Review Article

Phototherapy for preterm newborns—historical controversies and RCT evidence

Cody Arnold, Jon E. Tyson

University of Texas at Houston McGovern Medical School, Houston, TX, USA

Contributions: (I) Conception and design: C Arnold; (II) Administrative support: C Arnold; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Cody Arnold, MD. McGovern Medical School Rm 3.236A, 6413 Fannin St, Houston, TX 77030, USA.
Email: cody.c.arnold@uth.tmc.edu.

Abstract: The Aggressive *vs.* Conservative Phototherapy for Infants with Extremely Low Birth Weight randomized controlled trial (A-v-C RCT), published in 2008, was designed to address two long standing intertwined controversies about bilirubin and phototherapy in preterm newborns. The older controversy, dating from the 1950s, was whether 'low' bilirubin levels might cause CNS injury in preterm newborns. The newer and less well-known controversy began when scrutiny of the 1974–1976 NICHD Collaborative Phototherapy Trial revealed that the results were consistent with increased mortality risk in the phototherapy arm for ELBW newborns: relative risk (RR) 1.49, 95% CI: 0.93, 2.40. The results of the A-v-C RCT fueled rather than settled the controversy regarding safety of phototherapy for ELBW newborns: mortality was higher with aggressive phototherapy in the 501–750 g stratum, but the strength of the association was not strong enough that the evidence of causation would be considered indisputable (RR 1.13, 95% CI: 0.96, 1.34). By contrast, the A-v-C RCT essentially proved that mean peak total serum bilirubin (TSB) levels ~10 mg/dL (~171 mmol/L) can cause lasting CNS injury in ELBW newborns: RR 0.86 (95% CI: 0.74, 0.99) for neurodevelopmental impairment (NDI) with aggressive phototherapy and mean peak TSB 7.0±1.8 mg/dL versus 9.8±2.1 mg/dL with conservative phototherapy (120±31 versus 168±36 mmol/L). For profound NDI, the RR was 0.68 (95% CI: 0.52, 0.89), and by Bayesian analysis the probability that aggressive phototherapy reduced profound NDI was 0.99. A recently begun large multicenter RCT evaluating cycled phototherapy as a means to reduce exposure to phototherapy in newborns with birth weight <751 g or gestational age <27 weeks could resolve the mortality risk controversy.

Keywords: Phototherapy; bilirubin; prematurity

Received: 23 April 2021; Accepted: 25 May 2021; Published: 28 November 2021.
doi: 10.21037/pm-21-42
View this article at: https://dx.doi.org/10.21037/pm-21-42

Introduction

The Aggressive *vs*. Conservative Phototherapy for Infants with Extremely Low Birth Weight randomized controlled trial (A v C RCT) was designed to address two long-standing controversies about the risks and benefits of phototherapy for very preterm infants (1). The older debate was whether 'low' bilirubin levels sometimes caused CNS injury in preterm newborns. The second and less well-known controversy, intertwined with the first, was whether phototherapy increased mortality among very preterm newborns. In this review, we summarize the histories of the controversies and discuss how the results of the A-v-C RCT have impacted the controversies. While the A-v-C RCT results fueled rather than resolved the controversy regarding phototherapy and mortality risk for our smallest and most preterm newborns, the results essentially resolved the older controversy to an extent not universally appreciated. Having reviewed this topic in 2014 (2), in retrospect we

believe that this last point perhaps deserved more emphasis. Additionally, in this review we include new information bearing on the mortality risk controversy.

Historical Debate 1: Bilirubin and neurodevelopment impairment in preterm newborns—cause or confounder?

Based on case reports and observational studies, there have been waxing and waning concerns for many decades that relatively low levels of unconjugated bilirubin might cause brain injury in newborns delivered at early gestations (3,4). We purposely use the term 'concern' rather than 'belief' in order to acknowledge the uncertainty and diversity of opinion that prevailed into the first decade of this century.

In a series of studies published from 1958 to 1972, kernicterus was described in preterm infants at TSB levels ranging from 9 to 18 mg/dL (154–306 mmol/L). This was a time of emerging new technologies in the management of smaller and more preterm neonates and for the first time included appreciable numbers of newborns with birth weights of less than 1,000 g and gestational ages of less than 28 weeks. It was also suggested that various clinical factors, such as hypothermia, and acidosis predisposed preterm infants to kernicterus, and should be considered in determining exchange transfusion levels for a given infant (4). In the 1970s guidelines that suggested the use of exchange transfusions in preterm newborns with serum bilirubin levels substantially less than 20 mg/dL began to appear in the neonatal textbooks, reviews, and American Academy of Pediatrics publications (3-5). Support for these recommendations was bolstered by the publication of the Collaborative Perinatal Project study that demonstrated an association between impaired psychomotor performance and peak bilirubin levels in the 10–14 mg/dL range (171–239 mmol/L) in low-birth-weight infants (3,6). Reflecting the concern for the occurrence of "low bilirubin kernicterus," the criteria for exchange transfusion was 10 mg/dL (171 mmol/L) in high-risk newborns with birth weights <1,250 g in the 1974–1976 National Institute of Child Health and Human Development (NICHD) randomized controlled study of phototherapy (3,7). By the 1980s, based on contemporary studies that failed to find an association of TSB levels and neurodevelopmental outcomes (4), bilirubin researchers began expressing doubts about the recommendations for prophylactic use of phototherapy and liberal use of exchange transfusions. By the 1990s, many were frankly skeptical. In a 1992 review, Jon Watchko stated (3):

