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# Cycled Phototherapy Dose-Finding Study for Extremely Low-Birth-Weight Infants
## A Randomized Clinical Trial

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**IMPORTANCE** Cycled (intermittent) phototherapy (PT) might adequately control peak total serum bilirubin (TSB) level and avoid mortality associated with usual care (continuous PT) among extremely low-birth-weight (ELBW) infants (401-1000 g).

**OBJECTIVE** To identify a cycled PT regimen that substantially reduces PT exposure, with an increase in mean peak TSB level lower than 1.5 mg/dL in ELBW infants.

**DESIGN, SETTING, AND PARTICIPANTS** This dose-finding randomized clinical trial of cycled PT vs continuous PT among 305 ELBW infants in 6 US newborn intensive care units was conducted from March 12, 2014, to November 14, 2018.

**INTERVENTIONS** Two cycled PT regimens (≥15 min/h and ≥30 min/h) were provided using a simple, commercially available timer to titrate PT minutes per hour against TSB level. The comparator arm was usual care (continuous PT).

**MAIN OUTCOMES AND MEASURES** Mean peak TSB level and total PT hours through day 14 in all 6 centers and predischarge brainstem auditory-evoked response wave V latency in 1 center. Mortality and major morbidities were secondary outcomes despite limited power.

**RESULTS** Consent was requested for 452 eligible infants and obtained for 305 (all enrolled) (mean [SD] birth weight, 749 [152] g; gestational age, 25.7 [1.9] weeks; 81 infants [27%] were multiple births; 137 infants [45%] were male; 112 [37%] were black infants; and 107 [35%] were Hispanic infants). Clinical and demographic characteristics of the groups were similar at baseline. After a preplanned interim analysis of 100 infants, the regimen of 30 min/h or more was discontinued, and the study proceeded with 2 arms. Comparing 128 infants receiving PT of 15 min/h or more with 128 infants receiving continuous PT among those surviving to 14 days, mean peak TSB levels were 7.1 vs 6.4 mg/dL (adjusted difference, 0.7; 95% CI, 0.4-1.1 mg/dL) and mean total PT hours were 34 vs 72 (adjusted difference, −39; 95% CI, −45 to −32). Wave V latency adjusted for postmenstrual age was similar in 37 infants receiving 15 min/h or more of PT and 33 infants receiving continuous PT: 7.42 vs 7.32 milliseconds (difference, 0.10; 95% CI, −0.11 to 0.30 millisecond). The relative risk for death was 0.79 (95% CI, 0.40-1.54), with a risk difference of −4.5% (95% CI, −10.9 to 2.0). Morbidities did not differ between groups.

**CONCLUSIONS AND RELEVANCE** Cycled PT can substantially reduce total PT with little increase in peak TSB level. A large, randomized trial is needed to assess whether cycled PT would increase survival and survival without impairment in small, preterm infants.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT01944696

Supplemental content

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Were they not born prematurely, infants with extremely low birth weight (ELBW; ≤1000 g) would have developed in darkness in utero for several months longer before birth. Yet their routine care involves administration of bright light during phototherapy (PT) to reduce their total serum bilirubin (TSB) level. The longstanding assumption that this therapy is innocuous with no serious adverse effects for even the most immature babies is neither evidence based nor biologically plausible.

In the only large, randomized trial comparing PT with no PT (the National Institute of Child Health and Human Development [NICHD] Collaborative PT trial[1]), the findings for mortality were compatible with a 49% increase with PT among ELBW infants (relative risk, 1.49; 95% CI, 0.93-2.40).[2] The only other large trial of PT (the Neonatal Research Network [NRN] trial of aggressive PT vs conservative PT) compared PT administered at different TSB levels.[3] Preplanned subgroup analyses of this trial found that aggressive PT increased mortality among infants with a birth weight (BW) of 750 g or less and who received ventilatory support (relative risk, 1.19; 95% CI, 1.02-1.39).[4] Moreover, conservative bayesian analyses[5,6] (using a neutral prior probability) identified a 99% likelihood that aggressive PT increased deaths among these infants in the NRN PT trial and found a 92% likelihood that PT increased deaths among all ELBW infants in the Collaborative Phototherapy Trial.[7]

The thin, translucent skin of ELBW infants and their high rate of serious illness and immature defense mechanisms may make them particularly vulnerable to the potential or documented adverse effects of PT, including photo-oxidative injury, lipid peroxidation, DNA damage, reduced mesenteric and cerebral blood flow, and hemolysis.[8-20] These adverse effects might increase not only their predischarge mortality but also their potential risk of epilepsy,[21,22] cancer,[23-25] or other disorders in survivors.

For these reasons, it would be prudent to limit the total PT exposure or "dose"[26] administered to small, preterm infants to no more than that needed to adequately control their TSB levels. Bilirubin in subcutaneous tissue or blood vessels near the skin surface is rapidly photoisomerized by exposure to light, and 6 small trials in term or near-term infants have found that cycled PT given as little as 15 of each 75 minutes results in minimal or no increase in TSB levels over the levels observed with continuous PT.[27-32] However, no trials have been performed to identify a cycled PT regimen that would substantially reduce PT exposure with minimal increase in TSB levels among ELBW infants—infants for whom excessive PT exposure is likely to be particularly hazardous.

