In the name of GOD

Neonatal Icter
(Unconjugated Hyperbilirubinemia)

By: Dr Behzad Barekatain, MD
Associate professor of pediatrics
neonatologist
IUMS

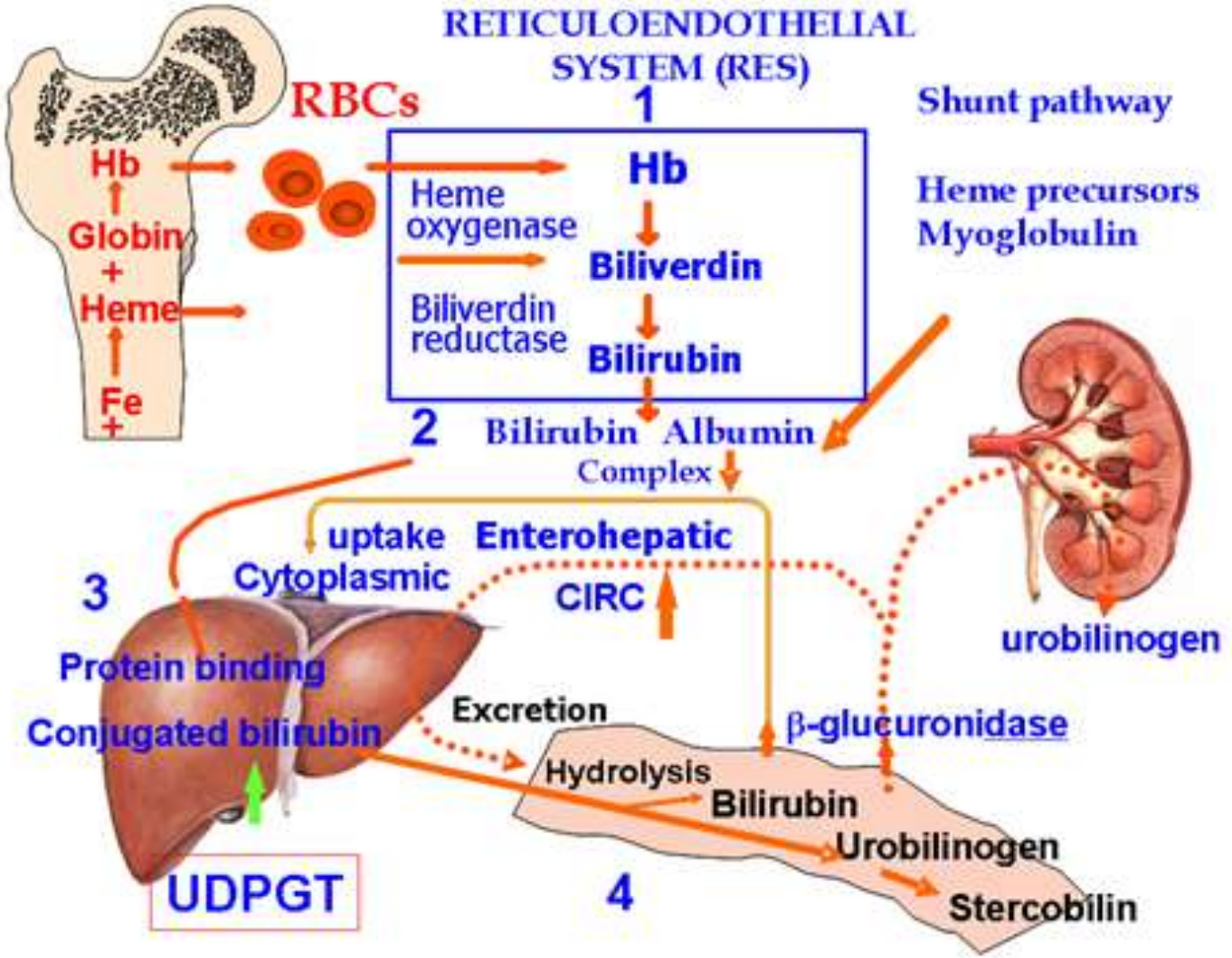
- Hyperbilirubinemia is a common and, in most cases, benign problem in neonates.

- Jaundice is observed during the 1st wk of life in approximately 60% of term infants and 80% of preterm infants.

IS BILIRUBIN a CURSE OR a BOON?

- For many years, unconjugated bilirubin (UCB) was thought to be a useless waste product of heme catabolism, with no physiological function, but with potential toxicity.

- Contrary to what you often will hear about how bilirubin levels increasing in a newborn is not a good thing, there is new research which is showing the importance of the presence of bilirubin.


RETICULOENDOTHELIAL SYSTEM (RES)
RBCs
1
Shunt pathway
Hb
Globin
+
Heme
Fe
+
Hb
Heme oxygenase
Biliverdin
Biliverdin reductase
Bilirubin
Heme precursors
Myoglobulin
2
Bilirubin Albumin Complex
uptake
Cytoplasmic
Enterohepatic CIRC
3
Protein binding
Conjugated bilirubin
Excretion
β-glucuronidase
Hydrolysis
Bilirubin
Urobilinogen
Stercobilin
urobilinogen
UDPGT
4

- Babies with higher bilirubin levels are more disease-resistant," said Dr. Sylvain Dore of Johns Hopkins School of Medicine, Baltimore, Maryland.

- Bilirubin has the ability to function as an antioxidant in the brain, scavenging free radicals and protecting the brain against oxidative damage.

- Dr. Dore has done research on the neuroprotective effect of bilirubin in the hippocampus. His studies have indicated that low concentrations of bilirubin decreased oxygen-radical mediated injury, suggesting that bilirubin could act as an antioxidant.

- Bilirubin also “protects against retinopathy in premature babies.”

Dore S, Snyder SH. Neuroprotective action of bilirubin against oxidative stress in primary hippocampal cultures. Ann N Y Acad Sci.72-890:167;1999.

- “Bilirubin also has bacteriostatic effect???

The antibacterial effects of bilirubin on gram-negative bacterial agents of sepsis. Huseyin Agah Terzi, Hakan Kardes. Biomedical Research (2016) Volume 27, Issue 1

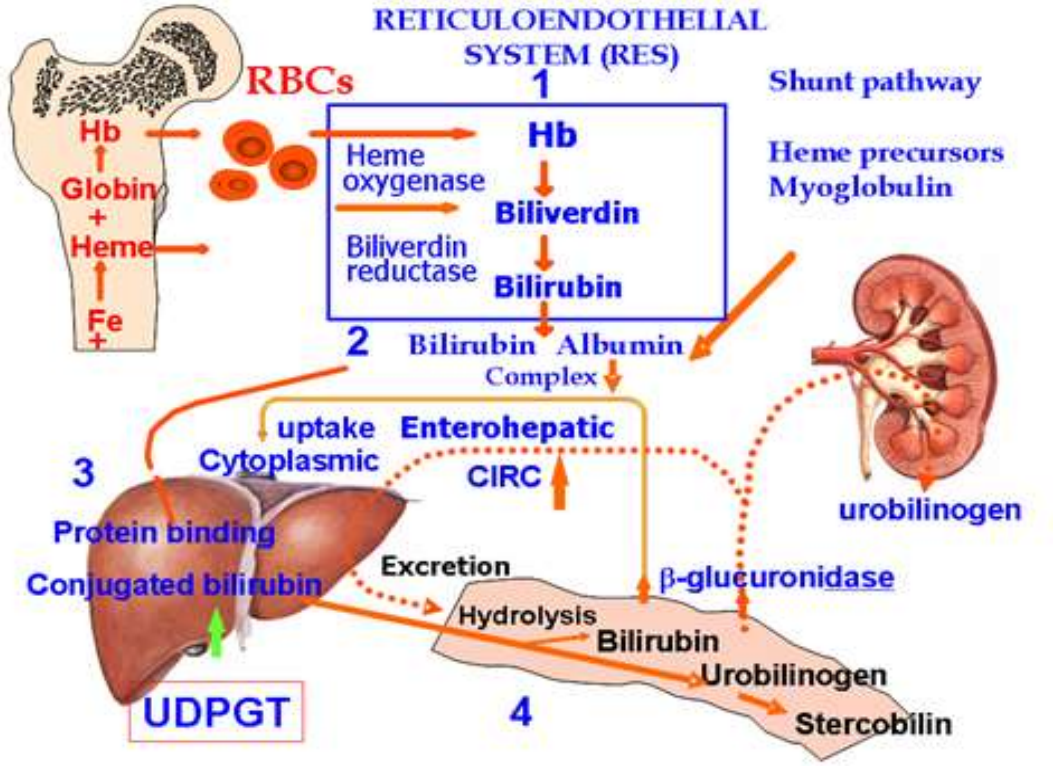
- In some experiments researchers prevented bilirubin synthesis by eliminating the gene for hemeoxygenase and found, as a result, twice the level of stroke damage in mice.

Tomaro ML, Batlle AMD. Bilirubin: its role in cytoprotection against oxidative stress.Int J Biochem Cell Biol 2002;34:216–20.

- UCB is a **curse** at high concentrations, producing apoptosis and cell death, but a **boon** at more physiological levels, protecting cells against oxidant damage.

J D Ostrow.Research Service, VA Puget Sound Health Care System-Seattle Division, and GI/Hepatology Division, Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA.

Treatment is undertaken to prevent neurological damage.



B-barekatain ,Neonatologist

MEASUREMENT OF BILIRUBIN FRACTIONS

VISUAL ASESSMENT- KRAMER's RULE

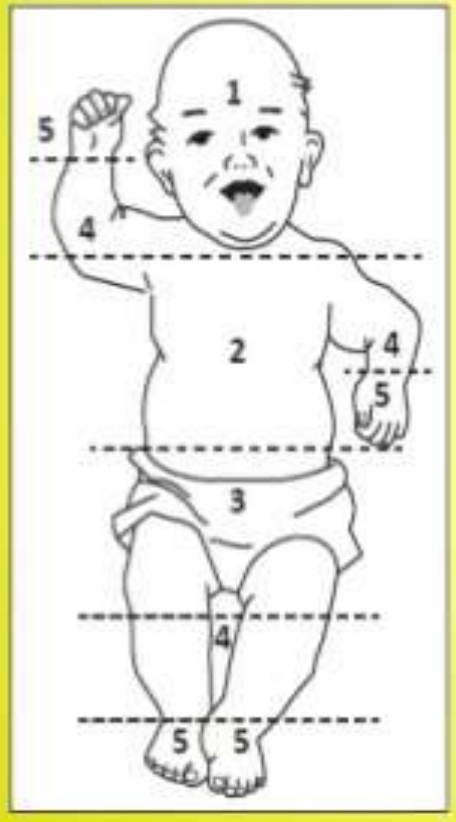


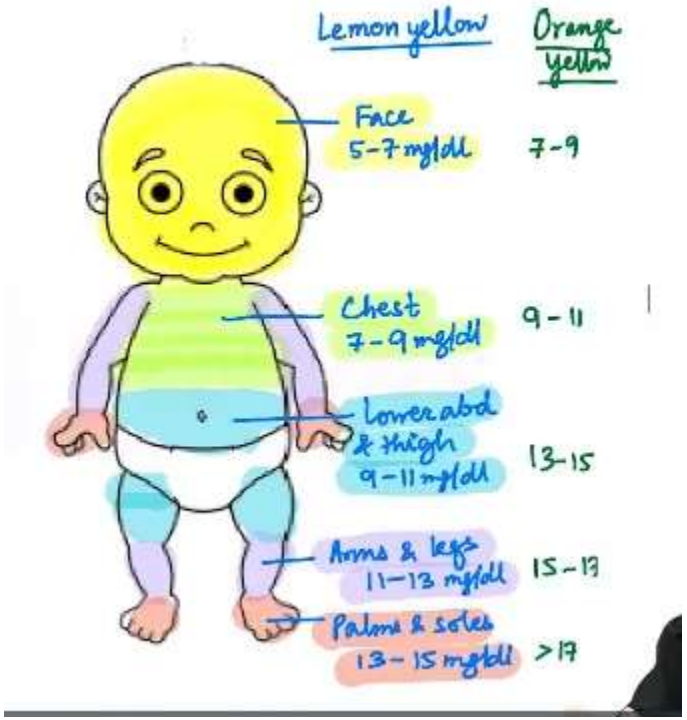
Table 1. Visual Assessment of Neonatal Jaundice (Kramer's rule)

Area of the Body	Level	Range of Serum Bilirubin	
		µmol/L	mg/dL
Head and neck	1	68 - 133	4 - 8
Upper trunk (above umbilicus)	2	85 - 204	5 - 12
Lower trunk and thighs (below umbilicus)	3	136 - 272	8 - 16
Arms and lower legs	4	187 - 306	11 - 18
Palms and soles	5	≥306	≥18

Kramer's rule describes the relationship between serum bilirubin levels & the progression of skin discolouration

- What is the cause of the cephalocaudal progression of jaundice?