"In the final analysis, we do not know the true potential (or lack thereof) for nonhemolytic hyperbilirubinemia to produce brain damage in the preterm newborn in the present era. Many of the studies included in this review would suggest that this potential is now low. Thus, we cannot be sure that the benefits of accepted (e.g., exchange transfusion based on NICHD phototherapy study criterion) and/or proposed (e.g., tin-protoporphyrin) therapeutic interventions outweigh their risks."

Over the decade, doubts were expressed with increasing confidence. In 2000, William Cashore stated in the summary of his review "Bilirubin and Jaundice in the Micropremie" (8):

"In summary, the observation of low-bilirubin kernicterus in low-birth weight infants and attempts at preventing it may more strongly reflect the limitations of knowledge and practice in an earlier period of neonatal intensive care than a quantifiable risk from indirect hyperbilirubinemia to the central nervous system of very low-birth weight infants… There are no data currently available to indicate whether a serum indirect bilirubin concentration in the range of 10 to 15 mg/dL poses any hazard to infants in the weight range of 500 to 1,000 g. The absence of post-discharge clinical findings compatible with kernicterus in most follow-up clinics suggest that in surviving infants, serum bilirubins of 10 and perhaps as high as 15 mg/dL are well tolerated."

Nevertheless, concerns regarding the possibility that 'low' bilirubin levels might harm very preterm newborns did not disappear. In a 2003 review, "Jaundice in low birthweight infants: pathobiology and outcome", Watchko and Maisels observed (4): "The literature on bilirubin induced neurological injury in the jaundiced preterm neonate reveals a complexity that is far greater than suggested by a simple a priori cause and effect relation between hyperbilirubinaemia and neuronal damage, leaving neonatologists in a clinical quandary with respect to the management of neonatal hyperbilirubinaemia in the preterm infant."

Almost simultaneous to the publication of Watchko's and Maisel's 2003 review (4), the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) published the strongest observational study to date addressing CNS injury from bilirubin in preterm newborns: a multicenter cohort study using prospectively collected data to test the association of peak total serum bilirubin (TSB) and neurodevelopmental outcomes in ELBW newborns surviving at least 14 days (9). Of 3,647 newborns with a TSB recorded prior to 14 days, 3,147

survived and 2,575 (81%) underwent rigorous standardized neurodevelopmental evaluation at post-menstrual age (PMA) 18–22 months. The neurodevelopmental variables considered were Bayley II Psychomotor Developmental Index (PDI) <70, Bayley II Mental Developmental Index (MDI) <70, moderate or severe cerebral palsy (diagnosed using the Amiel-Tison method), hearing impairment (requiring hearing aids), and a dichotomous composite neurodevelopmental impairment (NDI) variable. Infants with any one or more of the outcomes below were considered to have experienced NDI: PDI <70, MDI <70, moderate to severe cerebral palsy (CP), bilateral blindness, or bilateral hearing impairment requiring amplification. Additionally, death or NDI was analyzed as a dichotomous composite outcome variable.