Therefore, we conducted a dose-finding randomized clinical trial in 6 US newborn intensive care units to assess the hypothesis that cycled PT can be used to substantially and safely reduce PT administration with a mean peak TSB level within 1.5 mg/dL (to convert TSB level to micromoles per liter, multiply by 17.104) of that with continuous PT and no higher than 8.0 mg/dL (a value well below the lowest mean TSB level identified in any clinical trial [9.8 mg/dL[3]] to increase the risk of neurodevelopmental impairment [NDI] in ELBW infants). We also hypothesized that the wave V latency of the brainstem auditory-evoked responses (BAERs)—a sensitive indicator of bilirubin neurotoxicity[33-35]—would be similar in the treatment groups (with a difference in mean values <0.3 ms, which is lower than the SD of 0.5 ms in preterm infants[36,37]).

### Key Points

**Question** Can cycled phototherapy control total serum bilirubin levels while reducing phototherapy exposure to potentially avoid increased mortality with continuous phototherapy among extremely low-birth-weight newborns?

**Findings** In this dose-finding randomized clinical trial of 305 infants, cycled phototherapy (≥15 min/h titrated to total serum bilirubin level) compared with continuous phototherapy substantially decreased mean phototherapy hours (34 vs 72) with a minimally higher mean peak total serum bilirubin level (7.1 vs 6.4 mg/dL), similar mean brainstem auditory-evoked response mean wave V latency (7.42 vs 7.32 milliseconds), and fewer deaths (10.2% vs 13.4%).

**Meaning** A large, randomized trial is needed to assess whether cycled phototherapy would increase survival and survival without impairment in small, preterm infants.

## Methods

### Eligibility

Newborns with a birth weight of 401 to 1000 g who were younger than 24 hours were eligible for this randomized clinical trial if they had not received PT and had no known hemolytic disease, overt nonbacterial infection, or major anomaly and were receiving full medical support and not moribund (pH <6.8 for >2 hours or persistent bradycardia <100 beats per minute associated with hypoxia for >2 hours). This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The institutional review board (IRB) at each of the 6 participating newborn intensive care units specified in the first paragraph of the Results section approved this study protocol (trial protocol in Supplement 1). Written informed patient consent was obtained from the parents or guardians as specified by the IRB in each of the participating centers, with the University of Texas Health Science Center at Houston (UT Houston) IRB acting as the central IRB for the 4 centers in the UT System. No one received compensation or was offered any incentive for participating in this study.

### Randomization

Participants were stratified by center and risk group (high risk: ≤750 g BW and ventilated at enrollment; low risk: >750 g BW or not ventilated) and randomized using a variable block size and a web-based computerized program (REDCap). Initially, participants were randomized using a 1:1:1 ratio to 3 treatment groups: continuous PT (usual care), a PT regimen of 30 minutes or more per hour (hereafter referred to as 30 min/h or more) for each cycle, or a PT regimen of 15 min/h or more. The minutes per hour of PT could be increased for the cycled treatments if TSB values reached specified thresholds. The study protocol allowed different cycled PT regimens to be

Table 1. Phototherapy Administration Protocol

| TSB level, mg/dL | Phototherapy, min/h | | | Irradiance, all groups, μW/cm²/nm |
|---|---|---|---|---|
| | Continuous | Cycled ≥30 | Cycled ≥15 | |
| BW ≤750 g | | | | |
| <5.0[a] | 0 | 0 | 0 | NA |
| 5.0-7.9 | 60 | 30 | 15 | 22 |
| 8.0-9.9 | 60 | 60 | 30 | 22 |
| 10.0-12.9 | 60 | 60 | 60 | 33 |
| ≥13.0 | 60 | 60 | 60 | 40 |
| BW 751-1000 g | | | | |
| <5.0 or <7.0[a] | 0 | 0 | 0 | NA |
| 5.0 or 7.0-9.9[a] | 60 | 30 | 15 | 22 |
| 10.0-11.9 | 60 | 60 | 30 | 22 |
| 12.0-14.9 | 60 | 60 | 60 | 33 |
| ≥15.0 | 60 | 60 | 60 | 40 |

Abbreviations: BW, birth weight; NA, not applicable; PT, phototherapy; TSB, total serum bilirubin.

SI conversion factor: To convert TSB level to micromoles per liter, multiply by 17.104.

[a] Consistent with the aggressive PT protocol from the Neonatal Research Network PT trial,[3] the TSB threshold level for PT in the present study was 5.0 mg/dL for 14 days if BW was 750 g or less. For BWs of 751 to 1000 g, the TSB threshold level was 5.0 mg/dL for days 1 through 7 and 7.0 mg/dL for days 8 through 14.

added or dropped based on the findings of preplanned interim analyses. After the analysis at 100 patients, we discontinued the PT regimen of 30 min/h or more and randomized all subsequent patients 1:1 to continuous PT or to 15 min/h or more.

## Treatment

Per study protocol, TSB levels were measured in the hospital laboratory at least once daily for the first 7 days after birth and on any day that PT was administered or had been stopped in the previous 24 hours during the second week after birth. If more than 1 TSB level per day was obtained, the TSB level obtained closest to 7:00 AM and the highest TSB of the day (if different) were both recorded. Light-emitting diode PT lamps were used to deliver narrow-spectrum blue light starting 24 hours after birth or earlier if a TSB level of 5.0 mg/dL or higher was identified. Once started, PT was stopped and resumed for all patients following the aggressive PT protocol used in the NRN PT trial[3] (**Table 1**). These TSB thresholds were used because the reduction in NDI with aggressive PT relative to conservative PT is the only reduction in NDI identified in any trial of PT.