Binding of bilirubin to albumin depends on the temperature and speed of blood flow



- Total Serum Bilirubin Measurement (Diazo, Spectrophotometry, HPLC, …)
- Transcutaneous Bilirubinometery

Today other noninvasive methods, specifically TcB, to assess jaundice have become routine practice in the newborn nursery as a screening method more sensitive than visual assessment for jaundice.

There are two commercially available transcutaneous instruments approved by the Food and Drug Administration (FDA) to measure TcB in neonates:

The Philips Children's Medical Ventures BiliChek (Respironics, Inc, Murrysville, PA)

and the Konica Minolta Air-Shields Transcutaneous Jaundice Meter 103 (JM-103,Draeger Medical Systems, Inc, Telford, PA).


Dräger


Dräger

- استفاده از دستگاه transcutaneous bilirubinometer از سالیان قبل به لحاظ داشتن مزایایی از جمله کاهش خون گیری و به دنبال آن کاهش درد ناشی از نمونه گیری و نیز کاهش هزینه های آزمایشگاهی مورد توجه قرار گرفته است.در این راستا دستگاه های متعددی برای اندازه گیری میزان بیلی روبین از طریق پوست ساخته شده است.

- در مورد تشخیص، درمان و پیگیری ایکتر نوزادی با استفاده از دستگاه transcutaneous bilirubinometer باید موارد زیر مورد توجه قرار گیرد:

1.دستگاه transcutaneous bilirubinometer میزان بیلی روبین در بافت های سطحی پوست را اندازه می گیرد نه میزان بیلی روبین موجود در گردش خون و به این دلیل تنها به عنوان وسیله ***غربالگری*** جهت ***تصمیم گیری برای ارسال بیلی روبین سرمی*** کاربرد دارد و از این طریق میزان ارسال آزمایشات سرمی بی مورد را کم می کند.

2.دستگاه transcutaneous bilirubinometer به دلیل غیر تهاجمی بودن می تواند مکرر استفاده شود و میزان افزایش بیلی روبین و تصمیم گیری برای ارسال آزمایشات سرمی را مشخص سازد.

3.با توجه به اختلاف هایی که در دستگاه های مختلف وجود دارد بایستی قبل از استفاده، دقت دستگاه با نتایج به دست آمده به روش آزمایشگاهی در آن مرکز مقایسه شود.

4.در مواردی که عدد دستگاه transcutaneous bilirubinometer بالاتر از 14 باشد باید میزان بیلی روبین به روش آزمایشگاهی تایید شود.

5.استفاده از دستگاه transcutaneous bilirubinometer جهت غربالگری در نوزادان ترم و نزدیک ترم (term & late preterm) کاربرد دارد و در مورد استفاده از آن برای نوزادان پره ترم اتفاق نظر وجود ندارد.

6.از پیشانی و یا استرنوم جهت قرار دادن پروب دستگاه و اندازه گیری بیلی روبین استفاده شود.

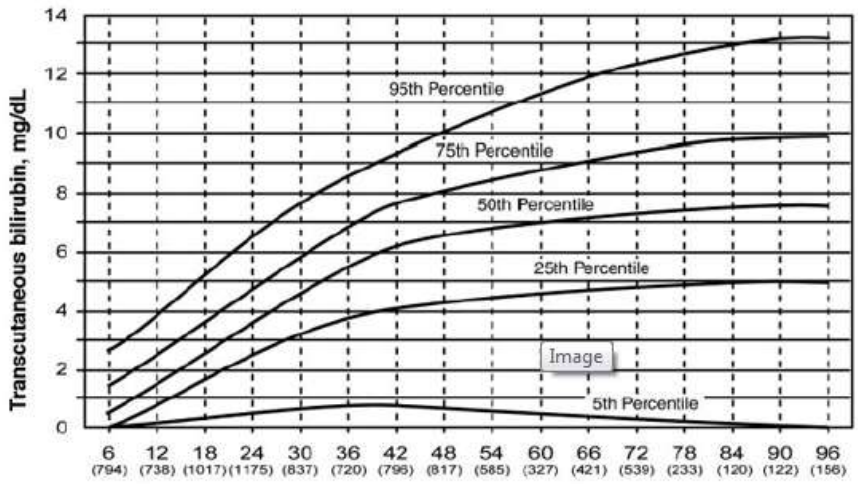
7.در صورتی که نوزاد تحت فوتوتراپی قرار گیرد استفاده از دستگاه transcutaneous bilirubinometer به منظور بررسی کاهش بیلی روبین قابل استفاده است. در این مورد باید از نواحی پوشیده شده پوست مانند ناحیه زیر پد چشمی اندازه گیری انجام شود.قطع فوتوتراپی باید براساس نتایج آزمایشگاهی صورت گیرد.

8.به دلیل این که در مقادیر بالای بیلی روبین سرمی، دستگاه transcutaneous bilirubinometer معمولا عدد بیلی روبین را کمتر از حد واقعی نشان می دهد توصیه می شود در موارد زیر حتما مقدار بیلی روبین به روش سرمی ارسال و اندازه گیری شود:

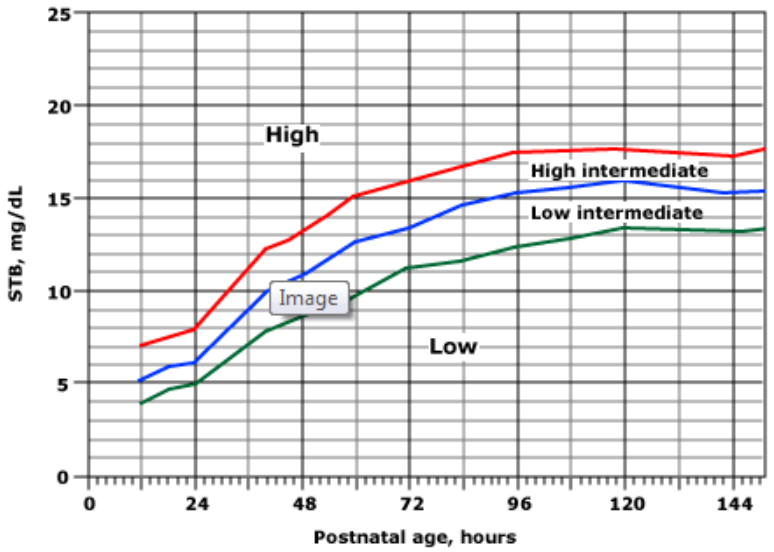
A confirmatory TB should be measured in the following settings:

1. *When TcB exceeds the 75th percentile on the TB nomogram for phototherapy (graph in R).*
2. *When the TcB exceeds the 95th percentile on the TcB nomogram (graph in L).*
3. *At follow-up after discharge, the TcB >13 mg/dL .*
4. *When therapeutic intervention is being considered. Therapy should be initiated while awaiting confirmatory results.*
5. *If the management plan would be altered by considering the TB to be equal to TcB + 3 mg/dL*
6. *The TcB value is at 70% of the TSB level recommended for the use of phototherapy.*

Nomogram of hour-specific transcutaneous bilirubin measurements (mg/dL) for healthy fullterm newborns



Nomogram of hour-specific serum total bilirubin (STB) concentration in healthy term and near-term newborns

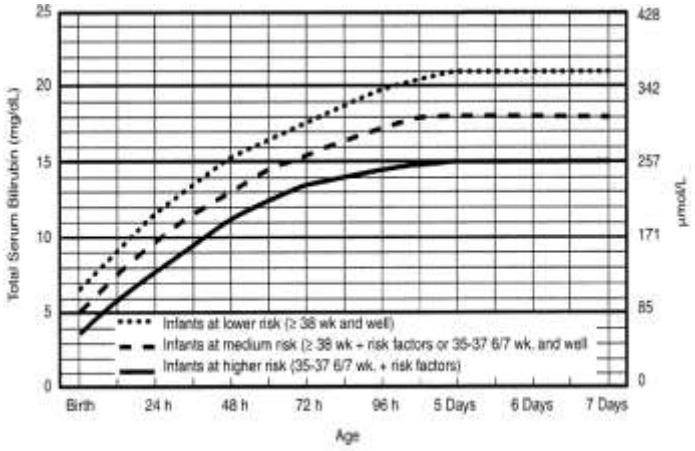


- The recommended treatment for hyperbilirubinemia is phototherapy. Exchange transfusion is recommended for the treatment of extreme hyperbilirubinemia. *(USPSTF, 2009; AAP, 2004)*

- The initiation of phototherapy should be based on the AAP guidelines, taking into account the infant's postnatal age in hours and the risk for bilirubin neurotoxicity. *(AAP, 2004)*

- Neurotoxic risk factors include:

isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis and albumin <3 g/dL



- How phototherapy came to be is a fascinating story, one with a nurse at its center

- Sister Jean Ward, the nurse in charge of the Premature Unit at Rochford General Hospital in Essex, England, firmly believed in the restorative powers of fresh air and sunshine (Fig)

Jean Ward in 1956, with one of the first infants given phototherapy at Rochford General Hospital.Photograph courtesy of BMJ Publishing Group. With permission

- On sunny days, she wheeled the infants outdoors into the hospital courtyard, returning them to the nursery just before the doctors—who were not as keen on this practice— arrived for ward rounds.

- One day in 1956, Sister Ward showed the physicians an undressed infant whose skin was pale except for a triangular area that appeared much more yellow than the rest of its body.

- Dr. RH Dobbs asked whether she had painted the infant's skin with iodine. She said she had not; what she held in her arms was a jaundiced infant whose color had faded except in an area that had been covered by the corner of a sheet

- Subsequently, physicians and scientists at Rochford Hospital discovered that the levels of bilirubin pigment in tubes of blood left in the sun also dropped dramatically.