Using logistic regression to evaluate the risk associated with peak TSB controlling for 14 covariates, the authors reported a statistically significant odds ratios for the following outcomes: PDI <70 (OR 1.057, 95% CI: 1.00–1.12), severe hearing impairment (OR 1.138, 95% CI: 1.00–1.30), and for the composite death or NDI (OR 1.068, 95% CI: 1.03–1.12). The 95% confidence intervals for MDI (OR 1.046, 95% CI: 0.997–1.099) and the NDI composite outcome (OR 1.048, 95% CI: 0.999–1.098) barely included the null value of 1.0. The OR point estimate for CP was similar to those for other NDI outcomes but the 95% CI was wider: 1.049 (0.97–1.14). These results provided convincing evidence that there was an association of peak TSB and neurodevelopmental outcomes in preterm newborns. However, even among the Oh *et al.* investigators, there was debate about the nature of the association. On one hand, a straightforward statistical interpretation of the results was that each 1 mg/dL rise in peak TSB increased the odds of NDI among survivors by approximately 5%. This interpretation implied that the risk of an adverse outcome among ELBW patients with peak TSB ~10 mg/dL would be approximately 15 percent higher than ELBW patients with peak TSB of ~7 mg/dL. On the other hand, some investigators regarded an OR of 1.05 as small and consistent with residual confounding. According to this interpretation, the association of higher peak TSB and NDI could be explained by unmeasured or imperfectly measured factors that caused both higher peak TSBs and also NDI (e.g., intracranial hemorrhage). The skeptics were not doubting that the association of peak TSB levels and risk of NDI was real; but they were not convinced that it was a causal association—and doubted that the cause-effect question could be resolved by observational studies. Contributing to the debate, recent research had revealed bilirubin's potentially beneficial antioxidant properties. And while the controversy regarding low bilirubin levels harming preterm newborns was the subject of published reviews and was widely discussed, a peripheral controversy was debated among a small number of bilirubin researchers: could it be that phototherapy was harming preterm newborns? (2).

Historical Debate 2: Safety of phototherapy in preterm newborns

The NICHD Collaborative Phototherapy Trial, conducted in six U.S. centers between 1974 and 1976, is the only large RCT to compare phototherapy against a control group not treated with phototherapy (10). The executive summary published in 1985 stated: "Phototherapy was effective in preventing hyperbilirubinemia in low-birth-weight infants (<2,000 g) who were placed under daylight fluorescent lights at 24±12 hours of life for 96 hours. In this weight group, the number of exchange transfusions that were required due to hyperbilirubinemia was significantly lower in infants receiving phototherapy (4.1%) than in control infants (24.4%, P<0.001)… During the entire first year of life, 10.7% of phototherapy-treated infants and 9.3% of control infants died. This difference is not significant. Analysis by various weight groups and age at death also failed to reveal any significant differences (10)."

More detail was provided in a report focused on mortality published in the same supplemental issue of Pediatrics, but the conclusion was the same: "Among newborns who weighed less than 2,000 g at birth, there were no statistically significant differences in mortality between those infants who were treated with phototherapy as compared with the control group. Separate analysis of the infants with birth weight 1,000 g or less and those who weighed 1,001 to 1,999 g similarly revealed no significant differences in mortality in relation to mode of therapy (11)."

As phototherapy was already widely used in developed countries in 1985, the investigators' verdict that phototherapy was safe and effective was not questioned by most neonatologists. However, a small minority were concerned about what they saw in the data, specifically in regard to mortality among the smallest and most preterm newborns. Ronald Poland, later to become a principal investigator in the NICHD Neonatal Research Network (NRN), wrote a letter to the editor pointing out that the results of the RCT were consistent with increased mortality risk in LBW and particularly in ELBW newborns (12):

"Lipsitz and co-workers report that infants with birth

weights of 1 kg or less exhibited a difference in mortality (39.5% of 38 control infants *vs.* 59% of 39 phototherapy infants) which they note was not statistically significant… Using the reported mortality rates for treated and control infants 1 kg or less at birth and a P value of .05 or less as the criterion for rejecting the null hypothesis, we find that there is a 42% probability that the observed difference in mortality of 19.5% is real (that is, not merely due to chance events)… We, therefore, cannot assume that enough work was done to eliminate the possibility of a significantly higher mortality rate in the smallest babies treated with prophylactic phototherapy v controls. The data, however, come closer to identifying a significant increase in mortality than to eliminating the possibility."

In the reply to the letter the investigators acknowledged a typographical error in the reported P value and defended their conclusion of 'no difference' based on the lack of statistical significance at P<0.05, but the reply did not address the fact that the results of the study were consistent with a substantial increase in mortality risk for LBW newborns (RR 1.32, 95% CI: 0.96, 1.82), and especially for ELBW newborns (RR 1.49, 95% CI: 0.93, 2.40) (6,13). Although the 'lack of statistical significance' argument satisfied most neonatologists, a minority remained concerned about the safety of phototherapy in very preterm newborns, including some of the authors of the 2003 Oh *et al.* publication. This is relevant to the history of controversy regarding the risks of mild hyperbilirubinemia because the implications of the Oh *et al.* study would differ depending on views regarding the safety of phototherapy. If phototherapy were essentially risk free, there would be no compelling reason to undertake a large and expensive RCT to prove or disprove a causal versus confounded association between mild hyperbilirubinemia and NDI in very preterm newborns: possible harms could be prevented by more liberal use of risk-free phototherapy. But for those who suspected that phototherapy might have serious adverse effects, a large RCT designed to simultaneously assess the safety of liberal use of phototherapy and the true (not confounded) risks of mild hyperbilirubinemia was exactly what was needed.