Simple, commercially available timers were used to provide cycled PT. To avoid administering more PT than needed to prevent high peak TSB values, we adjusted the minutes per hour of cycled PT according to prespecified TSB level thresholds based on our judgment in weighing the uncertain risks of PT against those of bilirubin neurotoxicity (Table 1). Because the risk of bilirubin neurotoxicity is considered to be greatest in the lowest BW infants, the TSB threshold levels for increasing the minutes per hour of cycled PT were lower for infants with BWs of 401 to 750 g than for infants with BWs of 751 to 1000 g.

The PT lamp irradiance intensities were preadjusted so that typical positioning of ELBW patients would result in delivery of approximately 22 μW/cm²/nm (the mean in the NRN trial) with low settings and 33 μW/cm²/nm on high settings. In treating each infant, the PT lamp was positioned to deliver the target irradiance. An exchange transfusion was considered to be indicated if the TSB level remained at 13 mg/dL or higher (for infants with BW ≤750 g) or 15 mg/dL or higher (for infants with BW of 751-1000 g) despite 8 hours of continuous PT at 40 μW/cm²/nm.

## Outcome Measures

The primary outcomes were mean peak TSB levels and mean PT hours through day 14 across all centers and predischarge wave V latency BAERs at the center of the principal investigator (UT Houston).

The BAERs were assessed by a single evaluator (A.D.) using carefully standardized methods and blinded to treatment group[37] and were routinely performed at 35 weeks postmenstrual age (PMA) (earlier if discharged from the hospital at <35 weeks' PMA or later if needed because of electrical interference associated with intensive care). The presence of satisfactory waveforms was verified by an expert in the recording and interpretation of BAERs in ELBW infants who was in a different center and blinded to treatment group.

Secondary outcomes included death and major predischarge morbidities, including severe (grade 3 or 4) intraventricular hemorrhage; bronchopulmonary dysplasia, defined as treated with supplemental oxygen at 36 weeks' PMA; surgical necrotizing enterocolitis; patent ductus arteriosus requiring treatment; severe retinopathy of prematurity, defined as stage 3 or higher or plus disease; and late-onset sepsis (all defined using NRN definitions[38]). The study was not powered for these secondary outcomes. However, based on the findings in prior trials,[2-4,7] we expected our findings to be compatible with a reduction in mortality with cycled PT with no discernible effect on these predischarge morbidities. Neurodevelopmental outcome is being assessed at 2 years' adjusted age for infants at UT Houston and will be reported separately.

## Statistical Analysis

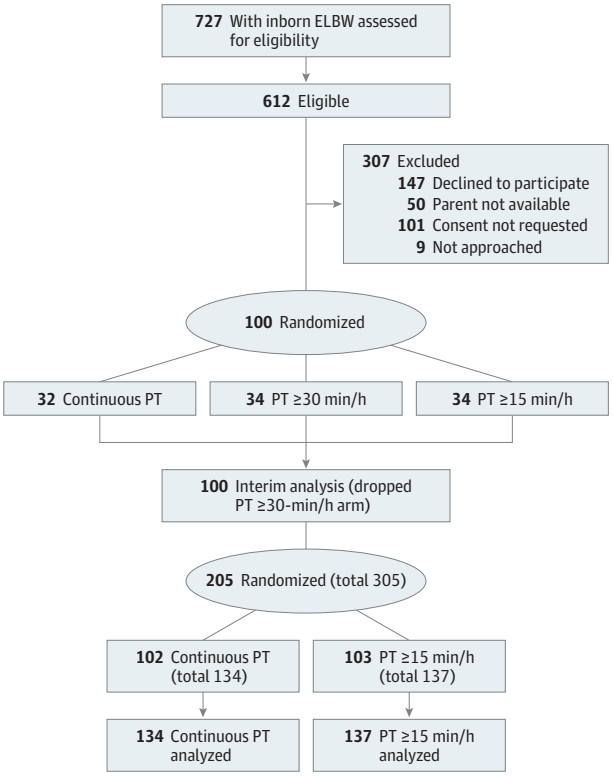
We originally planned to assess BAERs in the first 40 infants in each treatment group at UT Houston to have more than 80% power at $P < .05$ to identify a difference between groups in wave V latency longer than 0.3 millisecond (SD of 0.5 millisecond) and to enroll 150 total infants to have more than 80% power to detect a difference between groups in their mean peak TSB levels greater than 1.5 mg/dL (SD of 2.1). However, we later

obtained IRB approval to increase the number of infants and centers (see the first paragraph of the Results section) to obtain more precise and generalizable estimates of any treatment effects of cycled PT on predischarge mortality and morbidity while we sought the means to undertake a much larger multicenter trial of cycled PT. We stopped enrollment at 305 infants when the NICHD Neonatal Network committed to conducting such a trial.

Because outcomes in the 30-min/h-or-more arm were assessed only in the first third of the trial and are of limited interest, the outcome analyses were focused on comparing the continuous PT with 15-min/h-or-more regimen. Linear mixed-effects models, including risk stratum and a treatment-by-risk stratum interaction term with a center-level random intercept, compared mean peak TSB levels and mean hours of PT exposure between intervention groups. We prespecified that TSB levels and PT exposure data from patients who died before day 14 would not be used in the analyses of peak TSB levels and PT hours because these patients died before these outcomes could be measured, and using incomplete measures would confer a spurious advantage to the study group with less time at risk due to early deaths.

The BAER wave V latencies were analyzed using linear regression to adjust for risk strata and PMA at testing. Mortality and other binary outcomes were analyzed using binomial regression with robust standard errors to adjust for correlated results within centers (with identity link for risk differences and log link for risk ratios). Analyses were performed with Stata, version 15 (StataCorp LLC).