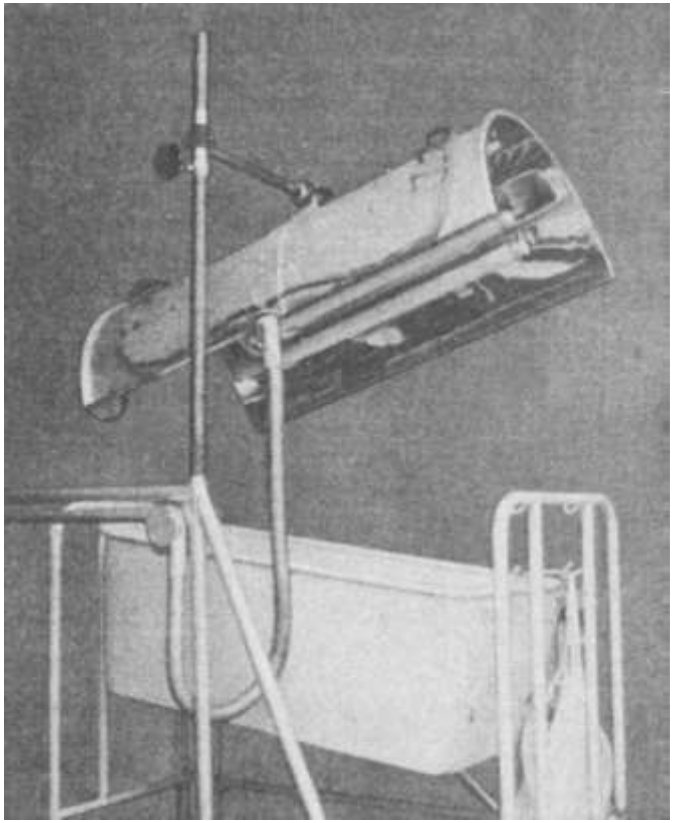
Serum from jaundiced babies was collected and taped to the window in direct sunlight. After only 24 hours in the sun, the bright yellow jaundiced serum had turned green, indicating the conversion of bilirubin to biliverdin.

Bilirubin concentrations were also measured over the following days and it was shown that there was a significant decrease in the bilirubin concentration even at day 1

Fig 4: Serum sample 24 hours after contact with direct sunlight

- Putting these 2 observations together, the idea of phototherapy for neonatal jaundice was born.

- The very first phototherapy unit incorporating an artificial light source instead of natural sunlight was devised and tested by Dr. RJ Cremer and colleagues at Rochford Hospital, and the results were reported in 1958.



The first artificial light apparatus devised for cradle illumination of infants at Rochford General Hospital.

The hemicylindrical stainless-steel reflector, suspended on a height-adjustable moveable gantry, contains 8 24-inch lightblue 40-watt fluorescent tubes spaced 2 inches apart.
A cot can be wheeled under the reflector, and the lights can be switched on separately to vary the amount of power delivered.

Reprinted from Cremer RJ, Perryman PW, Richards DH.
Influence of light on the hyperbilirubinaemia of infants.
Lancet. 1958;1:1094-1097. With permission.

- Phototherapy was not used in the United States until the landmark study of Lucey et al was published a decade later.

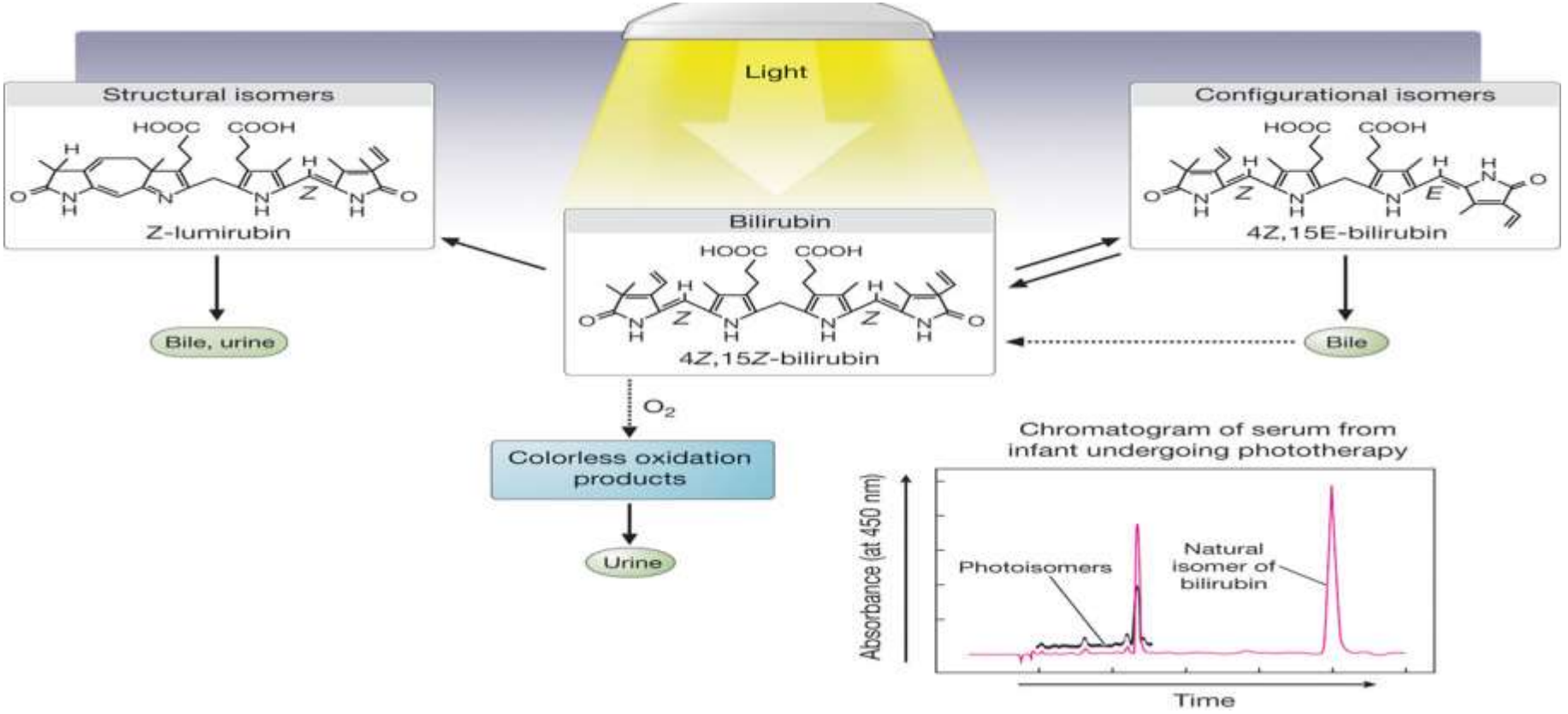
- This randomized controlled trial demonstrating the effectiveness of phototherapy led to its acceptance as a simple, inexpensive, and relatively safe way to prevent hyperbilirubinemia in premature infants *(Lucey J, Ferriero M, Hewitt J. Prevention of hyperbilirubinemia of prematurity by phototherapy. Pediatrics. 1968;41:1047-1054.)*

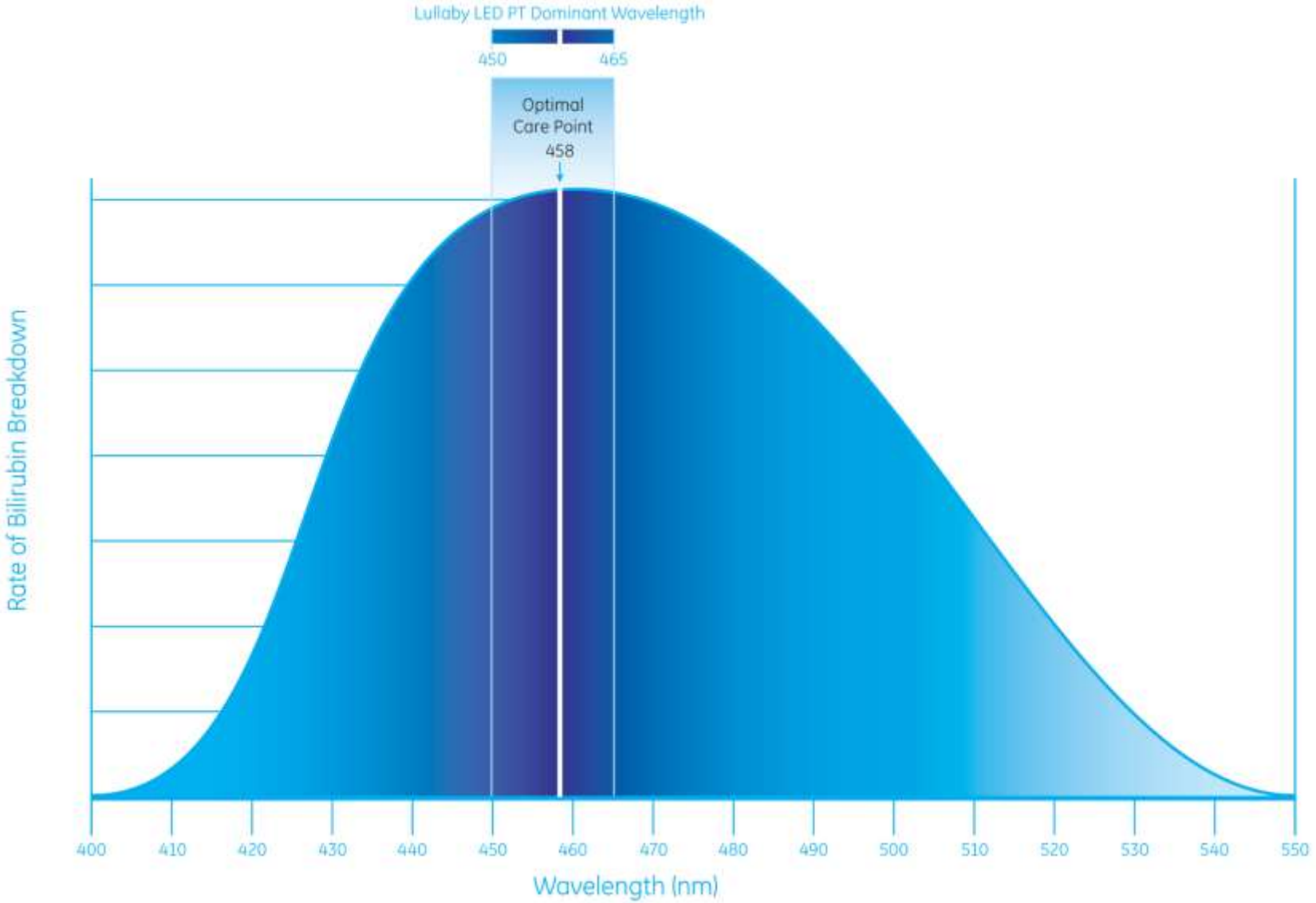
- Maisels, a noted bilirubin expert, suggests that phototherapy is much like a percutaneous drug.

- When phototherapy illuminates the skin, an infusion of discrete photons of energy, like molecules of a drug, are absorbed by bilirubin in the same way that a drug molecule binds to a receptor. Bilirubin molecules in skin exposed to light undergo relatively quick photochemical reactions— configurational isomerization, structural isomerization, and photo-oxidation— to form nontoxic, excretable isomers.

- Phototherapy is the use of visible light for the treatment of hyperbilirubinemia in the newborn.

- This relatively common therapy lowers the serum bilirubin level by transforming bilirubin into water-soluble isomers that can be eliminated without conjugation in the liver.





B-barekatain ,Neonatologist

Irradiance

- Irradiance is the light intensity, or number of photons, delivered per square centimeter of exposed body surface.
- The higher the irradiance the larger the rate of bilirubin decline.