The A-v-C Phototherapy Randomized Controlled Trial

There was substantial overlap in the investigators in the Oh *et al.* observational study and the A-v-C RCT (1,9). Between 2002 and 2005, 1,974 ELBW newborns were enrolled in 16 perinatal centers in a RCT comparing TSB thresholds for administering phototherapy. The phototherapy regimen in the aggressive phototherapy arm was intended to allow very few peak TSB values in the 10–15 mg/dL range that previous observational studies had suggested might result in NDI (4). The phototherapy regimen in the conservative phototherapy arm of the trial was intended to limit exposure to potentially harmful phototherapy while tolerating more peak TSB values in the 10–15 mg/dL range which Cashore and other experts believed were likely to be safe (4,8). The composite outcome death or NDI (defined similarly to NDI in the 2003 Oh *et al.* study) was the prespecified primary outcome because death and NDI are competing outcomes (i.e., it is possible that a study group could have less NDI among survivors because of more deaths). However, there was greater than usual interest in 'secondary' outcomes in this study: some investigators were most concerned that excessive phototherapy might increase mortality risk, while others were more concerned that conservative phototherapy might result in more bilirubin induced NDI among survivors. To follow we first focus on mortality risk; subsequently, we will examine risk of NDI among survivors.

Unfortunately, the A-v-C RCT did not settle the controversy over the safety of phototherapy in extremely preterm newborns. Much like in the Collaborative Phototherapy RCT, the mortality rate among the smallest most preterm newborns was higher in patients exposed to more phototherapy, but again the difference was not statistically significant. Per study protocol, randomization was stratified on center and birth weight, 501–750 or 751–1,000 g. Among the 501–750 g patients, 163 of 417 (39%) patients in the aggressive phototherapy group died prior to discharge compared to 142 of 412 (34%) in the conservative phototherapy group. The reported RR point estimate of 1.13 and the 95% confidence limits of 0.96–1.34 were adjusted for correlated outcomes within centers but both were essentially equivalent to the crude (unadjusted) results that can be calculated using the reported data. Although the mortality difference in 501–750 g stratum did not reach statistical significance (the lower limit of the 95% CI for the RR dropped just below the null value of 1.0), the mortality difference was statistically significant in a post hoc analysis of infants with birth weight ≤650 g: 106 of 214 (50%) died in the aggressive-phototherapy group compared with 80 of 212 (38%) in the conservative-phototherapy group (P=0.03). Additionally, the results of preplanned Bayesian analyses (published in the on-line Supplementary Appendix) estimated that the posterior probability was

0.89 that aggressive phototherapy increased mortality for the 501–750 g infants (1,14,15). Published separately, Bayesian analyses were also performed in which the need for mechanical ventilation at randomization was used in addition to birth weight strata to control for baseline risk of death or NDI and NDI among survivors (16). In preplanned analyses of the highest risk infants (mechanically ventilated infants ≤750 g BW; n=684), conservative Bayesian analyses identified a 0.99 posterior probability that aggressive phototherapy increased mortality. Although there were not more deaths in the aggressive phototherapy arm in the 751–1,000 g stratum, the 95% confidence interval was consistent with increased mortality risk with aggressive phototherapy (RR 0.90, 95% CI: 0.66, 1.21).

We find these data worrisome and note that were phototherapy a drug, it is unlikely that it would be approved for use in this population. However, given that the increased mortality risk in the A-v-C RCT was observed only in the 501–750 g stratum, and more so for those who still adhere to the statistical significance paradigm (17,18), the evidence supporting increased mortality risk was not indisputable.

Cycled phototherapy

Recognizing that the question of safety of phototherapy in ELBW newborns remained unsettled, in 2014 we launched a dose finding pilot RCT evaluating cycled (intermittent) phototherapy as a method that might control TSB levels in ELBW patients with less phototherapy (19). Starting at the University of Texas at Houston McGovern Medical School and joined by collaborating investigators at Stanford University, University of Alabama Birmingham, and University of Texas System, the study demonstrated that in 271 ELBW patients (mean GA, 26.1±1.9 weeks, mean BW 745±150 g) cycled phototherapy beginning at 15 minutes per hour (increasing cycle time and irradiance if needed) could maintain peak TSB at levels very close to those with continuous phototherapy (usual care, 60 minutes per hour), while decreasing exposure to phototherapy by approximately half. Among newborns surviving 14 days, 128 treated with cycled phototherapy were exposed to 34±19 hours of phototherapy versus 72±34 hours in 128 newborns treated with continuous phototherapy (difference of 39 hours, 95% CI: 45–32, P<0.0001, adjusted for center and birth weight strata). The difference in phototherapy exposure was also less intense in that exposure was spread over more days with cycled phototherapy, with the largest decrease in exposure in the first days after birth. This pilot RCT was not powered to evaluate mortality risk but the results were consistent with previous RCTs with 5% fewer deaths in the cycled phototherapy arm (risk difference 95% CI: –10.9%, 2.0%).

