

Journal of Neonatal Care and Pediatric Research

Review Article

Comparative Analysis of phototherapy protocols versus Standard Care in preterm birth complications

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Received: 2 January 2026; Accepted: 8 April 2026; Published: 3 July 2026.

Citation of this article: Rodriguez M, Vargas L, Ramirez M (2026) Comparative Analysis of phototherapy protocols versus Standard Care in preterm birth complications. J Neonatal Care Pediatr Res, 1(1): 01-08. DOI: [10.5281/zenodo.22814765](https://doi.org/10.5281/zenodo.22814765)

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Abstract

Background: Unconjugated hyperbilirubinemia is nearly universal in preterm infants, and their more permeable blood-brain barrier makes even moderate bilirubin elevations a meaningful neurotoxic risk.

Objective: This review compares standard, gestational-age-threshold-guided phototherapy against more aggressive, high-intensity or double-surface protocols in preterm hyperbilirubinemia, and evaluates the contribution of device-level advances such as light-emitting diode phototherapy.

Methods: We synthesized randomized trials, cohort studies, systematic reviews, and guideline documents addressing phototherapy thresholds, treatment intensity, light-source technology, and safety outcomes in preterm infants.

Findings: Aggressive phototherapy reduced neurodevelopmental impairment among extremely low birth weight survivors above roughly 750 g but showed a nonsignificant mortality signal in the smallest infants; LED and double-surface devices achieved faster bilirubin decline with less thermal burden; and severe outcomes tracked more with delayed treatment escalation than with the threshold framework chosen.

Conclusions: Protocol selection should be individualized by birth weight and gestational age, with device-level improvements offering a low-risk route to better efficacy and prompt, reliable delivery mattering as much as the numeric threshold itself.

Keywords: phototherapy; neonatal hyperbilirubinemia; preterm birth; kernicterus; extremely low birth weight

1. Introduction

Unconjugated hyperbilirubinemia is nearly universal among preterm infants and remains the most common reason for extended neonatal intensive care unit monitoring in this population. Because the preterm liver has a limited capacity to conjugate bilirubin and the preterm blood-brain barrier is more permeable to unbound bilirubin than that of the term infant, even modest elevations in total serum bilirubin can pose a disproportionate risk of bilirubin-induced neurologic dysfunction and kernicterus spectrum disorder in infants born before 35 weeks of gestation [1,2]. Phototherapy, introduced into routine neonatal practice more than five decades ago, remains the primary noninvasive treatment for hyperbilirubinemia, converting circulating unconjugated bilirubin into water-soluble photoisomers excreted without hepatic conjugation [3]. Its optimal use in preterm and especially extremely low birth weight infants remains genuinely contested, because the population most vulnerable to bilirubin neurotoxicity is also the population in which aggressive light exposure carries its own uncertain risks [4,5].

Two broad approaches shape contemporary practice. Standard care applies gestational-age- and risk-stratified bilirubin thresholds, typically drawn from American Academy of Pediatrics nomograms, to decide when phototherapy is started, intensified, or discontinued [6,7]. More aggressive or prophylactic protocols initiate high-irradiance, double-surface phototherapy earlier and at lower thresholds specifically in extremely low birth weight infants, on the premise that preventing any excursion into the neurotoxic range outweighs the theoretical costs of additional light exposure [4]. Between these poles sit device-level choices, conventional fluorescent tubes, halogen-quartz lamps, fiberoptic blankets, and narrow-band blue or blue-green light-emitting diode (LED) systems, each with different irradiance profiles and practical implications for thermoregulation [8,9]. This review compares the

evidence for standard, threshold-driven phototherapy against more aggressive and technologically advanced protocols in preterm hyperbilirubinemia, synthesizing efficacy, dose-response, safety, and long-term outcome data.

2. Mechanisms and rationale for phototherapy in preterm hyperbilirubinemia

Phototherapy works by exposing skin to light in the blue-to-green spectrum, roughly 425 to 475 nanometers, absorbed by bilirubin in the superficial dermis. This absorption drives photoisomerization of native bilirubin into more polar isomers, principally lumirubin, excreted in bile and urine without requiring hepatic glucuronidation, the step developmentally deficient in preterm neonates [3,10]. Because the reaction depends on cutaneous light exposure rather than hepatic enzymatic maturity, phototherapy suits the preterm infant well, but the same immaturity that limits conjugation also affects the pharmacokinetics of resulting photoproducts, since preterm skin is thinner and more translucent than term skin, altering light penetration in ways not fully captured by dosing algorithms developed in term cohorts.