Figure 1. Consort Diagram




ELBW indicates extremely low birth weight; PT, phototherapy.

## Results

Between March 12, 2014, and November 14, 2018, we screened 727 inborn ELBW infants; 612 were eligible for this study (**Figure 1**). Parental or guardian informed consent was requested for 452 infants and obtained for 305 infants (all enrolled): 180 (59%) at UT Houston, 43 (14%) at University of Alabama Birmingham, 31 (10%) at Stanford University, 24 (8%) at UT Medical Branch (Galveston), 17 (6%) at UT Southwestern (Dallas), and 10 (3%) at UT San Antonio. Enrollment rates were constrained by limited external funding and unavailability of study personnel on some days. Of the 305 infants enrolled, the mean (SD) BW was 749 (152) g and the gestational age was 25.7 (1.9) weeks; 81 infants (27%) were multiple births, 137 infants (45%) were male, 112 (37%) were black infants, and 107 (35%) were Hispanic infants.

Randomization to the cycled PT regimen of 30 min/h or more was discontinued after the interim analysis of the first 100 patients because the mean peak TSB level was similar to that for the 15-min/h-or-more regimen. By contrast, PT exposure was substantially less with the 15-min/h-or-more regimen than with the 30-min/h-or-more regimen (eTable 1 in Supplement 2). The clinical and demographic characteristics of 134 patients randomized to continuous PT and of 137 patients randomized to cycled PT were similar at baseline (**Table 2**). No patients were lost to follow-up, and all were analyzed as randomized.

### Outcomes

Consistent with our hypotheses, the cycled PT regimen of 15 min/h or more resulted in a mean peak TSB level that was below 8.0 mg/dL (crude mean, 7.1; adjusted mean, 7.2; 95% CI, 6.7-7.8 mg/dL) and only 0.7 mg/dL higher (95% CI, 0.4-1.1 mg/dL) than with continuous PT while reducing the mean PT exposure from 72 to 34 hours, an adjusted difference of 39 hours (95% CI, 32-45 hours) (**Table 3**). In subgroup analyses, the difference between cycled and continuous PT in peak TSB level was 0.4 mg/dL (95% CI, −0.1 to 0.8 mg/dL) in the high-risk stratum compared with 1.0 mg/dL (95% CI, 0.5-1.6 mg/dL) in the low-risk stratum ($P$ = .08 for treatment by risk group interaction). However, there was no evidence of a treatment-by-risk stratum interaction for the reduction in PT, which was 39 hours in both strata (Table 3). This combination of subgroup findings presumably reflects both the more aggressive PT administration of infants with a BW of less than 750 g (Table 1) and their greater translucency.

The largest reduction in PT occurred in the first days after birth (**Figure 2**). Phototherapy was given no more than 15 min/h to 82% of patients who received cycled PT. Phototherapy was administered more than 15 min/h on more than 2 days in 9 patients who underwent cycled PT, occurring in 4 patients as the result of a protocol violation. One patient randomized to continuous PT and 3 randomized to cycled PT met criteria to increase irradiance. No patient met criteria for exchange transfusion. The number of days with any increased PT through day

Table 2. Baseline Clinical and Demographic Comparisons

| Characteristic | No. (%) of patients | |
|---|---|---|
| | Continuous PT (n = 134) | Cycled PT ≥15 min/h (n = 137) |
| Gestational age, mean (SD), wk | 26.1 (1.9) | 26.1 (1.9) |
| Birth weight, mean (SD), g | 736 (151) | 754 (149) |
| Male sex | 64 (48) | 63 (46) |
| Race/ethnicity | | |
| White | 75 (56) | 77 (56) |
| Black | 51 (38) | 50 (37) |
| Hispanic | 47 (35) | 52 (38) |
| Antenatal steroid | 125 (93) | 119 (87) |
| Magnesium sulfate | 125 (93) | 119 (87) |
| Multiple birth | 27 (20) | 40 (29) |
| Cesarean delivery | 113 (84) | 104 (76) |
| Apgar score, median (IQR) | | |
| 1 min | 4 (4) | 4 (4) |
| 5 min | 7 (3) | 7 (3) |
| Baseline hematocrit, mean (SD) | | |
| % | 43.6 (6.9) | 42.3 (7.1) |
| Age, h | 2.5 (2.8) | 2.1 (2.8) |
| Positive Coombs test result | | |
| Mother (indirect antibody screen) | 5 (4) | 4 (3) |
| Infant (direct antibody test) | 0 | 2 (1.5) |
| Maternal blood group O | 63 (47) | 81 (59) |
| Maternal Rh positive | 122 (92) | 133 (97) |
| Infant blood group O | 65 (49) | 84 (61) |
| Infant Rh positive | 119 (89) | 123 (90) |
| Baseline TSB level, mean (SD), mg/dL | 3.4 (1.0) | 3.6 (1.1) |
| Baseline TSB age, mean (SD), h | 11.7 (5.7) | 11.9 (5.8) |
| High risk | 60 (45) | 61 (45) |
| Intubated at randomization, No./total No. (%) | 60/60 (100) | 61/61 (100) |
| Birth weight ≤750 g, No./total No. (%) | 60/60 (100) | 61/61 (100) |
| Birth weight, mean (SD), g | 629 (99) | 626 (86) |
| Gestational age, mean (SD), wk | 25.0 (1.4) | 24.8 (1.5) |
| Low risk | 74 (55) | 76 (55) |
| Intubated at randomization, No./total No. (%) | 27/74 (37) | 36/76 (47) |
| Birth weight ≤750 g, No./total No. (%) | 16/74 (22) | 11/76 (14) |
| Birth weight, mean (SD), g | 823 (129) | 857 (103) |
| Gestational age, mean (SD), wk | 27.0 (1.7) | 27.1 (1.7) |

Abbreviations: IQR, interquartile range; PT, phototherapy; TSB, total serum bilirubin.