Although the reduction in phototherapy exposure with cycled phototherapy was almost identical across birth weight strata, the results suggested a modest differential effect on mean TSB. In the ≤750 g strata, the mean peak TSB through day 14 was 6.6±1.4 in the cycled phototherapy patients versus 6.2±1.2 in the continuous phototherapy patients (difference 0.4 mg/dL, 95% CI: –0.1, 0.8). In the 751–1,000 g newborns, the mean peak TSB through day 14 was 7.5±1.9 in the cycled phototherapy patients versus 6.5±1.5 in the continuous phototherapy patients (difference 1.0, 95% CI: 0.5, 1.6). For the sake of comparison, cycled PT in this RCT maintained mean peak TSBs very close to the mean peak of 7.0 mg/dL achieved with aggressive phototherapy in the A-v-C RCT yet limited mean phototherapy exposure to 37 hours—very close to the 35 hours reported for conservative phototherapy arm of the A-v-C RCT in which the mean peak TSB was 9.8 mg/dL (1,19).

This pilot study has prompted a NICHD NRN trial of cycled PT with a goal of enrolling 1,700 extremely premature newborns (20). That eligibility for this study is limited to newborns <27 weeks gestational age or ≤750 g birthweight makes it more likely to detect any decrease in mortality associated with less exposure to phototherapy. Additionally, research evaluating metalloporphyrins as a therapy that might augment or even replace phototherapy is ongoing (21,22).

The aggressive versus conservative phototherapy RCT—neurodevelopmental outcomes

The A-v-C Phototherapy RCT did not resolve the controversy regarding the safety of phototherapy in extremely preterm newborns. By contrast, it provided solid experimental evidence that mild hyperbilirubinemia is a cause of NDI in ELBW newborns. Randomization to phototherapy regimens that result in substantially different TSB levels provides the best method to avoid known and unknown confounders in assessing the neurodevelopment effects of hyperbilirubinemia, particularly with a large sample size (n=1,974) and masked neurodevelopmental evaluations. Assuming aggressive phototherapy would not reduce NDI by any mechanism other than by lowering TSB, this RCT can be viewed as an experiment to

Table 1 Neurodevelopmental outcomes at 18 to 22 months from the Aggressive *vs.* Conservative Phototherapy for Infants with Extremely Low Birth Weight Randomized Controlled Trial (1)

	Aggressive, n [%]	Conservative, n [%]	RR (95% CI)[†]
Neurodevelopmental impairment	235/902 [26%]	275/902 [30%]	0.86 (0.74, 0.99)[§]
Profound impairment[¶]	80/895 [9%]	119/896 [13%]	0.68 (0.52, 0.89)[§]
Mental Developmental Index <85[ǂ]	380/905 [42%]	429/904 [47%]	0.89 (0.80, 0.98)[§]
Mental Developmental Index <70[ǂ]	194/905 [21%]	234/904 [26%]	0.83 (0.71, 0.98)[§]
Severe hearing loss	9/925 [1%]	28/922 [3%]	0.32 (0.15, 0.68)[§]
Athetosis	2/929 [0.2%]	10/923 [1.1%]	0.20 (0.04, 0.90)[§]
Psychomotor Developmental Index <85[ǂ]	262/898 [29%]	299/894 [33%]	0.88 (0.77, 1.01)
Psychomotor Developmental Index <70[ǂ]	127/898 [14]	152/894 [17]	0.84 (0.68, 1.04)
Cerebral palsy			
All	81 [9]	91 [10]	0.89 (0.67,1.18)
Moderate/severe	38 [4]	53 [6]	0.71 (0.47, 1.07)
Blindness	2 [0.2%]	7 [<1]	0.28 (0.06, 1.37)
Seizures	29 [3]	28 [3]	1.03 (0.62, 1.71)
Gross motor function, normal	556 [60]	545 [59]	1.01 (0.94, 1.08)
Ability to walk fluently	544 [59]	529 [57]	1.02 (0.95, 1.10)
Fine pincer grasp	606 [65]	582 [63]	1.03 (0.97, 1.10)

[†]The relative risk of each outcome was calculated using aggressive phototherapy as the reference group and controlling for birth weight strata and center (center was removed from the model when there were no events at several centers). The denominator used to calculate the percentage of infants with a specific outcome was the number of infants randomly assigned to each treatment group for whom that outcome was known at 18 to 22 months. [§]P<0.05. [¶]Infants with profound impairment included 22 with a Mental Developmental Index score of 50 and 121 with a score of less than 50. [ǂ]The Mental and Psychomotor Developmental Indexes are from the Bayley Scales of Infant Development II (on which scores can range from 50 to 150, with 150 indicating the most advanced development). The ability to walk fluently was defined as the ability to take 10 steps, unassisted, with a normal gait for the age.

determine whether moderate hyperbilirubinemia causes lasting neurotoxicity in ELBW infants (1).