- There may be a saturation point at 30 μW/cm^2/ nm where an increase in irradiance has no increased benefit in decreasing bilirubin levels. But,currently we do not know the maximum effective dose of phototherapy.

(American Academy of Paediatrics Clinical practice guideline. Management of hyperbilirubinaemia in the newborn infant 35 or more weeks gestation. Paediatrics 2004; 114: 297-316)

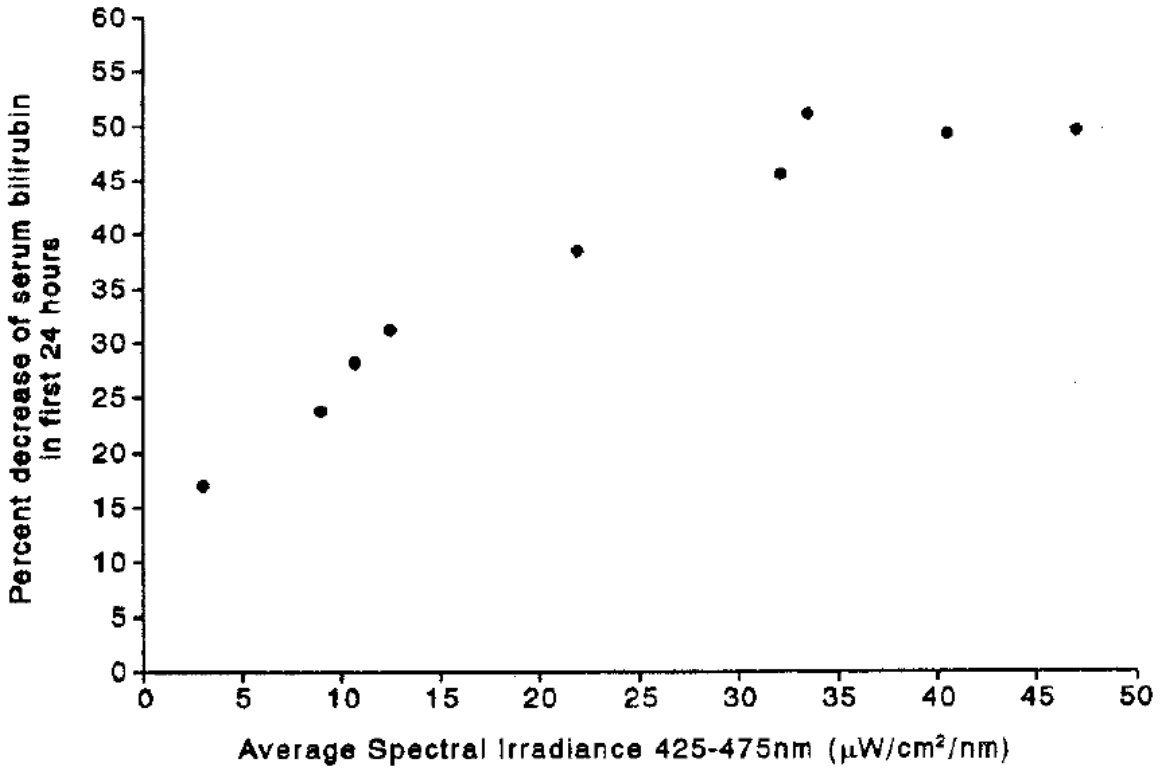
(Tan KL. The pattern of bilirubin response to phototherapy for neonatal hyperbilirubinaemia. Pediatr Res. 4-670)

- The current AAP guidelines suggest that if intensive phototherapy is required then blue lights should be used to deliver at least 30 μW/cm^2/ nm to the greatest surface area available.
- Aim for an irradiance of >12 μW/cm^2/ nm in conventional phototherapy

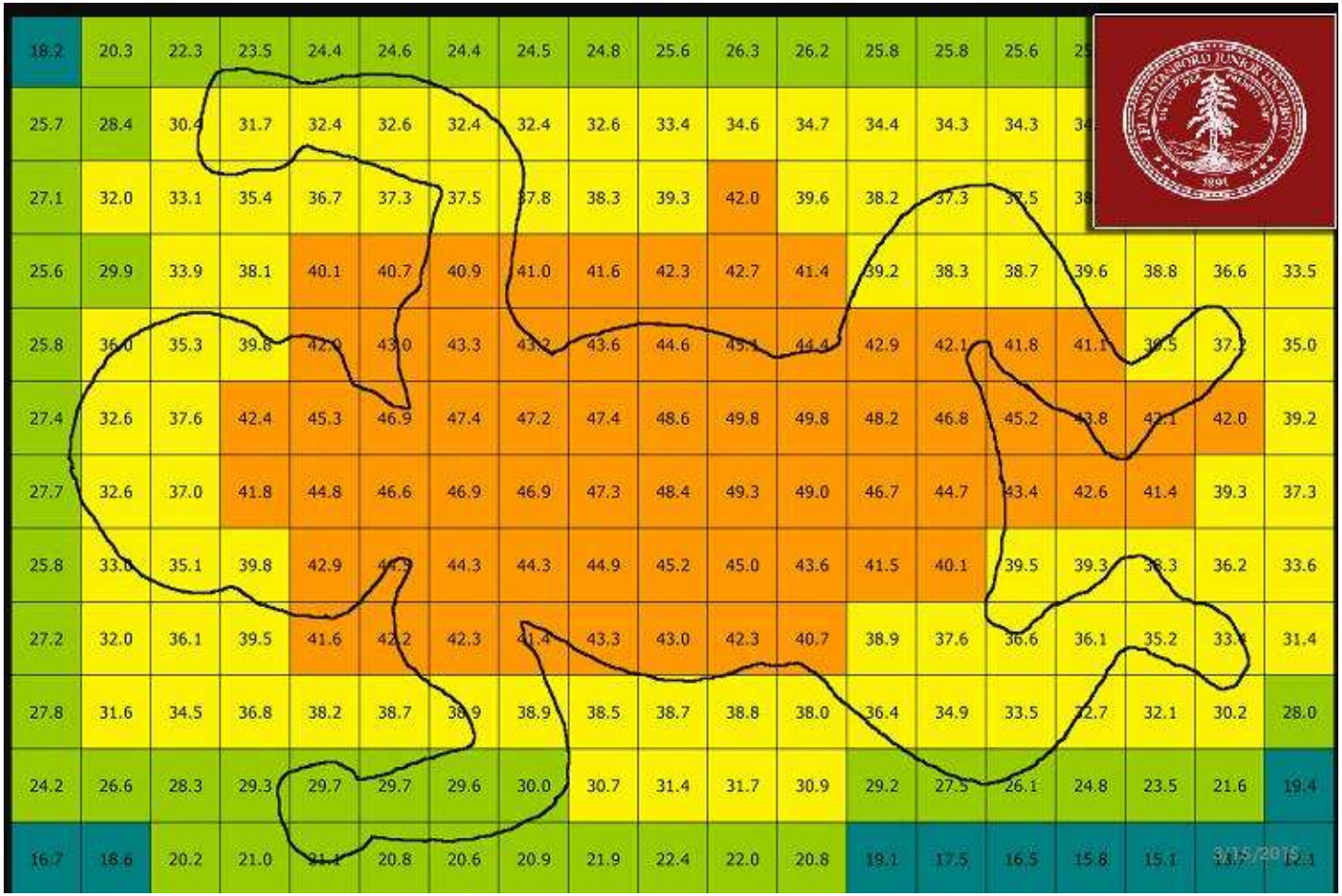
(American Academy of Paediatrics Clinical practice guideline. Management of hyperbilirubinaemia in the newborn infant 35 or more weeks gestation. Paediatrics 2004; 114: 297-316)

Relationship between average spectral irradiance and decrease in serum bilirubin concentration.

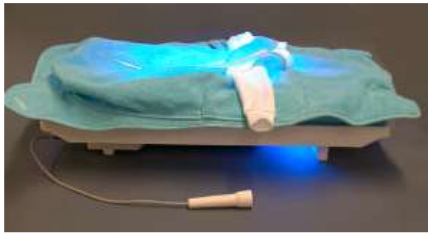
Term infants with nonhemolytic hyperbilirubinemia were exposed to special blue lights (Phillips TL 52/20W) of different intensities. Spectral irradiance was measured as the average of readings at the head, trunk, and knees.
Source: Pediatrics. 1996;98:283-287.



Vreman HJ, Wong RJ, Murdock JR, Stevenson DK. Standardized bench method for evaluating the efficacy of phototherapy devices. Acta Paediatr. 2008;97:308-316



B-barekatain ,Neonatologist



B-barekatain ,Neonatologist

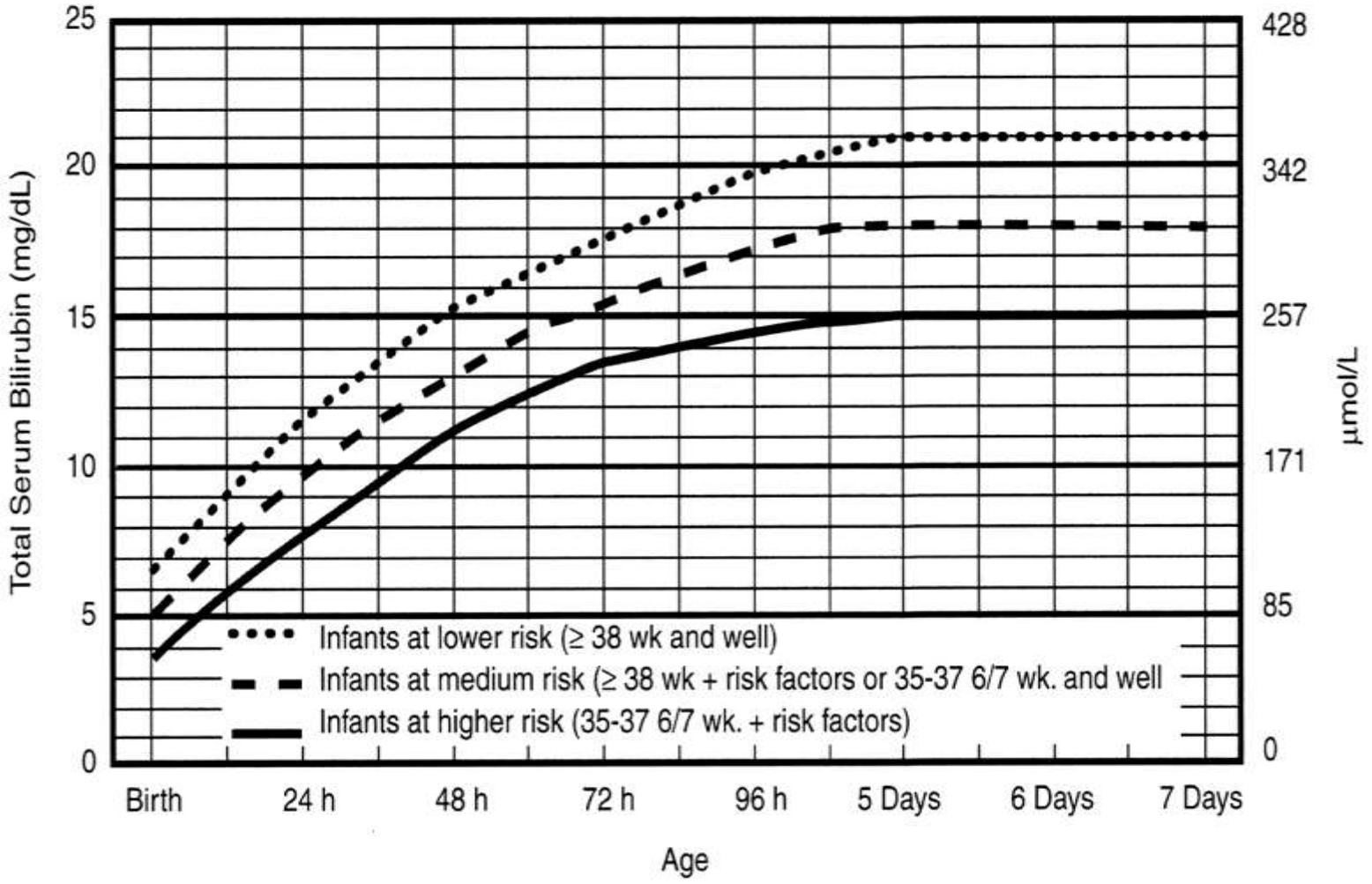
Observations

All infants in Newborn Care receiving phototherapy should have a temperature, pulse and respiration rate documented 4 hourly.