SI conversion factor: To convert TSB level to micromoles per liter, multiply by 17.104.

14 for patients who underwent cycled PT is presented in eTable 2 in Supplement 2.

We were able to obtain BAERs at UT Houston through 2016, at which time 111 patients had been enrolled and wave V latency had been successfully measured in 90 patients (33 in the continuous PT arm, 37 in the ≥15-min/h arm, and 20 in the ≥30-min/h arm). As hypothesized, the mean wave V latencies adjusted for PMA at testing were similar: 7.32 milliseconds for continuous PT vs 7.42 milliseconds for cycled PT (difference, 0.10 millisecond; 95% CI, −0.11 to 0.30 millisecond). Similar results were obtained for the smaller number of patients treated in the 30-min/h-or-more arm: 7.36 milliseconds (95% CI, 7.20-7.50 milliseconds) (eTable 3 in Supplement 2).

As expected, the risk for death with cycled PT was not statistically significant, but adjusted point estimates for relative risk (0.79; 95% CI, 0.40-1.54) and absolute risk reduction (−4.5%; 95% CI, −10.9 to 2.0) were consistent with the findings of prior trials.[1,3,4] Wide confidence intervals and no significant differences between groups were identified for virtually all of the assessed morbidities and for the composite outcomes of death or these individual morbidities (eTable 4 in Supplement 2).

## Discussion

Bilirubin encephalopathy at low TSB levels is unpredictable and rare but does occur,[39] which is a reason that conventional approaches to PT emphasize the goal of minimizing peak TSB levels in ELBW infants. However, the use of PT should be tempered by recognition of the following:

1. Bilirubin has antioxidant properties that may be beneficial to ELBW infants with mildly elevated TSB levels,[9,40] and bilirubin levels that are too low are potentially harmful.
2. The TSB values that cause NDI have been underestimated in observational studies owing to hypoxia/ischemia, intracranial hemorrhage, infection, hypoglycemia, or other confounders that themselves cause NDI.[41] The lowest mean peak TSB value found in any randomized trial to increase NDI rates among ELBW infants is 9.8 mg/dL (the value associated with conservative PT in the NRN trial[3]). No neurodevelopmental benefits of PT were identified in the Collaborative PT Trial in the 1970s,[1] in which LBW and ELBW infants were randomized to PT or to no PT.
3. As specified above, PT has a broad variety of serious, potential short- and long-term adverse effects in ELBW infants.[8-26]

The decades-long failure to seriously consider whether PT might increase deaths among some infants followed the widely accepted conclusion of the investigators in the Collaborative PT Trial that PT was both safe and effective.[1] The findings for mortality were largely ignored because their analyses indicated values of $P > .05$, a problem that reflects a long-standing and pervasive misunderstanding of frequentist statistics in the medical literature[42] that has now prompted a strong call to abandon the concept of statistical significance.[43] Because the probability of treatment benefit or harm can be directly assessed in bayesian but not frequentist analyses, bayesian analyses are now increasingly used in analyzing clinical trials.[6,44-47] Such analyses[4] identified a 92% probability that PT increased deaths among ELBW infants in the Collaborative PT Trial and found a 99% probability that aggressive use of PT increased deaths among ventilated infants with a BW of 750 g or less in the NRN PT Trial.[7]

Table 3. Main Outcomes

| Outcome | Phototherapy | | Adjusted difference (95% CI)[a,b] |
|---|---|---|---|
| | Continuous | ≥15 min/h | |
| Primary outcomes | | | |
| Peak TSB level, mg/dL[c] | | | |
| All patients, No.[d] | 128 | 128 | |
| Mean (SD) | 6.4 (1.4) | 7.1 (1.7) | 0.7 (0.4 to 1.1) |
| High risk, No. | 55 | 53 | |
| Mean (SD) | 6.2 (1.2) | 6.6 (1.4) | 0.4 (−0.1 to 0.8) |
| Low risk, No. | 73 | 75 | |
| Mean (SD) | 6.5 (1.5) | 7.5 (1.9) | 1.0 (0.5 to 1.6) |
| Phototherapy, h[c] | | | |
| All patients, No. | 128 | 128 | |
| Mean (SD) | 72 (34) | 34 (19) | −39 (−45 to −32) |
| High risk, No. | 55 | 53 | |
| Mean (SD) | 70 (30) | 31 (20) | −39 (−49 to −29) |
| Low risk, No. | 73 | 75 | |
| Mean (SD) | 75 (36) | 36 (18) | −39 (−48 to −30) |
| Secondary outcome of mortality, No./total No. (%) | 18/134 (13.4%) | 14/137 (10.2%) | −4.5% (−10.9 to 2.0) |
| Adjusted relative risk (95% CI)[a,e] | | | 0.79 (0.40 to 1.54) |

Abbreviations: PT, phototherapy; TSB, total serum bilirubin.

SI conversion factor: To convert TSB level to micromoles per liter, multiply by 17.104.

[a] Results adjusted using linear mixed-effects models, including risk stratum and a treatment by risk stratum interaction term with a center-level random intercept.