At 18–22 months PMA 1,356 of 1,526 (89%) surviving patients underwent neurodevelopment evaluation. Neurodevelopmental impairment (NDI) was defined as blindness (no functional vision in either eye), severe hearing loss (for which bilateral hearing aids were prescribed), moderate or severe cerebral palsy, or a score below 70 on the Mental or Psychomotor Developmental Index of the Bayley Scales of Infant Development. Infants were classified as having moderate or severe cerebral palsy if they were able to walk only with assistive devices or were unable to walk at all, respectively. Profound impairment was defined as a score of 50 or less on the Mental or Psychomotor Developmental Index, or 5 on the gross motor function classification system, with 5 indicating that movement requires assistance by an adult.

The aggressive and conservative phototherapy regimens resulted in mean peak TSB levels of 7.0±1.8 and 9.8±2.1 mg/dL, respectively (difference 2.8 mg/dL, P<0.001). *Table 1* shows that relative risks (RR) for NDI, profound NDI, and various specific neurosensory outcomes consistently favored the aggressive phototherapy group. For those that might remain skeptical, below we review aspects of the results in *Table 1* that convince us that this RCT generated overwhelming evidence of the capacity for 'low' bilirubin levels to cause NDI in ELBW newborns (1).

- Focusing of profound impairment, which is measured more reliably and less likely to change over time than milder impairment (23), the probability of observing a RR as extreme as, or more extreme than 0.68 as a result of chance

Table 2 Composite neurodevelopmental outcomes at 18 to 22 months by birth weight strata from the Aggressive *vs.* Conservative Phototherapy for Infants with Extremely Low Birth Weight Randomized Controlled Trial (1)

	Aggressive, n [%]	Conservative, n [%]	RR (95% CI)
Neurodevelopmental impairment			
501–750 g	109 [27]	128 [32]	0.86 (0.70, 1.05)
751–1,000 g	126 [25]	147 [29]	0.86 (0.71, 1.05)
Profound impairment			
501–750 g	39 [10]	58 [14]	0.67 (0.46, 0.98)
751–1,000 g	41 [8]	61 [12]	0.68 (0.47, 0.99)

(sampling error) is approximately 0.004 or 1 in 250 if the null hypothesis is correct. We must say 'approximate' because the p value was not published and it is not possible to reproduce the regression analysis adjusting for center and birth weight strata. However, we can be confident that the p value was very close to 0.004 because that is the p value for the crude RR and 95% confidence intervals calculated using the published raw data [80/895 (9%) in the aggressive arm versus 119/896 (13%) in conservative arm], and the crude results (RR 0.67, 95% CI: 052–0.88) are essentially identical to the published adjusted RR and confidence intervals.

- The differences in NDI outcomes are not explainable by excess deaths in the aggressive phototherapy arm.
- The protective effect for NDI and profound NDI was similar in both birthweight strata while excess deaths were only present in one stratum (*Table 2*), and the RRs are essentially unchanged when all patients, including deaths, comprise the denominators.
- Results of preplanned Bayesian analyses (14,15) reported in the supplement to the New England Journal of Medicine publication estimated that the probability that aggressive phototherapy reduced profound NDI was 0.99 (overall and in both birth weight strata).
- The results of frequentist and Bayesian analyses were confirmed in the previously mentioned publication of secondary analyses in which need for mechanical ventilation at randomization was used in addition to birth weight strata to characterize baseline risk (16).
- The statistically significant protective effects of aggressive phototherapy on the RR scale were largest for precisely the specific outcomes predicted by the current understanding bilirubin toxicity: athetosis RR 0.20 and severe hearing loss RR 0.32.
- Unbound (free) bilirubin (UB), the agent believed to be responsible for neurologic injury, was measured in a subset of infants at 5±1 days of age. UB levels were significantly higher (P<0.001) in newborns treated with conservative phototherapy: 0.48±0.33 µg/dL versus 0.33±0.25 µg/dL (8.2±5.6 nM versus 5.6±4.3 nM). In a separate publication, the data were analyzed across the RCT study groups (i.e., analyzed as a cohort study) (24). Adjusting for potential confounders, increasing levels of UB, had a straightforward positive association with higher rates of death or NDI, death or cerebral palsy, death or hearing loss and death before follow-up.