Two physical parameters largely determine efficacy: spectral irradiance and exposed surface area. Sisson and colleagues established that the rate of bilirubin decline increases with light intensity across a clinically relevant range, providing the physiological basis for high-intensity protocols, while also demonstrating a plateau beyond which further irradiance yields diminishing returns [11]. Narrow-band blue sources are more efficient per unit irradiance than broad-spectrum white or daylight lamps because their emission overlaps more precisely with the bilirubin absorption peak. Double-surface delivery, combining an overhead unit with a fiberoptic blanket, increases exposed body surface and accelerates bilirubin decline relative to single-surface conventional phototherapy, forming the rationale for aggressive double-surface protocols in extremely low birth weight

infants [12].

3. Standard, threshold-guided phototherapy protocols

Standard care follows hour-specific or gestational-age-specific bilirubin nomograms defining thresholds for initiating phototherapy, intensifying it, and considering exchange transfusion. The American Academy of Pediatrics guideline for infants of 35 or more weeks of gestation, and its companion guidance for lower gestational ages, remain the most widely adopted framework, translating bilirubin, gestational age, and risk factors into an action threshold [6,7]. Bhutani and colleagues' predischarge hour-specific bilirubin nomogram, developed largely in term and near-term infants, underlies much of this risk-stratified approach and remains the most externally validated tool for predicting which newborns will cross a treatment threshold [13].

For infants below 35 weeks, threshold guidance is considerably less standardized. Maisels and colleagues proposed an approach scaling phototherapy and exchange-transfusion thresholds inversely with gestational age, adjusted for birth weight and clinical risk, while acknowledging that evidence below 28 weeks remains sparse [14]. Newman and colleagues, applying AAP-consistent thresholds to a large managed-care cohort, calculated the number needed to treat with phototherapy to prevent one case of severe hyperbilirubinemia and found it high in lower-risk strata, evidence often invoked against escalating treatment for every borderline value [15]. This tension, between intervening early enough to prevent neurotoxicity and avoiding unnecessary treatment, is the central dilemma both protocol types attempt to resolve from opposite directions.

Guideline bodies outside North America converge on similar principles while adapting numeric thresholds locally. The Scandinavian guidelines described by Bratlid

and colleagues also retain gestational-age-adjusted thresholds, reinforcing threshold-guided care as the international norm [16].

Table 1: Representative gestational-age-adjusted phototherapy initiation thresholds under standard, threshold-guided care [6,14,13].			
Gestational age	Approx. phototherapy threshold (TSB, mg/dL)	Primary source of guidance	Notes
35-37 weeks (low risk)	13-15	AAP hour-specific nomogram	Adjusted upward for absence of hemolysis or other risk factors
32-34 weeks	10-12	Maisels preterm approach	Lower threshold reflecting reduced albumin-binding reserve
28-31 weeks	8-10	Maisels preterm approach	Evidence base sparser; extrapolated from higher gestational ages
<28 weeks	5-7	Maisels preterm approach	Often treated prophylactically from birth in many units

4. Aggressive and high-intensity protocols in extremely low birth weight infants

The single most influential trial comparing treatment intensity in preterm infants is the NICHD Neonatal Research Network's randomized comparison of aggressive versus conservative phototherapy. Morris and colleagues randomized more than 1,900 infants weighing 501 to 1,000 grams to an aggressive protocol, using a lower threshold and more continuous treatment, or a conservative protocol with higher thresholds, and found aggressive phototherapy significantly reduced neurodevelopmental impairment among survivors above 750 grams, though it did not improve the composite death-or-impairment outcome overall and was associated with a nonsignificant mortality increase among the smallest infants [4]. This asymmetric result, benefit in larger infants alongside a possible-harm signal in the smallest, has shaped nearly every subsequent preterm phototherapy guideline.

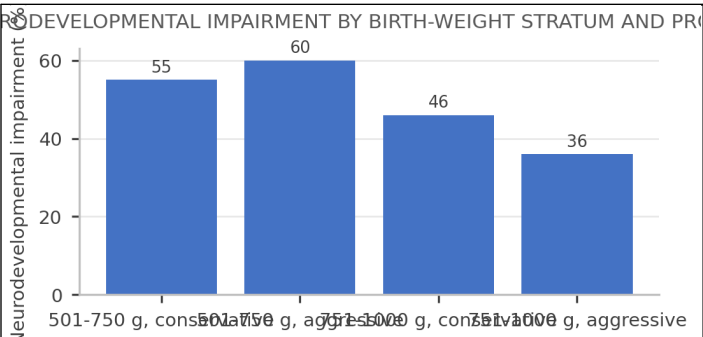


Figure 1: Rate of neurodevelopmental impairment among extremely low birth weight survivors by birth-weight stratum and phototherapy protocol in the NICHD Neonatal Research Network randomized trial, showing benefit from aggressive phototherapy concentrated in infants above 750 g at birth [4].