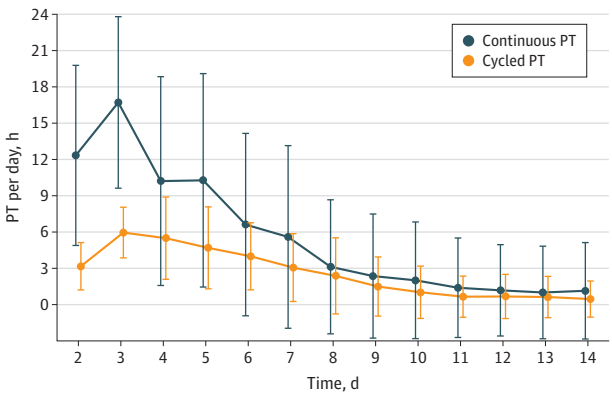
[b] Continuous PT is the reference category and cycled PT the comparator category.

[c] Data from 15 patients not surviving to day 14 were not included in these analyses.

[d] $P = .08$ for treatment by risk group interaction.

[e] Adjusted for risk strata using binomial regression (identity link for risk differences and log link for risk ratios) and using robust standard errors to adjust for correlated results within centers.

Figure 2. Phototherapy (PT) Hours per Day




Markers represent mean PT hours per day; error bars, 1 SD.

In trying to increase the safety of PT, we administered PT to both treatment groups in the present study using narrow-spectrum blue light, which is likely to have a more favorable risk to benefit ratio[48,49] than the white light administered to most or all infants in the NRN PT and Collaborative PT Trials. Reduced irradiance levels were not used in the present study because of the mortality findings in the Collaborative PT Trial, in which irradiance levels were substantially lower than those with current PT lamps.[7]

Our cycled PT regimen of 15 min/h or more substantially reduced PT exposure below that with conventional continuous PT, particularly during the first few days after birth when ELBW infants are often sickest and their skin most translucent. The mean total PT (37 hours) was also much lower than with aggressive PT (88 hours) and close to that with conservative PT (35 hours) in the NRN PT trial.[3] Yet, the mean peak TSB level was 7.2 mg/dL, which is only 0.7 mg/dL higher than that with continuous PT in our trial, only 0.2 mg/dL higher than with aggressive PT, and only 2.6 mg/dL lower than with conservative PT.[3] Our BAER findings were reassuring that cycled PT did not result in discernible bilirubin neurotoxicity. It is plausible that the use of cycled rather than continuous PT would reduce the risk of NDI at the same peak TSB level by preventing life-threatening illness or other problems or cointerventions that displace bilirubin from albumin or compromise the blood-brain barrier.[7-9,12,15,50]

### Limitations

The limitations of our study include a majority of patients from a single center and a sample size too small to identify whether cycled PT increased survival or survival without NDI of ELBW infants (an outcome to be reported separately for UT Houston). However, our trial did involve the second-largest number of ELBW infants studied in any PT trial to date.

## Conclusions

Whether conventional continuous PT should be routinely administered to extremely premature infants is called into question by the present findings, the disturbing mortality data of the prior Collaborative and Network trials,[1,3] and the accruing evidence that exposure to bright light may be hazardous to these infants. The mean peak TSB level was only 0.4 mg/dL higher with cycled PT than continuous PT in our highest-risk stratum of patients, and the use of cycled PT may be most beneficial for the smallest and most immature infants.

Because the toxicity of most therapies is dose related, a clinical maxim has been to use the lowest effective dose of therapy. Based on this maxim and the findings of all major PT trials to date, cycled PT is an evidence-based treatment option for ELBW infants. Indeed, the burden of proof should ar-

guably be on those who recommend continuous PT to show that it has a more favorable risk to benefit ratio than cycled PT for extremely premature infants. To augment the evidence base about how best to treat these infants, a large, randomized trial of cycled or continuous PT is needed to assess the effects on their rates of survival and of survival without NDI.

## ARTICLE INFORMATION

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**Author Contributions:** Dr Arnold had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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**Data Sharing Statement:** See Supplement 3.

**Additional Contributions:** We thank Michael Church, PhD, formally affiliated with Wayne State School of Medicine, Detroit, Michigan, for ensuring the quality of brainstem audio-evoked response results. He was not compensated for his work.

**Additional Information:** Coauthor Robert E. Lasky, PhD, died.

## REFERENCES

1. Scheidt PC, Graubard BI, Nelson KB, et al. Intelligence at six years in relation to neonatal bilirubin levels: follow-up of the National Institute of Child Health and Human Development Clinical Trial of Phototherapy. *Pediatrics*. 1991;87(6):797-805.

2. Maisels MJ. Neonatal jaundice. In: Sinclair JC, Bracken MB, eds. *Effective Care of the Newborn Infant*. Oxford University Press; 1992:532.