If an infant requires continuous cardio-respiratory monitoring for other reasons, then, this should continue whilst under phototherapy.

Infants under the Blue fluorescent lights need at least saturation monitoring as it is difficult to assess the infants colour under these lights.

Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation



Subcommittee on Hyperbilirubinemia, Pediatrics 2004;114:297-316

Copyright ©2004 American Academy of Pediatrics

PEDIATRICS®

TABLE 32.25

Suggested Use of Phototherapy and Exchange Transfusion in Preterm Infants <35 Wk of Gestational Age

	Phototherapy	Exchange Transfusion
Gestational Age (Week)	Initiate Phototherapy Total Serum Bilirubin (mg/dL)	Total Serum Bilirubin (mg/dL)
<28 0/7	5–6	11–14
28 0/7–29 6/7	6–8	12–14
30 0/7–31 6/7	8–10	13–16
32 0/7–33 6/7	10–12	15–18
34 0/7–34 6/7	12–14	17–19

- This table is modified from Maisels et al,[51] and reflects the authors' recommendations for operational or therapeutic TSB thresholds—bilirubin levels at, or above which, treatment is likely to do more good than harm.[52] They are not based on good evidence.
- Use total bilirubin. Do not subtract direct-reacting or conjugated bilirubin from the total.
- For infants ≤26 weeks gestation, it is an option to use phototherapy prophylactically starting soon after birth.
- Measure irradiance at regular intervals with an appropriate spectroradiometer.
- Measure the serum albumin level in all infants <35 weeks gestation.
- Use the lower range of the listed TSB levels for infants at greater risk for bilirubin toxicity, for example, those with rapidly rising TSB levels, suggesting hemolytic disease, those with serum albumin levels <2.5 g/dL and those who have one or more of the following:. (a) blood pH <7.15; (b) capillary or arterial PCO_2 >50 mm Hg; (c) blood culture positive sepsis; (d) apnea and bradycardia requiring bagging or intubating; (e) hypotension requiring pressor treatment; and (f) mechanical ventilation at the time of blood sampling.
- Use post-conceptional age for phototherapy, for example, when a 29 0/7 week infant is 7 days old, use the TSB level for 30 0/7 weeks.
- In the NICHD, Neonatal Research Network there was a 5% increase in mortality observed in infants <750 g who received intensive phototherapy. This observation and the evidence in neonatal rats of an increase in oxidative injury with increasing irradiance[55] suggest that it is prudent to use less intensive levels of irradiance in these infants. In VLBW infants, phototherapy is almost always prophylactic—it is used to prevent a further increase in the TSB, and TSB levels can usually be controlled by phototherapy that is less intensive. Thus, although there are no studies that show a significant increase in mortality in infants <1500 g, the trends toward a possible increase[18,96,98] suggest that it is reasonable in infants <1500 g to start phototherapy at irradiance levels of about 15 μW/cm² per nm. If the TSB continues to rise, additional phototherapy should be provided by increasing the surface area exposed (phototherapy above and below the infant, reflecting material around the incubator). If the TSB, nevertheless, continues to rise, the irradiance should be increased by switching to a higher-intensity setting on the device or by bringing the overhead light closer to the infant. Fluorescent and LED light sources can be brought closer to the infant, but this cannot be done with halogen or tungsten lamps because of the danger of a burn.

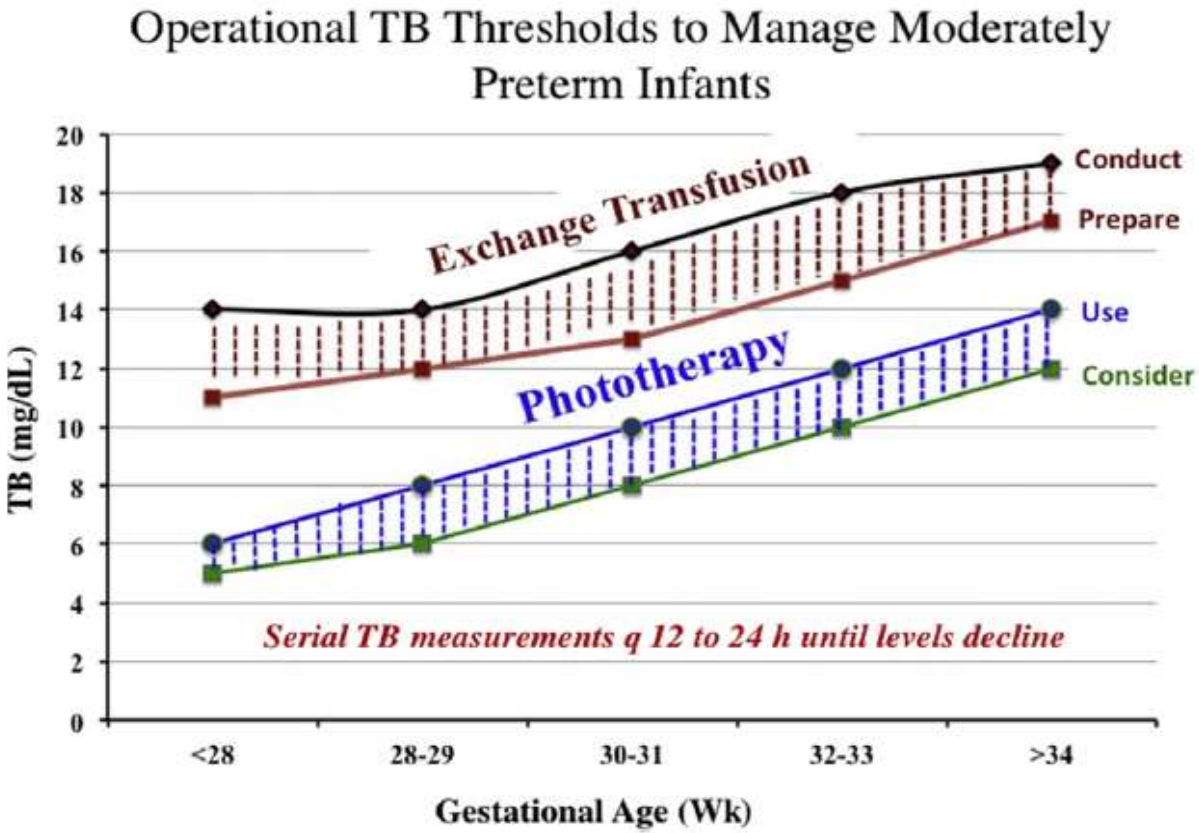


Fig. 1. Suggested use of phototherapy and exchange transfusion in preterm infants less than 35 weeks GA. The operational thresholds have been demarcated by recommendations of an expert panel. The shaded bands represent the degree of uncertainty. Recommended thresholds to prepare for exchange transfusion assume that these infants are already being managed by effective phototherapy. Increase in exposure of body surface area to phototherapy may inform the decision to conduct an exchange transfusion based on patient response to phototherapy. (*Adapted from* Maisels MJ, Watchko JF, Bhutani VK, et al. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. J Perinatol 2012;32:660–4; with permission.)

WHEN TO STOP PHOTOTHERAPY

- There is no standard for discontinuing phototherapy.
- The TSB level for discontinuing phototherapy depends on the age at which phototherapy is initiated and the cause of the hyperbilirubinemia.
- In infants who are readmitted for phototherapy following discharge after their birth hospitalization (usually for TSB levels of 18–20 mg/dL or higher), phototherapy may generally be discontinued when the TSB falls below 13–14 mg/dL. *(Maisels)*
- In infants who receive phototherapy during the birth hospitalization, phototherapy can be discontinued when two consecutive TSB values fall below the level at which phototherapy was initiated. *(Maisels)*
- (Some reference: half of exchange level or 3 below of phototherapy threshold)

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Re: Chang's Score Is Only Helpful Within the First 4 to 5 Days of Life

Eckhard Korsch

Pediatrics 2017;140;; originally published online July 31, 2017;
DOI: 10.1542/peds.2017-1694A

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/140/2/e20171694A.full.html

WHEN TO STOP PHOTOTHERAPY

- On the basis of a huge cohort of newborns treated for hyperbilirubinemia, Chang et al thankfully provided an evidence-based prediction tool (score) to help clinicians decide when to stop phototherapy in birth-hospitalized infants with rebound hyperbilirubinemia to avoid readmission and retreatment

15 (if gestational age<38 weeks) – 7 x (age in days at phototherapy initiation) – 4 x (AAP phototherapy threshold – TSB at phototherapy termination) + 50

- 3 predictors:

•Gestational age •Age at initiation of phototherapy •Relative TSB at phototherapy termination

- However, applying this prediction score is only sensible in newborns that need phototherapy within the first 4 to 5 days of life

Results Using Score

TABLE 4 Risk of Rebound Hyperbilirubinemia by Score

	Infants With Rebound Hyperbilirubinemia			
	Derivation Group ($N = 3518$)		Validation Group ($N = 3530$)	
Prediction Score	*N*	%	*N*	%
≤9	6/1792	0.3	5/1723	0.3
10–19	20/707	2.8	13/708	1.8
20–29	27/568	4.8	38/617	6.1
30–39	56/303	18.5	55/316	17.4
40–49	36/109	33.0	32/124	25.8
≥50	19/39	48.7	17/42	40.5

<10% risk of rebound if score <30

<4% with score <20

Re: Chang's Score Is Only Helpful Within the First 4 to 5 Days of Life

The American Academy of Pediatrics Subcommittee on Hyperbilirubinemia acknowledged the fact that there is no standard for discontinuing phototherapy.[1] For infants who are readmitted after birth, it recommends that phototherapy may be discontinued when the total serum bilirubin level (TSB) falls to <13 to 14 mg/dL (239–239 μmol/L).[1]

On the basis of a huge cohort of newborns treated for hyperbilirubinemia, Chang et al[2] thankfully provided an evidence-based prediction tool (score) to help clinicians decide when to stop phototherapy in birth-hospitalized infants with rebound hyperbilirubinemia to avoid readmission and retreatment.

However, applying this prediction score (Score = 15 [if gestational age <38 weeks] − 7 × [age in days at phototherapy initiation] − 4 × [AAP phototherapy threshold (TSBth)] − total serum bilirubin at phototherapy termination [TSBtm] + 50) is only sensible in newborns that need phototherapy within the first 4 to 5 days of life.