Device-level intensification offers a second route to aggressive treatment without lowering the bilirubin threshold. Garg and colleagues showed high-intensity double-surface phototherapy on a fluid bed produced faster bilirubin decline than conventional single-surface phototherapy without increased short-term adverse events [12]. Seidman and colleagues compared blue and blue-green LED devices against halogen-quartz phototherapy and found LED systems achieved comparable or superior decline while generating substantially less radiant heat, an advantage for thermoregulation in the smallest infants [8]. A Cochrane review of LED phototherapy concluded LED devices are at least as effective as conventional sources and may reduce treatment duration, though trial quality and preterm-specific reporting remained limited [9]. A separate meta-analysis comparing LED against other sources reached a similar conclusion, again noting scarcity of extremely preterm participants [17].

Dose-response modeling clarifies why aggressive protocols achieve faster decline without proportional risk increase. Vandborg and colleagues modeled irradiance against bilirubin decline across clinically used devices and confirmed a curvilinear relationship consistent with Sisson and colleagues, providing a quantitative basis for titrating irradiance [18,11].

5. Safety, adverse effects, and long-term outcomes

Table 2: Reported adverse associations with neonatal phototherapy and their current evidence strength [19,20,23,25,24].			
Adverse association	Study design	Evidence strength	Preterm-specific data
Increased melanocytic nevi	Twin cohort	Moderate	Limited
Childhood myeloid leukemia	Retrospective cohort	Weak-moderate; small absolute risk	Not isolated in cohort
Overall childhood cancer risk	Retrospective cohort	Inconsistent across cohorts	Not isolated in cohort
Insensible water loss / loose stools	Systematic review	Strong; well established	Applies broadly to preterm infants

Short-term adverse effects, increased insensible water loss, loose stools, transient rash, and bronze baby syndrome with concurrent cholestasis, are well characterized and generally manageable, but a systematic review by Xiong and colleagues catalogued a broader set of reported associations, including altered heart rate variability and retinal changes with inadequate eye shielding, while noting evidence quality remained low and preterm-specific data sparse [19]. Csoma and colleagues, using a twin design to control for genetic confounding, found neonatal blue-light phototherapy associated with increased melanocytic nevi in later childhood, renewing attention to long-term dermatologic surveillance in phototherapy-exposed preterm cohorts [20].

Practical bedside delivery also affects efficacy and safety, since irradiance at the manufacturer's specification frequently differs from irradiance actually delivered once distance, bulb age, and shielding are accounted for; Stokowski's review of phototherapy fundamentals emphasized routine irradiance measurement and device maintenance as prerequisites for either protocol type to perform as intended [21]. Hansen's commentary on the resurgence of kernicterus argued that lapses in basic delivery and follow-up, rather than deficiencies in threshold frameworks, explained most preventable severe cases, a caution equally applicable to preterm infants [22].

Concern about a possible carcinogenic effect of phototherapy has generated a substantial and somewhat inconsistent literature. Wickremasinghe and colleagues, in a large retrospective cohort, reported an association between phototherapy and subsequent childhood myeloid leukemia, though the absolute risk increase was small and required replication given potential confounding by indication [23]. Newman and colleagues, examining an overlapping Northern California cohort, found associations with specific cancer subtypes but not overall childhood cancer risk [24]. Auger and colleagues reported a modest but significant association between phototherapy exposure and later childhood cancer risk in a large Canadian cohort, without resolving whether the association reflects a causal mechanism or confounding by underlying hemolytic conditions [25]. None of these studies isolated the preterm subpopulation or altered current guidelines, but the signal is consistently cited as a reason to avoid unnecessarily low thresholds even within aggressive frameworks.

On the neuroprotective side, the evidence is more directly reassuring. Watchko and Tiribelli's review of bilirubin-induced neurologic damage summarized the basis for treating even moderate hyperbilirubinemia aggressively in preterm infants, whose bilirubin-albumin binding capacity and blood-brain barrier integrity are both compromised relative to term infants [26]. Kuzniewicz and colleagues, studying hazardous hyperbilirubinemia incidence, and Donneborg and colleagues, describing extreme hyperbilirubinemia and kernicterus spectrum disorder in a Danish cohort, both found severe outcomes concentrated among infants with delayed treatment escalation rather than among infants managed under either protocol applied promptly, suggesting adherence and timeliness may matter more than the specific threshold [27,28]. Mreihil and colleagues' pharmacokinetic study of bilirubin photoisomer formation showed the biologically active response begins within the first hours of light exposure, reinforcing the

rationale for prompt initiation regardless of framework [29].

6. Comparative efficacy: standard versus aggressive protocols

Direct, preterm-specific head-to-head efficacy data remain concentrated in the NICHD trial, which found aggressive phototherapy reduced peak bilirubin and, in an important subgroup, reduced neurodevelopmental impairment, but did not clearly improve the overall composite outcome and raised a mortality signal in the smallest infants that has tempered enthusiasm for universal early aggressive treatment [4]. Arnold and colleagues' earlier appraisal, published before the NICHD results, anticipated this tension, questioning whether neuroprotection through lower peak bilirubin would translate into measurable outcome benefit, and cautioning that any protocol change needed to weigh a plausible but unproven mortality risk against a plausible but unproven neuroprotective benefit [5].