3. Morris BH, Oh W, Tyson JE, et al; NICHD Neonatal Research Network. Aggressive vs. conservative phototherapy for infants with extremely low birth weight. *N Engl J Med*. 2008; 359(18):1885-1896. doi:10.1056/NEJMoa0803024

4. Tyson JE, Pedroza C, Langer J, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Does aggressive phototherapy increase mortality while decreasing profound impairment among the smallest and sickest newborns? *J Perinatol*. 2012;32(9):677-684. doi:10.1038/jp.2012.64

5. Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR. Methods in health service research: an introduction to bayesian methods in health technology assessment. *BMJ*. 1999;319(7208): 508-512. doi:10.1136/bmj.319.7208.508

6. Wijeysundera DN, Austin PC, Hux JE, Beattie WS, Laupacis A. Bayesian statistical inference enhances the interpretation of contemporary randomized controlled trials. *J Clin Epidemiol*. 2009;62(1):13-21. doi:10.1016/j.jclinepi.2008.07.006

7. Arnold C, Pedroza C, Tyson JE. Phototherapy in ELBW newborns: does it work? is it safe? the evidence from randomized clinical trials. *Semin Perinatol*. 2014;38(7):452-464. doi:10.1053/j.semperi.2014.08.008

8. Stevenson DK, Wong RJ, Arnold CC, Pedroza C, Tyson JE. Phototherapy and the risk of photo-oxidative injury in extremely low birth weight infants. *Clin Perinatol*. 2016;43(2):291-295. doi:10.1016/j.clp.2016.01.005

9. Shekeeb Shahab M, Kumar P, Sharma N, Narang A, Prasad R. Evaluation of oxidant and antioxidant status in term neonates: a plausible protective role of bilirubin. *Mol Cell Biochem*. 2008;317(1-2):51-59. doi:10.1007/s11010-008-9807-4

10. Kurt A, Aygun AD, Kurt ANC, Godekmerdan A, Akarsu S, Yilmaz E. Use of phototherapy for neonatal hyperbilirubinemia affects cytokine production and lymphocyte subsets. *Neonatology*. 2009;95(3):262-266. doi:10.1159/000171216

11. Nandraziova L, Matasova K, Gumulak R. Phototherapy and its effect on some physiological functions in newborns. *ACTA Medica Martiniana*. 2018;18(1):5-13. doi:10.2478/acm-2018-0001

12. Benders MJ, van Bel F, van de Bor M. The effect of phototherapy on cerebral blood flow velocity in preterm infants. *Acta Paediatr*. 1998;87(7):786-791. doi:10.1111/j.1651-2227.1998.tb01748.x

13. Yao AC, Martinussen M, Johansen OJ, Brubakk AM. Phototherapy-associated changes in mesenteric blood flow response to feeding in term neonates. *J Pediatr*. 1994;124(2):309-312. doi:10.1016/S0022-3476(94)70325-6

14. Pezzati M, Biagiotti R, Vangi V, Lombardi E, Wiechmann L, Rubaltelli FF. Changes in mesenteric blood flow response to feeding: conventional versus fiber-optic phototherapy. *Pediatrics*. 2000; 105(2):350-353. doi:10.1542/peds.105.2.350

15. Aouthmany MM. Phototherapy increases hemoglobin degradation and bilirubin production in preterm infants. *J Perinatol*. 1999;19(4):271-274. doi:10.1038/sj.jp.7200184

16. Karakukcu C, Ustdal M, Ozturk A, Baskol G, Saraymen R. Assessment of DNA damage and plasma catalase activity in healthy term hyperbilirubinemic infants receiving phototherapy. *Mutat Res*. 2009;680(1-2):12-16. doi:10.1016/j.mrgentox.2009.07.016

17. Ramy N, Ghany EA, Alsharany W, et al. Jaundice, phototherapy and DNA damage in full-term neonates. *J Perinatol*. 2016;36(2):132-136. doi:10.1038/jp.2015.166

18. Yahia S, Shabaan AE, Gouida M, et al. Influence of hyperbilirubinemia and phototherapy on markers of genotoxicity and apoptosis in full-term infants. *Eur J Pediatr*. 2015;174(4):459-464. doi:10.1007/s00431-014-2418-z

19. Karadag A, Yesilyurt A, Unal S, et al. A chromosomal-effect study of intensive phototherapy versus conventional phototherapy in newborns with jaundice. *Mutat Res*. 2009;676(1-2): 17-20. doi:10.1016/j.mrgentox.2009.03.008

20. Tozzi E, Tozzi-Ciancarelli MG, Di Giulio A, et al. In vitro and in vivo effects of erythrocyte phototherapy on newborns. *Biol Neonate*. 1989;56 (4):204-209. doi:10.1159/000243124

21. Maimburg RD, Olsen J, Sun Y. Neonatal hyperbilirubinemia and the risk of febrile seizures and childhood epilepsy. *Epilepsy Res*. 2016;124:67-72. doi:10.1016/j.eplepsyres.2016.05.004

22. Newman TB, Wu YW, Kuzniewicz MW, Grimes BA, McCulloch CE. Childhood seizures after phototherapy. *Pediatrics*. 2018;142(4):e20180648. doi:10.1542/peds.2018-0648

23. Wickremasinghe AC, Kuzniewicz MW, Grimes BA, McCulloch CE, Newman TB. Neonatal phototherapy and infantile cancer. *Pediatrics*. 2016; 137(6):e20151353. doi:10.1542/peds.2015-1353

24. Newman TB, Wickremasinghe AC, Walsh EM, Grimes BA, McCulloch CE, Kuzniewicz MW. Retrospective cohort study of phototherapy and childhood cancer in northern California. *Pediatrics*. 2016;137(6):e20151354. doi:10.1542/peds.2015-1354

25. Tyson JE, Miller CC. Whether neonatal phototherapy increases the risk of cancer in children is a disturbing unresolved issue. *Evid Based Med*. 2017;22(1):39-40. doi:10.1136/ebmed-2016-110528

26. Lamola AA. A pharmacologic view of phototherapy. *Clin Perinatol*. 2016;43(2):259-276. doi:10.1016/j.clp.2016.01.004

27. Cremer RJ, Perryman PW, Richards DH. Influence of light on the hyperbilirubinaemia of infants. *Lancet*. 1958;1(7030):1094-1097. doi:10.1016/S0140-6736(58)91849-X