This is because when applying the score for a mature infant on its sixth day of life with an initial TSB of 20 mg/dL, the rebound likelihood according to the Chang score would be 0 when the TSB came only down to 18 mg/dL (50 − [7 × 6] − 4 × [20 mg/dL − 18 mg/dL] = 50 − [42] − 8 = 0). From the seventh day onward, virtually no more phototherapy would be necessary at all, irrespective of the bilirubin levels.

In the case of the recent 100 mature newborns referred to our communal children's hospital in Cologne, Germany, for treatment of hyperbilirubinemia, 35.2% of infants were ≥6 days of age.

Most of these ≥6 days of age infants were breastfed, with huge problems in the initiation of the nursing management in combination with weakness of drinking, which was documented in the weight loss (up to 15% of the birth weight) in these infants.

In our experience, a sufficient milk supply is essential in an effective therapy of hyperbilirubinemia, and it is necessary to apply the Chang rule even in the first days of life.

In summary, I want to emphasize that Chang's score is only helpful to decide when to terminate a first phototherapy within the first 4 to 5 days of life and, importantly, only if a safe milk supply is established.

Eckhard Korsch
Pediatric Neonatologist, Children's Hospital of the City of Cologne, Cologne, Germany
E-mail: korsche@kliniken-koeln.de

CONFLICT OF INTEREST: The author has indicated he has no potential conflicts of interest to disclose.

REFERENCES

1. American Academy of Pediatrics, Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114(1):297–316
2. Chang PW, Kuzniewicz MW, McCulloch CE, Newman TB. A clinical prediction rule for rebound hyperbilirubinemia following inpatient phototherapy. *Pediatrics*. 2017; 139(3):e20162896

doi:10.1542/peds.2017-1694A

Authors' Response

We thank Dr Korsch for his insightful comments. The study cohort in which we developed and validated our prediction rule is younger than the one Dr Korsch describes. Of the infants in our cohort, 96.5% started their first inpatient phototherapy before age 5 days, and we agree that the prediction rule did not capture the probability of rebound hyperbilirubinemia in older infants who undergo their first inpatient phototherapy. For these older infants with significant weight loss, presumably once their feeding difficulties are resolved, their probability of rebound hyperbilirubinemia would be low, although certainly not 0.

In addition, we agree with Dr Korsch that adequate feeding is an essential part of the treatment of hyperbilirubinemia. We do not believe, however, that a sufficient milk supply is necessary to apply the prediction rule. Given the young age of our study cohort (average age of 2.3 days at phototherapy initiation), it is likely that breastfeeding was not well established for many of these infants, and 70% of our cohort received at least 1 formula feeding during phototherapy hospitalization. The senior authors of this article are currently investigating weight loss and feeding in more detail as predictors of readmission for phototherapy.

Pearl W. Chang
Pediatric Hospitalist, Seattle Children's Hospital, Seattle, Washington
E-mail: pearlchangmd@gmail.com

CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

doi:10.1542/peds.2017-1694B

B-barekatain ,Neonatologist

REBOUND BILIRUBIN LEVELS

- It is unnecessary to keep a baby in hospital for a rebound bilirubin level.

American Academy of Pediatrics, Subcommittee on Hyperbilirubinaemia.. Management of hyperbilirubinaemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004; 114: 297-316

Maisels MJ, Kring E. Rebound in serum bilirubin level following intensive phototherapy. Arch Pediatr Adolesc Med 2002; 156: 669-672.

- If a baby does not appear visibly jaundiced 48 hours after stopping phototherapy then they do not require a repeat bilirubin level.

- Term babies who are readmitted for phototherapy (usually between day 3-6) for physiological jaundice do not require a routine rebound level after lights are stopped.

Kaplan M, Kaplan E, Hammerman C et al. Post-phototherapy neonatal bilirubin rebound: a potential cause of significant hyperbilirubinaemia. Arch Dis Child 2006; 91: 31-34.

- Reasons to check a rebound bilirubin 24 hours after stopping phototherapy may include:

**positive direct Coombs*

**<37 weeks gestation*

**bruising*

**early use of phototherapy (started < 72 hours of age)*

Maisels MJ, Kring E. Rebound in serum bilirubin level following intensive phototherapy. Arch Pediatr Adolesc Med 2002; 156: 669-672.

- Consider using the transcutaneous billirubinometer to assess the need for further bilirubin levels to prevent unnecessary blood tests.

Use of phototherapy in newborns with direct hyperbilirubinemia

Recommendation of AAP about phototherapy in neonatal hyperbillirubinemia:
use total bilirubin. Do not subtract direct reacting or conjugated billirubin

If there is a need for phototherapy, particularly in LBW, sick neonates, the presence of direct-reacting hyperbilirubinemia should not be considered a contraindication to its use.

In ***almost all*** circumstances, the direct-reacting serum bilirubin should not be subtracted from the TSB concentration in making decisions about phototherapy or exchange transfusions.

Nevertheless, in our experience, infants with direct-reacting hyperbilirubinemia often show some response to phototherapy

Because the products of phototherapy are excreted in the bile, the presence of cholestasis will decrease the efficacy of phototherapy.

When infants with cholestasis (direct hyperbilirubinemia) are exposed to phototherapy, they will often develop a grayish-brown discoloration of the skin, serum, and urine known as the bronze baby syndrome (BBS).

The pathogenesis of this condition is not fully understood, and, although it occurs exclusively in infants with cholestasis, not all infants with cholestatic jaundice develop this syndrome.

Infants with cholestasis accumulate porphyrins and other metabolites in the plasma, and some investigators have suggested that photosensitization of the porphyrins by bilirubin produces the color changes seen.

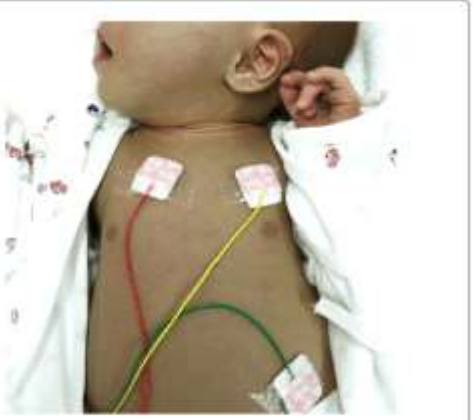


Figure 1: Day 26 infant showing greyish skin diagnosed as bronze baby syndrome.

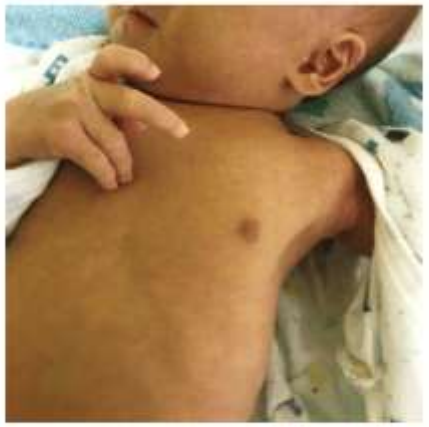


Figure 2: After 1 month health checkup showing normal skin color.

Mortality in Very Low Birth Weight Infants

In the recent NICHD NRN trial there was a 5% increase in mortality in infants with birth weights 501–750 g who received aggressive phototherapy.

This was not statistically significant, but a post hoc, Bayesian analysis estimated an 89% probability that aggressive phototherapy increased the rate of death in the subgroup.

It is unclear why phototherapy might increase mortality in these tiny infants but it is likely that light penetrates more deeply through the thin, gelatinous skin, reaching the subcutaneous tissues and possibly producing oxidative injury to cell membranes.

Vreman HJ, Knauer Y, Wong RJ, Chan M-L, Stevenson DK. Dermal carbon monoxide excretion in neonatal rats during light exposure. Pediatr Res . 2009;66:66–69.

An accepted principle of pharmacology is that we administer a drug in a dose that is adequate to provide therapeutic blood levels while minimizing the risks of toxicity.

The same principles apply too for phototherapy.

Thus, for infants <1500 g, it is reasonable to start phototherapy at lower irradiance levels of about 15 μW/cm2 per nm. If this does not lead to a decrease in TSB, additional phototherapy can be provided by increasing the surface area exposed (phototherapy above and below the infant, reflecting material around the incubator). If this does not prevent an increase in TSB, the irradiance can be increased.

Exchange Transfusion

- The use of high-intensity blue light (460–490 nm) phototherapy applied to a large surface area of the neonate, and prevention of Rh isoimmunization with Rh immunoglobulin, have greatly reduced the need for an exchange transfusion

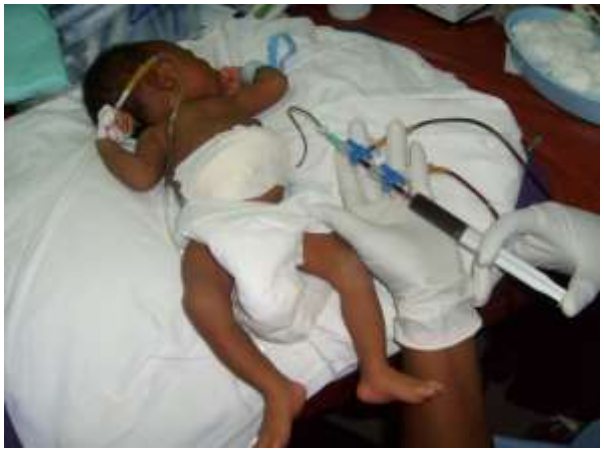
- However, there are still circumstances, most often in the context of hemolytic disease, when exchange transfusion is necessary to prevent or correct hazardous levels of hyperbilirubinemia and reduce the risk of kernicterus.

- Exchange transfusion removes bilirubin-laden blood and in the treatment of immunemediated hemolytic disease also achieves:

(i) the removal of antibody-coated red blood cells (a source of “potential” bilirubin)

(ii) the correction of anemia (if present)