At the population level, the case for vigilant standard care is reinforced by data on what happens when thresholds are missed rather than by data favoring one numeric threshold over another. Slusher and colleagues' systematic review of the global burden of severe neonatal jaundice found most bilirubin-related morbidity and mortality worldwide occurs where phototherapy access or timely escalation is inadequate, and Olusanya and colleagues' global perspective reached a parallel conclusion, framing threshold refinement in high-resource settings as secondary to ensuring universal, timely access elsewhere [30,31]. Maisels' review of persistent challenges concluded the marginal difference between well-implemented standard and aggressive protocols is likely smaller than the difference between either delivered promptly versus delayed, consistent with the cohort findings from Kuzniewicz and colleagues and Donneborg and colleagues [32,27,28].

Device choice interacts with this threshold question.

Because LED systems achieve comparable or superior bilirubin decline with less thermal load, several reviewers suggest upgrading the light source, rather than lowering the numeric threshold, may be the more favorable route to improving efficacy without incurring the theoretical risks of earlier or prolonged light exposure [9,17,8]. This device-centered strategy sidesteps the unresolved NICHD mortality signal while capturing much of the efficacy gain historically associated with aggressive dosing.

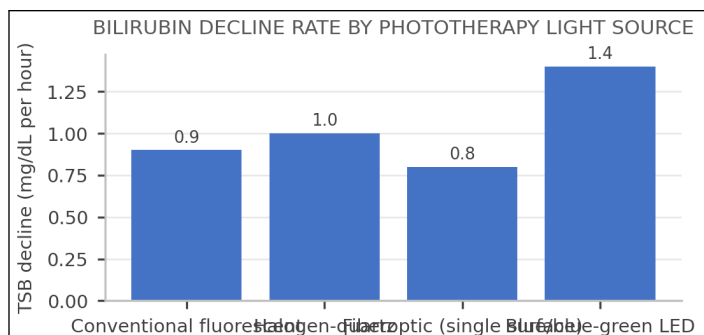


Figure 2: Mean rate of total serum bilirubin decline per light-source category, illustrating the graded efficacy advantage of narrow-band LED devices over halogen-quartz and conventional fluorescent phototherapy sources [8,17,9].

7. Discussion

Taken together, the evidence supports a nuanced rather than binary conclusion. Aggressive, early, high-intensity phototherapy delivers a measurable neurodevelopmental benefit in extremely low birth weight infants above roughly 750 grams, but the same intensity in the smallest and most immature infants carries an unresolved mortality signal, leaving guideline bodies to recommend weight-stratified rather than uniform intensification [4,14]. Standard, threshold-guided care remains appropriate for the majority of preterm infants outside the extremely low birth weight category where the aggressive-protocol trial was conducted, and number-needed-to-treat data argue against extending aggressive thresholds indiscriminately to lower-risk strata [6,15].

Device-level advances, particularly narrow-band and LED phototherapy, offer efficacy gains largely orthogonal to

the threshold debate and may represent the more broadly applicable improvement to preterm practice, since they improve decline rate and reduce thermal burden without changing when treatment starts [9,17,8,12]. The long-term safety literature, spanning dermatologic, hematologic, and oncologic outcomes, has not produced findings strong or preterm-specific enough to change thresholds, but it reinforces the principle, already embedded in both frameworks, that phototherapy should be used at the lowest effective intensity and duration for a given infant's risk profile [19,20,23,25,24]. Future preterm-specific randomized trials incorporating modern LED devices, weight-stratified reporting, and long-term follow-up would meaningfully narrow the uncertainty the 2008 NICHD trial could not fully resolve [4,5].

8. Conclusion

Phototherapy remains the cornerstone of hyperbilirubinemia management in preterm infants, and the choice between standard, guideline-threshold care and more aggressive protocols should be individualized primarily by birth weight and gestational age rather than treated as a uniform policy. The strongest randomized evidence supports selective aggressive phototherapy above approximately 750 grams for its neurodevelopmental benefit, tempered caution in the smallest extremely low birth weight infants given an unresolved mortality signal, and continued reliance on well-implemented standard threshold care for the broader preterm population, with LED and other device-level improvements offering a comparatively low-risk route to better efficacy across both strategies [4,7,9]. Timely, correct application of whichever protocol a unit adopts appears, across the cohort literature, to matter more for preventing severe hyperbilirubinemia and its neurologic sequelae than the precise numeric threshold chosen, underscoring that protocol adherence and system-level reliability deserve as much attention as the ongoing standard-versus-aggressive debate [27,28,30,31].

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