It is noteworthy that the UB results were based on a single measurement of UB at 5±1 days of age, and that there are good reasons to believe that the method used to measure UB would cause the strength of associations to be underestimated (25,26). Of note, TSB levels measured in the same blood samples as UB did not have a similar straightforward association with the NDI outcomes (24). These findings provide strong support for the theory that UB, not TSB, is the agent that causes CNS injury, and demonstrates why researchers should not interpret a lack of association between TSB levels and adverse outcomes as absolving bilirubin.

To an extent not uniformly appreciated by neonatologists, we believe that this RCT essentially proved that TSB levels of ~10 mg/dL (~171 mmol/L) are associated with lasting neurologic injury in ELBW newborns and effectively confirmed the theory that the toxic effects are mediated (caused) by UB. Although the largest effects on relative

risk scale were for pathologies well-known to be associated with hyperbilirubinemia, it is noteworthy that there was a statistically significant and clinically important protective effect of aggressive phototherapy for cognitive injury as measured by the Bayley II Mental Developmental Index at cut-points <85 and <70 (*Table 1*). These results would not be expected based on classic kernicterus outcomes in term newborns in which cognitive function is typically preserved but are consistent with results from earlier observational studies in preterm newborns (4,9). This finding is important because cognitive deficit has become the most common form of CNS injury associated with extreme prematurity, a considerable portion of which is not explained by brain imaging at term or morbidities known to be associated with NDI (27-29). Exposure to UB might be responsible for an important part of unexplained NDI associated with prematurity. Going beyond the evidence provided by the A-v-C Phototherapy RCT, there are good reasons to suspect that CNS injury from UB might contribute to the increase in autism spectrum disorder among very premature survivors (30-32). As developmental outcomes were measured at an age before autism spectrum disorders would be diagnosed, any difference in risk associated with phototherapy regimen would not have been detected.

The A-v-C RCT demonstrated that ELBW newborn treated with the conservative regimen experienced NDI at a rate approximately 5 percent higher than those treated with the aggressive regimen. Nevertheless, 26% of newborns treated with aggressive phototherapy experienced NDI (9% profound NDI), and an unknown proportion would have developed adverse outcomes such as autism spectrum disorder at older ages. Whether exposure to UB is a cause of lasting CNS injury among very preterm newborns treated with aggressive phototherapy is unknown. Recent reports of elevated UB levels associated with elevated free fatty acid levels with typical intravenous lipid infusion regimens raise concerns that it may take more than aggressive phototherapy to eliminate preterm newborns' exposure to harmful levels of UB (33-37). This is an area of ongoing research.

Acknowledgments

We thank David K. Stevenson and Ronald J. Wong for their editorial comments and suggestions.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (David K. Stevenson and Ronald J Wong) for the series "Neonatal Jaundice" published in *Pediatric Medicine*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-21-42/coif). The series "Neonatal Jaundice" was commissioned by the editorial office without any funding or sponsorship. JT reports grants from NICHD Neonatal Research Network Grant, during the conduct of the study. The authors have no other conflict of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Morris BH, Oh W, Tyson JE, et al. Aggressive vs. conservative phototherapy for infants with extremely low birth weight. N Engl J Med 2008;359:1885-96.
2. 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;38:452-64.
3. Watchko JF, Oski FA. Kernicterus in preterm newborns: past, present, and future. Pediatrics 1992;90:707-15.
4. Watchko JF, Maisels MJ. Jaundice in low birthweight infants: pathobiology and outcome. Arch Dis Child Fetal Neonatal Ed 2003;88:F455-8.
5. American Academy of Pediatrics. Standards and Recommendations for Hospital Care of Newborn