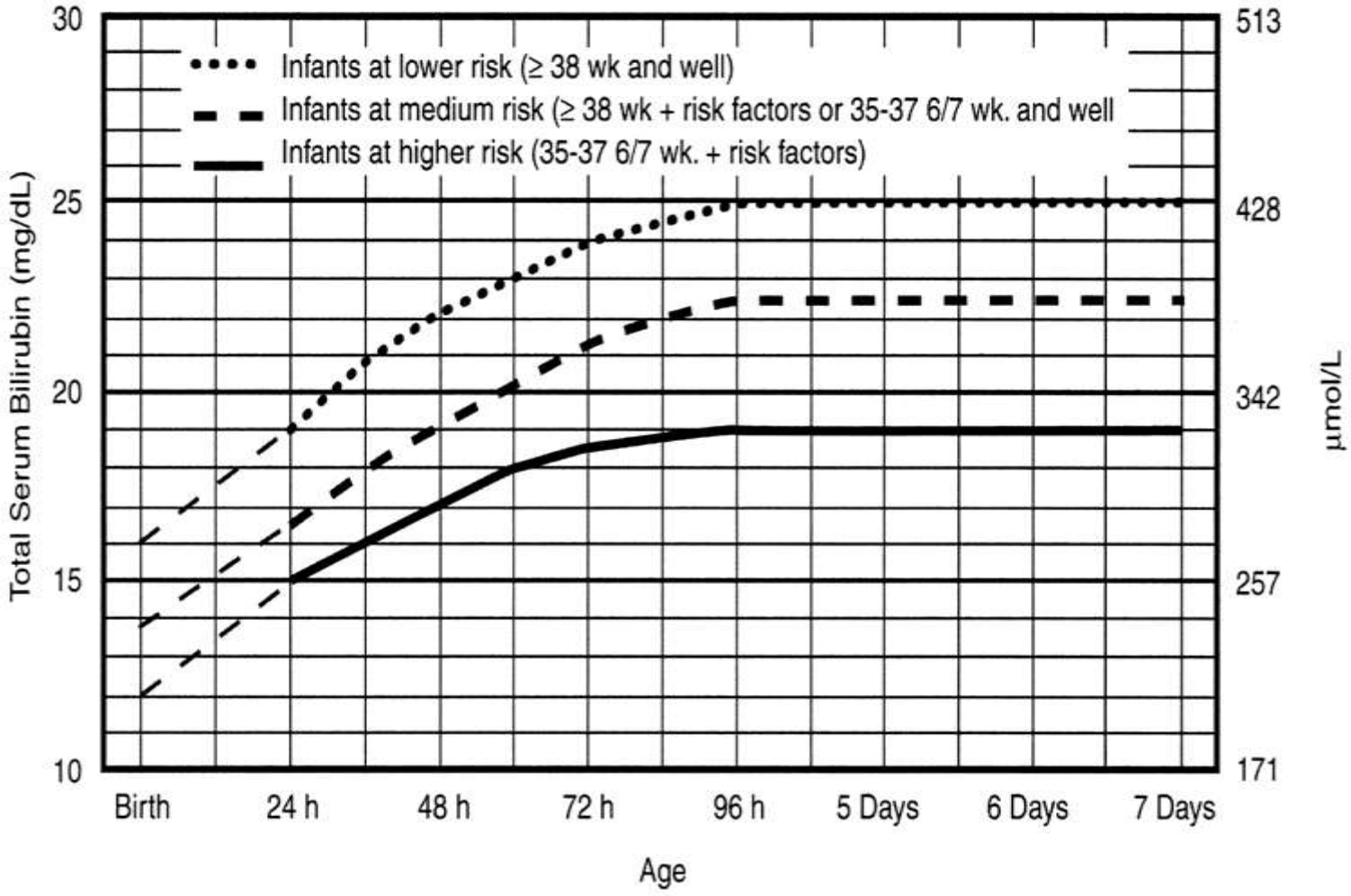
(iii) removal of maternal antibody.



Dr Louis Diamond,

First Exchange Transfusion, Umbilical Vein

Guidelines for exchange transfusion in infants 35 or more weeks' gestation



Subcommittee on Hyperbilirubinemia, Pediatrics 2004;114:297-316

Copyright ©2004 American Academy of Pediatrics

PEDIATRICS®

TABLE 32.25

Suggested Use of Phototherapy and Exchange Transfusion in Preterm Infants <35 Wk of Gestational Age

	Phototherapy	Exchange Transfusion
Gestational Age (Week)	Initiate Phototherapy Total Serum Bilirubin (mg/dL)	Total Serum Bilirubin (mg/dL)
<28 0/7	5–6	11–14
28 0/7–29 6/7	6–8	12–14
30 0/7–31 6/7	8–10	13–16
32 0/7–33 6/7	10–12	15–18
34 0/7–34 6/7	12–14	17–19

- This table is modified from Maisels et al,[51] and reflects the authors' recommendations for operational or therapeutic TSB thresholds—bilirubin levels at, or above which, treatment is likely to do more good than harm.[52] They are not based on good evidence.
- Use total bilirubin. Do not subtract direct-reacting or conjugated bilirubin from the total.
- For infants ≤26 weeks gestation, it is an option to use phototherapy prophylactically starting soon after birth.
- Measure irradiance at regular intervals with an appropriate spectroradiometer.
- Measure the serum albumin level in all infants <35 weeks gestation.
- Use the lower range of the listed TSB levels for infants at greater risk for bilirubin toxicity, for example, those with rapidly rising TSB levels, suggesting hemolytic disease, those with serum albumin levels <2.5 g/dL and those who have one or more of the following:. (a) blood pH <7.15; (b) capillary or arterial PCO_2 >50 mm Hg; (c) blood culture positive sepsis; (d) apnea and bradycardia requiring bagging or intubating; (e) hypotension requiring pressor treatment; and (f) mechanical ventilation at the time of blood sampling.
- Use post-conceptional age for phototherapy, for example, when a 29 0/7 week infant is 7 days old, use the TSB level for 30 0/7 weeks.
- In the NICHD, Neonatal Research Network there was a 5% increase in mortality observed in infants <750 g who received intensive phototherapy. This observation and the evidence in neonatal rats of an increase in oxidative injury with increasing irradiance[55] suggest that it is prudent to use less intensive levels of irradiance in these infants. In VLBW infants, phototherapy is almost always prophylactic—it is used to prevent a further increase in the TSB, and TSB levels can usually be controlled by phototherapy that is less intensive. Thus, although there are no studies that show a significant increase in mortality in infants <1500 g, the trends toward a possible increase[18,96,98] suggest that it is reasonable in infants <1500 g to start phototherapy at irradiance levels of about 15 μW/cm² per nm. If the TSB continues to rise, additional phototherapy should be provided by increasing the surface area exposed (phototherapy above and below the infant, reflecting material around the incubator). If the TSB, nevertheless, continues to rise, the irradiance should be increased by switching to a higher-intensity setting on the device or by bringing the overhead light closer to the infant. Fluorescent and LED light sources can be brought closer to the infant, but this cannot be done with halogen or tungsten lamps because of the danger of a burn.

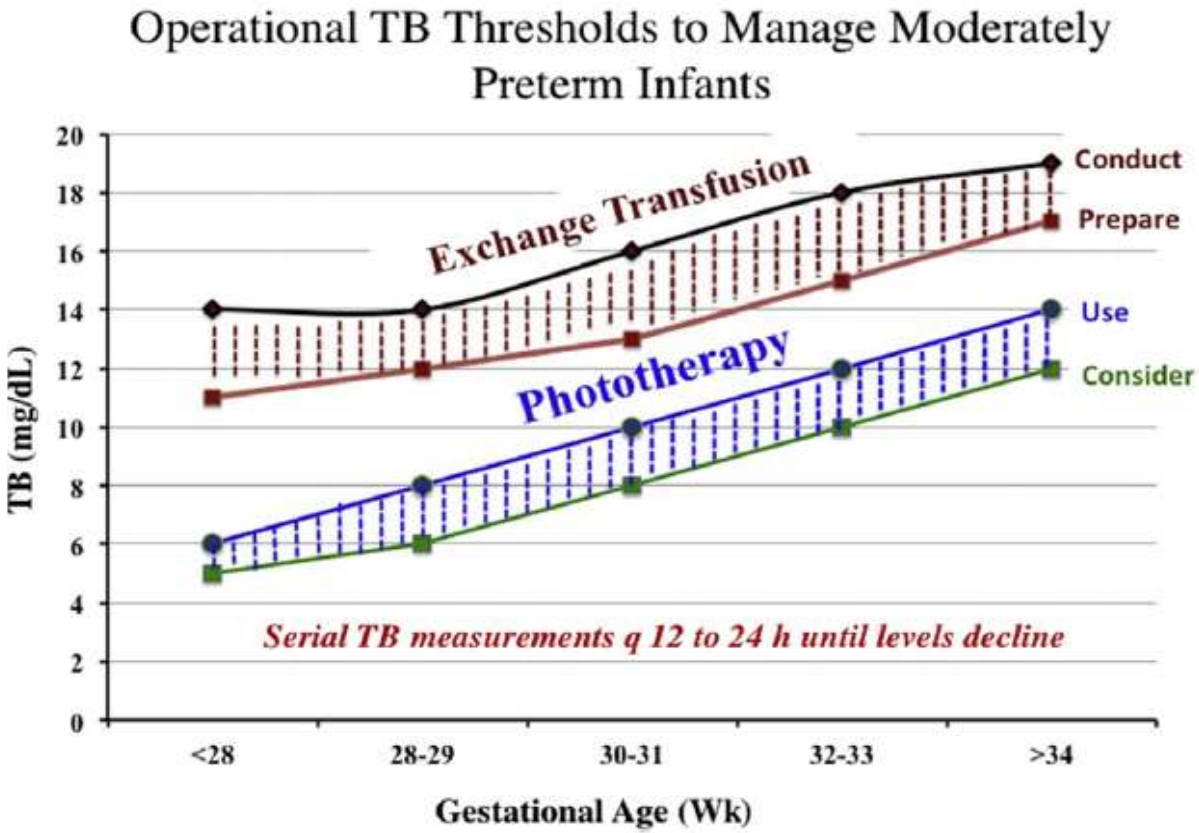


Fig. 1. Suggested use of phototherapy and exchange transfusion in preterm infants less than 35 weeks GA. The operational thresholds have been demarcated by recommendations of an expert panel. The shaded bands represent the degree of uncertainty. Recommended thresholds to prepare for exchange transfusion assume that these infants are already being managed by effective phototherapy. Increase in exposure of body surface area to phototherapy may inform the decision to conduct an exchange transfusion based on patient response to phototherapy. (*Adapted from* Maisels MJ, Watchko JF, Bhutani VK, et al. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. J Perinatol 2012;32:660–4; with permission.)

BILIRUBIN-TO-ALBUMIN MOLAR RATION

RECOMMENDATION of AAP 2017: *(num 7.1.5)*

It is an option to measure the serum albumin level and consider an albumin level of less than 3.0 g/dL as one risk factor for lowering the threshold for phototherapy use

RECOMMENDATION of AAP 2017: *(num 7.1.6)*

If an exchange transfusion is being considered, the serum albumin level should be measured and the bilirubin/albumin (B/A) ratio used in conjunction with the TSB level and other factors in determining the need for exchange transfusion

TABLE 48–2 Bilirubin-to-Albumin Molar Ratio (BAMR) as a Determinant of the Need for Exchange Transfusion

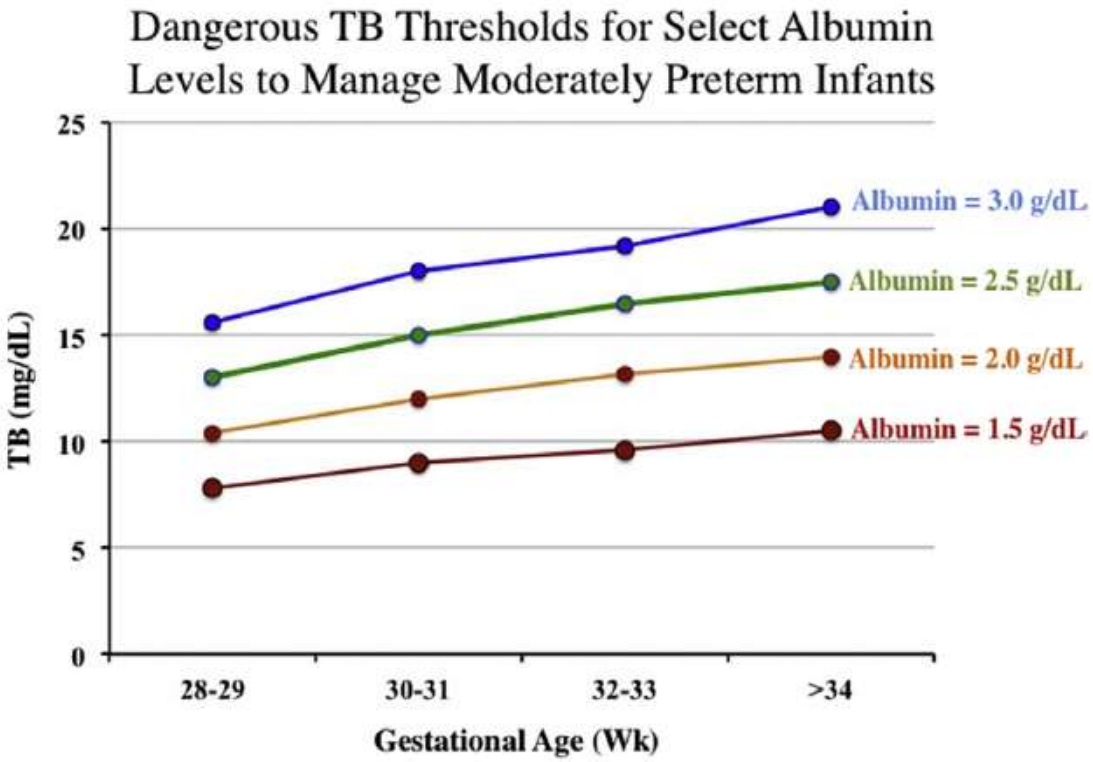
Risk Category	BAMR AT WHICH EXCHANGE TRANSFUSION SHOULD BE CONSIDERED	
	TB (mg/dL)/Albumin (g/dL)	*TB (μmol/L)/Albumin (μmol/L)*
Infants ≥$38^0/_7$ wk	8.0	0.94
Infant $35^0/_7$ to $37^6/_7$ wk and well or ≥$38^0/_7$ wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	7.2	0.84
Infant $35^0/_7$ to $37^6/_7$ wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	6.8	0.80