28. Zachman RD. Alternate phototherapy in neonatal hyperbilirubinemia. *J Pediatr*. 1972;81(1): 178. doi:10.1016/S0022-3476(72)80405-0

29. Vogl TP, Hegyi T, Hiatt IM, Polin RA, Indyk L. Intermediate phototherapy in the treatment of jaundice in the premature infant. *J Pediatr*. 1978;92 (4):627-630. doi:10.1016/S0022-3476(78)80308-4

30. Lau SP, Fung KP. Serum bilirubin kinetics in intermittent phototherapy of physiological jaundice. *Arch Dis Child*. 1984;59(9):892-894. doi: 10.1136/adc.59.9.892

**31**. Niknafs P, Mortazavi A-A, Torabinejad MH, Bahman-Bijari B, Niknafs N. Intermittent versus continuous phototherapy for reducing neonatal hyperbilirubinemia. *Iran J Pediatr*. 2008;18:251-256.

**32**. Sachdeva M, Murki S, Oleti TP, Kandraju H. Intermittent versus continuous phototherapy for the treatment of neonatal non-hemolytic moderate hyperbilirubinemia in infants more than 34 weeks of gestational age: a randomized controlled trial. *Eur J Pediatr*. 2015;174(2):177-181. doi:10.1007/s00431-014-2373-8

**33**. Shapiro SM, Popelka GR. Auditory impairment in infants at risk for bilirubin-induced neurologic dysfunction. *Semin Perinatol*. 2011;35(3):162-170. doi:10.1053/j.semperi.2011.02.011

**34**. Wennberg RP, Ahlfors CE, Bickers R, McMurtry CA, Shetter JL. Abnormal auditory brainstem response in a newborn infant with hyperbilirubinemia: improvement with exchange transfusion. *J Pediatr*. 1982;100(4):624-626. doi:10.1016/S0022-3476(82)80771-3

**35**. Kuriyama M, Tomiwa K, Konishi Y, Mikawa H. Improvement in auditory brainstem response of hyperbilirubinemic infants after exchange transfusions. *Pediatr Neurol*. 1986;2(3):127-132. doi:10.1016/0887-8994(86)90002-0

**36**. Lasky RE, Church MW, Orlando MS, et al. The effects of aggressive vs. conservative phototherapy on the brainstem auditory evoked responses of extremely-low-birth-weight infants. *Pediatr Res*. 2012;71(1):77-84. doi:10.1038/pr.2011.17

**37**. Lasky RE. A developmental study on the effect of stimulus rate on the auditory evoked brain-stem response. *Electroencephalogr Clin Neurophysiol*. 1984;59(5):411-419. doi:10.1016/0168-5597(84)90042-X

**38**. Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA*. 2015;314(10):1039-1051. doi:10.1001/jama.2015.10244

**39**. Watchko JF, Maisels MJ. The enigma of low bilirubin kernicterus in premature infants: why does it still occur, and is it preventable? *Semin Perinatol*. 2014;38(7):397-406. doi:10.1053/j.semperi.2014.08.002

**40**. Gazzin S, Vitek L, Watchko J, Shapiro SM, Tiribelli C. A novel perspective on the biology of bilirubin in health and disease. *Trends Mol Med*. 2016;22(9):758-768. doi:10.1016/j.molmed.2016.07.004

**41**. Oh W, Tyson JE, Fanaroff AA, et al; National Institute of Child Health and Human Development Neonatal Research Network. Association between peak serum bilirubin and neurodevelopmental outcomes in extremely low birth weight infants. *Pediatrics*. 2003;112(4):773-779. doi:10.1542/peds.112.4.773

**42**. Wasserstein RL, Lazar NA. The ASA statement on *p*-values: context, process, and purpose. *Am Stat*. 2016;70(2):129-133. doi:10.1080/00031305.2016.1154108

**43**. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature*. 2019;567(7748):305-307. doi:10.1038/d41586-019-00857-9

**44**. Lilford RJ, Thornton JG, Braunholtz D. Clinical trials and rare diseases: a way out of a conundrum. *BMJ*. 1995;311(7020):1621-1625. doi:10.1136/bmj.311.7020.1621

**45**. Lee JJ, Chu CT. Bayesian clinical trials in action. *Stat Med*. 2012;31(25):2955-2972. doi:10.1002/sim.5404

**46**. Laptook AR, Shankaran S, Tyson JE, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy: a randomized clinical trial [published correction appears in *JAMA*. 2018;319(10):1051]. *JAMA*. 2017;318(16):1550-1560. doi:10.1001/jama.2017.14972

**47**. Lewis RJ, Angus DC. Time for clinicians to embrace their inner bayesian? reanalysis of results of a clinical trial of extracorporeal membrane oxygenation. *JAMA*. 2018;320(21):2208-2210. doi:10.1001/jama.2018.16916

**48**. Vreman HJ, Wong RJ, Stevenson DK. Phototherapy: current methods and future directions. *Semin Perinatol*. 2004;28(5):326-333. doi:10.1053/j.semperi.2004.09.003

**49**. Morris BH, Tyson JE, Stevenson DK, et al. Efficacy of phototherapy devices and outcomes among extremely low birth weight infants: multi-center observational study. *J Perinatol*. 2013;33(2):126-133. doi:10.1038/jp.2012.39

**50**. Amin SB. Bilirubin binding capacity in the preterm neonate. *Clin Perinatol*. 2016;43(2):241-257. doi:10.1016/j.clp.2016.01.003