}/\text{cm}^2/\text{nm}$ )	0.47 (0.31 to 0.63)	<.001
TsB <sub>0</sub> ( $\mu\text{mol}/\text{L}$ )	-0.01 (-0.04 to 0.03)	.74
Gestational age (d)	-0.04 (-0.18 to 0.09)	.52
Birth wt (kg)	-4.33 (-7.76 to -0.91)	.01
Postnatal age (h)	0.02 (-0.00 to 0.04)	.07
Infant formula (mL/kg)	0.03 (0.00 to 0.07)	.04

was calculated as the sum of irradiances measured from above and below the infant. This might affect the results when compared with unidirectional phototherapy. In the current study, the light-exposed area was held constant. Thus, another explanation of the difference between Tan's<sup>10</sup> and our results might be due to Tan's<sup>10</sup> somewhat imperfect study design.

Although we could not demonstrate a "saturation point" at light irradiances even up to 55  $\mu\text{W}/\text{cm}^2/\text{nm}$ , we cannot rule out that it exists at a higher irradiance level. However, this is doubtful for the following reasons: the rates of formation of E-isomers in the skin will increase with increasing irradiance; the formation of the most important excretion products, lumirubins, is irreversible; and under clinical circumstances, it is unlikely that the excretion capacity of lumirubins is limited because the

plasma half-life of lumirubins is short and they do not accumulate in plasma.<sup>2</sup>

The negative association between  $\Delta$  TsB<sub>0-24</sub> (%) and birth weight was in the expected direction. As birth weight increases, the body surface area in relation to weight decreases, that is, the light-exposed area in relation to weight decreases. Moreover, with increasing birth weight, the skin becomes thicker and more mature, which might reduce the effect of phototherapy.

A positive association was seen between  $\Delta$  TsB<sub>0-24</sub> (%) and formula volume. Approximately 60% of the breastfed infants were supplemented by formula during phototherapy, but most often in small amounts. The infants received formula due to suspicion that they were not receiving enough breast milk. That formula supplement enhances the decrease of TsB during phototherapy has been previously observed.<sup>16</sup>

The reason might be that both breastfeeding and breast milk increase hyperbilirubinemia.<sup>17</sup>

We found a nearly significant positive correlation between  $\Delta$  TsB<sub>0-24</sub> (%) and the postnatal age. The relationship between TsB and postnatal age can be explained by the natural history of hyperbilirubinemia, ie, the spontaneous accumulation of unconjugated bilirubin decreases during the first days of life as the infants' ability to clear bilirubin increases and the enterohepatic recirculation decreases.

We found that  $\Delta$  TsB<sub>0-24</sub> (%) was independent of TsB<sub>0</sub>. In contrast, Jahrig et al<sup>18</sup> apparently showed a positive correlation between initial TsB<sub>0</sub> and  $\Delta$  TsB<sub>0-24</sub> (%).

During phototherapy with fluorescent light, infants have an increased insensible water loss.<sup>19</sup> This finding has not been studied using LEDs, which, because of their low heat output, should be less likely to cause insensible water loss. During routine care, we found that the infants had an average weight gain of 1%, and it was independent of the light irradiance. We did not prove any side effects of the phototherapy with irradiances up to 55  $\mu\text{W}/\text{cm}^2/\text{nm}$ . However, there are no data confirming the safety of such high irradiance level.

Strengths of our study include that the sensitivity of the radiometer corresponds to the emission spectrum of the light source, we used a single light source, and the light-exposed area was held constant.

A limitation of the study was that the concentration of bilirubin in serum was measured as the total bilirubin concentration determined by the Vitros method. For this reason, the photoisomers were included in the measurement. Before phototherapy, the concentration of photoisomers is low, but it increases during the treatment. Thus, under optimal conditions, the bilirubin concentration should have been

determined by the high performance liquid chromatography, but this method cannot be used clinically.

To minimize the risk of bilirubin encephalopathy and to shorten the time of phototherapy and thus diminish the negative effect on parent-infant attachment, neonatologists wish to provide the best phototherapy possible to the jaundiced infants. On the basis of Tan et al's studies,<sup>10</sup> the irradiances used have been up to  $\sim 30 \mu\text{W}/\text{cm}^2/\text{nm}$  the past 3 decades. Phototherapy equipment has improved significantly, and the treatment has become more efficacious. Moreover, no serious side

effects to phototherapy have been reported. Together, these factors have given NICU caregivers confidence in this treatment. Therefore, phototherapy is today the first-line treatment in hyperbilirubinemia, and the results of this study support its effectiveness. By using neoBLUE LED, we observed a linear relationship between the light irradiance in the range of 20 to  $55 \mu\text{W}/\text{cm}^2/\text{nm}$  and a decrease in TsB, that is, we found no evidence of a saturation point.

## CONCLUSIONS

During phototherapy with LED, we recommend that the distance from the light

source to the infant should be reduced as much as possible to obtain an optimal light irradiance, when intensive phototherapy is needed in late preterm and term infants. With neoBLUE LED, this is the distance from the light source to infant of  $\sim 12 \text{ cm}$ , or an irradiance up to  $55 \mu\text{W}/\text{cm}^2/\text{nm}$ . The small positive effect of formula supplementation is relevant if a maximal TsB fall is essential and may be used with due support of breastfeeding.

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