Infants. 6th ed. Evanston, IL: American Academy of Pediatrics; 1977
6. Scheidt PC, Mellits ED, Hardy JB, et al. Toxicity to bilirubin in neonates: infant development during first year in relation to maximum neonatal serum bilirubin concentration. J Pediatr 1977;91:292-7.
7. National Institute of Child Health and Human Development randomized, controlled trials of phototherapy for neonatal hyperbilirubinemia. Pediatrics 1985;75:385-441.
8. Cashore WJ. Bilirubin and jaundice in the micropremie. Clin Perinatol 2000;27:171-9.
9. Oh W, Tyson JE, Fanaroff AA, et al. Association between peak serum bilirubin and neurodevelopmental outcomes in extremely low birth weight infants. Pediatrics 2003;112:773-9.
10. Randomized, controlled trial of phototherapy for neonatal hyperbilirubinemia. Executive summary. Pediatrics 1985;75:385-6.
11. Lipsitz PJ, Gartner LM, Bryla DA. Neonatal and infant mortality in relation to phototherapy. Pediatrics 1985;75:422-6.
12. Poland RL. Phototherapy for neonatal hyperbilirubinemia. Pediatrics 1986;78:179-81.
13. The pediatric intensivists' viewpoint. Pediatrics 1986;78:181-2.
14. Wijeysundera DN, Austin PC, Hux JE, et al. Bayesian statistical inference enhances the interpretation of contemporary randomized controlled trials. J Clin Epidemiol 2009;62:13-21.e5.
15. Zampieri FG, Casey JD, Shankar-Hari M, et al. Using Bayesian methods to augment the interpretation of critical care trials. an overview of theory and example reanalysis of the alveolar recruitment for acute respiratory distress syndrome trial. Am J Respir Crit Care Med 2021;203:543-52.
16. Tyson JE, Pedroza C, Langer J, et al. Does aggressive phototherapy increase mortality while decreasing profound impairment among the smallest and sickest newborns? J Perinatol 2012;32:677-84.
17. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature 2019;567:305-7.
18. Greenland S, Senn SJ, Rothman KJ, et al. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. Eur J Epidemiol 2016;31:337-50.
19. Arnold C, Tyson JE, Pedroza C, et al. Cycled phototherapy dose-finding study for extremely low-birth-weight infants: a randomized clinical trial. JAMA Pediatr 2020;174:649-56.
20. Available online: https://clinicaltrials.gov/show/NCT03927833
21. Stevenson DK, Wong RJ. Metalloporphyrins in the management of neonatal hyperbilirubinemia. Semin Fetal Neonatal Med 2010;15:164-8.
22. Bhutani VK, Poland R, Meloy LD, et al. Clinical trial of tin mesoporphyrin to prevent neonatal hyperbilirubinemia. J Perinatol 2016;36:533-9.
23. Taylor GL, Joseph RM, Kuban KCK, et al. Changes in neurodevelopmental outcomes from age 2 to 10 years for children born extremely preterm. Pediatrics 2021;147:e2020001040.
24. Oh W, Stevenson DK, Tyson JE, et al. Influence of clinical status on the association between plasma total and unbound bilirubin and death or adverse neurodevelopmental outcomes in extremely low birth weight infants. Acta Paediatr 2010;99:673-8. Erratum in: Acta Paediatr 2013;102:326.
25. Ahlfors CE, Vreman HJ, Wong RJ, et al. Effects of sample dilution, peroxidase concentration, and chloride ion on the measurement of unbound bilirubin in preterm newborns. Clin Biochem 2007;40:261-7.
26. McDonagh AF, Vreman HJ, Wong RJ, et al. Photoisomers: obfuscating factors in clinical peroxidase measurements of unbound bilirubin? Pediatrics 2009;123:67-76.
27. Slaughter LA, Bonfante-Mejia E, Hintz SR, et al. Early conventional MRI for Prediction of neurodevelopmental impairment in extremely-low-birth-weight infants. Neonatology 2016;110:47-54.
28. Schmidt B, Asztalos EV, Roberts RS, et al. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. JAMA 2003;289:1124-9.
29. Bassler D, Stoll BJ, Schmidt B, et al. Trial of Indomethacin Prophylaxis in Preterms Investigators. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. Pediatrics 2009;123:313-8.
30. Joseph RM, O'Shea TM, Allred EN, et al. Prevalence and associated features of autism spectrum disorder in extremely low gestational age newborns at age 10 years. Autism Res 2017;10:224-32.
31. Shapiro SM. Definition of the clinical spectrum of kernicterus and bilirubin-induced neurologic dysfunction (BIND). J Perinatol 2005;25:54-9.
32. Amin SB, Smith T, Wang H. Is neonatal jaundice

associated with autism spectrum disorders: a systematic review. J Autism Dev Disord 2011;41:1455-63.
33. Amin SB, Harte T, Scholer L, et al. Intravenous lipid and bilirubin-albumin binding variables in preterm infants. Pediatrics 2009;124:211-7.
34. Amin SB. Effect of free fatty acids on bilirubin-albumin binding affinity and unbound bilirubin in preterm infants. JPEN J Parenter Enteral Nutr 2010;34:414-20.
35. Hegyi T, Kleinfeld A, Huber A, et al. Effects of Soybean Lipid Infusion on Unbound Free Fatty Acids and Unbound Bilirubin in Preterm Infants. J Pediatr 2017;184:45-50.e1.
36. Amin SB, Maisels MJ, Watchko JF. Early lipid infusions and unbound bilirubin in preterm neonates: a cause for concern? J Pediatr 2017;184:6-7.
37. Hegyi T, Kleinfeld A, Huber A, et al. Effects of soybean lipid infusion on triglyceride and unbound free fatty acid levels in preterm infants. J Matern Fetal Neonatal Med 2019;32:3226-31.

doi: 10.21037/pm-21-42
Cite this article as: Arnold C, Tyson JE. Phototherapy for preterm newborns—historical controversies and RCT evidence. Pediatr Med 2021;4:35.