If TB is at or is approaching the exchange level, send blood for immediate type and crossmatch. Blood for exchange transfusion is modified whole blood (red blood cells and plasma) crossmatched against the mother and compatible with the infant.
G6PD, glucose-6-phosphate dehydrogenase; TB, total bilirubin.
From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, *Pediatrics* 114:297, 2004.

Recommended use of BAMR for initiation of exchange transfusions

BAMR values have been calculated to bilirubin (mg/dL)/albumin (g/dL).
Values above the thresholds for select serum albumin values of 1.5, 2.0, 2.5, and 3.0 g/dL are presented as bands above which bilirubin is likely to be displaced and may be neurotoxic.

(*Data from Ahlfors CE. Criteria for exchange transfusion in jaundiced newborns. Pediatrics 1994;93:488–94.)*



Guidelines according to Birth Weight for Exchange Transfusion in Low-Birth-Weight Infants Based on Total Bilirubin (mg/dL) and Bilirubin-to-Albumin Ratio (mg/g) (Whichever Comes First)

	<1,250 g	1,250–1,499 g	1,500–1,999 g	2,000–2,499 g
Standard risk				
Total bilirubin	13	15	17	18
B:A ratio	5.2	6.0	6.8	7.2
High risk[a]				
Total bilirubin	10	13	15	17
B:A ratio	4.0	5.2	6.0	6.8

[a]Risk factors: Apgar <3 at 5 minutes; PaO_2 < 40 mm Hg ≥2 h; pH ≤ 7.15 ≥1 h; birth weight <1,000 g, hemolysis; clinical or CNS deterioration; total protein ≤4 g/dL; or albumin ≤2.5 g/dL. B:A ratio, bilirubin-to-albumin ratio.

From Ahlfors CE. Criteria for exchange transfusion in jaundiced newborns. *Pediatrics* 1994;93:488–494, with permission.

- Albumin priming to improve the efficiency of the exchange transfusion is not likely to be successful in this regard and not routinely recommended.

- The infusion of albumin while awaiting blood for exchange transfusion may facilitate a shift of bilirubin from the extravascular to intravascular compartment and increase the efficacy of the exchange, although the impact of this intervention may be modest, is difficult to predict, and should not delay initiating the exchange transfusion itself.

Ahlfors CE. Pre-exchange transfusion of albumin: an overlooked adjunct in the treatment of severe neonatal jaundice. Indian Pediatr. 2010;47:231–232.

PHARMACOLOGICAL THERAPY

- **Intra Venous Immunoglobulin (IVIG)**

Controlled trials have confirmed that the administration of IVIG to infants with Rh and ABO hemolytic disease will significantly reduce the need for exchange transfusion.

The doses usually range from 500 mg/kg given slowly over 2 hours soon after birth to 800 mg/kg given daily for 3 days.

The 2004 AAP guideline recommends the use of IVIG if the TSB is rising in spite of intensive phototherapy or if the TSB is within 2–3 mg/dL of the exchange level. (some references:when the serum bilirubin continues to rise by more than 8.5 micromol/litre/hour (0/5 mg/dl/h))

The mechanism of action of IVIG is unknown but it is possible that it might alter the course of hemolytic disease by blocking Fc receptors and thus inhibit hemolysis.

Drugs That Decrease Bilirubin Production

Perhaps the most promising candidate drugs for the prevention of hyperbilirubinemia are the **metalloporphyrins**.

These compounds are synthetic analogs of heme, iron protoporphyrin containing various metals complexed with protoporphyrin, deuteroporphyrin, mesoporphyrin, or glycol-substituted porphyrins

They inhibit the first step in the two-step conversion of heme to bilirubin by competitively inhibiting HO.

Phototoxicity is an inherent potential undesirable side effect of many metalloporphyrin drugs.

The most well studied metalloporphyrin is tin protoporphyrin (SnPP), which was the first tested in human neonates.It is potent, but also has potentially serious phototoxicity

It was replaced by tin mesoporphyrin (SnMP), which also been tested in human neonates and shows promise because of its even greater potency, allowing be used at much lower doses, although it still has phototoxic potential and requires intramuscular injection for administration.

A series of controlled clinical trials in Greece and Argentina have demonstrated that SnMP is highly effective in reducing TSB levels and the requirements for phototherapy in term and preterm infants, including those with G6PD deficiency.

Valaes T, Drummond GS, Kappas A. Control of hyperbilirubinemia in glucose-6-phosphate dehydrogenase deficient newborns using an inhibitor of bilirubin production, Sn-mesoporphyrin. Pediatrics . 1998;101(5):e1.

The only side effect reported to date has been a transient, non-dose-dependent erythema that developed in infants who received white light phototherapy after SnMP administration, but disappeared without sequelae.

SnMP has produced a temporary reduction in TSB levels in children with the Crigler–Najjar syndrome.

Another promising metalloporphyrin is zinc protoporphyrin (ZnPP).

Hungarian investigators reported in the 1970s that IV **D -penicillamine** lowers bilirubin levels in newborns, including infants with ABO hemolytic disease.

In addition to metalloporphyrins, **imidazole dioxolanes** inhibit HO in vitro and in vivo and have high selectivity for HO-1.

To date over 800 infants in controlled trials have received these drugs and trials are ongoing in the United States,

but these drug has not yet been approved by the FDA.

DRUGS INCREASING CONJUGATION OF BILIRUBIN

Phenobarbital induces a number of hepatic enzymes, including uridine diphosphoglucuronosyltransferase (UGT), and the phenobarbital response enhancer sequence of the UGT1A1 gene has been delineated.

Its role in reducing TSB levels in different populations has been well studied, including populations at higher risk for developing hyperbilirubinemia because of a genetic predisposition, where phenobarbital, administered to the mother antenatally, has been used successfully to lower the incidence of significant hyperbilirubinemia and exchange transfusion.

Nevertheless, concerns about long-term toxicity when given to pregnant women militate against the use of phenobarbital for this purpose.

The postnatal use of phenobarbital is less effective, because the TSB has often peaked prior to the clinical effectiveness of the drug.

OTHER DRUGS FOR HYPERBILIRUBINEMIA

A few other drugs deserve mention, but are not typically used for treatment of transitional hyperbilirubinemia in the newborn.

They include **minocycline**, a semisynthetic second-generation tetracycline, which may afford neuroprotection against damage caused by hyperbilirubinemia through as yet not well-defined mechanisms;

clofibrate, the ethyl ester of 2-chlorophenoxy-2-methylpropionic acid, which has primarily been used as an antilipemic agent in adult patients with hyperlipoproteinemia; Certain **Chinese herbal remedies**; and **ursodeoxycholic acid (Actigall).**

both **charcoal** and **agar** have been used to accelerate the elimination of bilirubin from the gut.

Of the various possible treatments besides phototherapy, the HO inhibitors are probably the most promising therapeutic agents for prevention and treatment of neonatal jaundice in order to avoid the risks of exchange transfusion.

Using a targeted approach to identify high producers of the pigment would increase the therapeutic:toxic ratio favorably and maximize benefit and minimize risk for the treated infants.

Until such an approach is feasible, phototherapy will remain the mainstay of treatment for neonatal jaundice.

Home Phototherapy

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Equipment designed for delivering phototherapy in the home has become available.

Home phototherapy for neonatal hyperbillirubinemia has been suggested as an alternative means of providing care for selected infants while saving much of the cost of continued or added hospitalization.

A **physician** who considers the use of home phototherapy should limit its use to infants with the following characteristics:

(1) term infants, older than 48 hours, otherwise healthy;

(2) serum bilirubin concentration greater than 14 mg/dL but less than 18 mg/dL;

(3) no elevation in direct-reacting bilirubin concentration; and

(4) diagnostic evaluation (described below) negative.

Prior to therapy, a diagnostic evaluation should include:

(1) history and physical examination;
(2) hemoglobin concentration or hematocrit;
(3) WBC count and differential count;
(4) blood smear for red cell morphology platelets;
(5) reticulocyte count;
(6) total and direct-reacting bilirubin concentration;
(7) maternal and infant blood typing and Coombs test; and
(8) urinalysis including a test for reducing substances.

- The physician should estimate the rate of rise of the serum bilirubin concentration with laboratory determinations at least four hours apart before home phototherapy is initiated.

- If the concentration of bilirubin is rising too sharply (more than 1 mg in three to four hours) or if there is no rise in serum bilirubin concentration at all in the absence of phototherapy, then home phototherapy is not advisable.

A candidate for home phototherapy should have home caretakers who, in the judgment of the pediatrician, are capable of following instructions.

The infant should be full term and otherwise meet the criteria for discharge from the hospital or for continuing care at home.

Arrangements must be made to measure the infant's serum bilirubin concentration at least every 12 to 24 hours depending on the previous concentration and the rate of rise.

The supervising physician should be in contact with the family daily during the period of treatment.

Parents should sign a consent form that explains the risks (including the possibility that displaced eye patches may occlude the infant's airway) and benefits of the procedure.

This form should also outline the roles of the physician, the equipment provider, and the parents in the subsequent care of the infant.

The parents should be taught how to use the equipment.

They should also be instructed to provide adequate hydration during phototherapy, to apply the eye patches correctly, and to report problems promptly.

Infants should be removed from phototherapy during feedings and diaper changes and when the parents are asleep.

Only equipment designed specifically for providing bilirubin reduction should be used for home phototherapy.

Home phototherapy should be discontinued once the serum bilirubin concentration falls below 14 mg/dL.

The serum bilirubin concentration should be remeasured 12 to 24 hours after cessation of phototherapy to look for a rebound in bilirubin concentration.

The infant should be rehospitalized if he/she shows signs of illness or side effects, or when the serum bilirubin concentration exceeds 18 mg/dl.

The JOURNEY of a premature baby is often ONE step forward and TWO steps back....

Photo: Lisa Nicole Imagery

Watch them breathe, watch them sleep and nourish them with 'LIQUID GOLD'. When strong enough, they will take three LEAPS forward and NEVER look back.....