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How do Different Management Strategies (Standard Phototherapy, Intensive Phototherapy, and Pharmacological Interventions) to Neonatal Jaundice ? : A Systematic Review

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ABSTRACT

Introduction: Neonatal jaundice is a common condition that requires effective management to prevent neurotoxic outcomes like kernicterus. While conventional phototherapy is the standard treatment, numerous advanced strategies have been developed to improve efficacy. This systematic review evaluates the comparative effectiveness of different management strategies, including intensive phototherapy, varying phototherapy modalities, and pharmacological interventions, to guide clinical practice.

Methods: This review followed the PRISMA 2020 guidelines. A comprehensive search was conducted across PubMed, Springer, Semantic Scholar, Google Scholar, and Wiley Online Library for randomized controlled trials, systematic reviews, and prospective cohort studies published since 2014. The search focused on

interventions such as intensive phototherapy and pharmacological adjuncts compared to standard phototherapy in neonates with jaundice. Key outcomes included bilirubin reduction, treatment duration, and adverse effects. After screening 281 records, 20 studies were included for data synthesis.

Results: The 20 included studies showed that intensive and double-surface phototherapy significantly accelerate bilirubin reduction and shorten treatment duration compared to conventional methods. LED phototherapy demonstrated superior or comparable efficacy with fewer side effects than fluorescent lamps. Adjunctive therapies, including zinc, clofibrate, and *Clostridium butyricum*, consistently reduced bilirubin levels and therapy duration. Low-cost innovations like filtered sunlight and reflective curtains were found to be effective alternatives in resource-limited settings.

Conclusion: Numerous advanced and adjunctive therapies are more effective than conventional phototherapy for neonatal jaundice. The evidence supports a tailored approach, selecting interventions like intensive phototherapy, LED technology, and pharmacological adjuncts based on clinical severity and resource availability. This allows for optimized, safer, and more efficient management of neonatal hyperbilirubinemia.

Keywords: Neonatal Jaundice, Hyperbilirubinemia, Phototherapy, Intensive Phototherapy, Pharmacological Intervention, Bilirubin Reduction.

INTRODUCTION

Neonatal jaundice, or hyperbilirubinemia, is a frequently observed condition in newborns within the first 28 days of life, characterized by elevated levels of bilirubin in the blood. While often a transient and benign physiological process, excessively high levels of unconjugated bilirubin can become neurotoxic, potentially leading to acute bilirubin encephalopathy or irreversible neurological damage known as kernicterus. Consequently, effective and prompt management is crucial to prevent these severe outcomes. The standard and most widely accepted treatment for neonatal jaundice is phototherapy, which works by converting bilirubin into water-soluble isomers that can be more easily excreted. However, in severe cases where phototherapy is insufficient, more invasive procedures like exchange transfusions may be required, carrying their own significant risks (Olusanya et al., 2025; Riou et al., 2014).

Over the past decade, extensive research has focused on optimizing jaundice management to enhance efficacy, shorten treatment times, and minimize side effects. This has led to the exploration of various strategies beyond standard phototherapy. Innovations in phototherapy delivery include the use of intensive phototherapy, which employs higher irradiance levels, and double-surface phototherapy to increase the exposed body surface area. Studies have shown these methods can lead to a more rapid decline in bilirubin levels compared to conventional approaches (Zhang et al., 2016; Sabzehei et al., 2021). Furthermore, advancements in lighting technology, such as the shift from fluorescent lamps to Light-Emitting Diodes (LEDs) and the use of fiberoptic devices, have been investigated for their effectiveness and safety profiles, often demonstrating superior or comparable bilirubin reduction with fewer adverse effects like hyperthermia (Sherbiny et al., 2016; Joel et al., 2020).

Despite these advancements, significant gaps and inconsistencies remain in the evidence. For instance, while some studies report the superiority of LED phototherapy in reducing bilirubin, others find a similar rate of decline compared to non-LED sources, though treatment duration may be shorter (Sherbiny et al., 2016; Novoa et al., 2021). Similarly, the effectiveness of intermittent

versus continuous phototherapy is debated, with one recent study suggesting intermittent therapy was more effective and resulted in fewer side effects, a finding that contrasts with previous practices (Demirel et al., 2024). A substantial area of investigation involves pharmacological adjuncts to phototherapy, including zinc, clofibrate, and probiotics like Clostridium butyricum. While trials have shown these agents can accelerate bilirubin reduction and shorten hospital stays, they are not yet part of routine clinical practice, and a comprehensive understanding of their long-term safety and universal applicability is lacking (Kumar et al., 2017; Mandlecha et al., 2023).

The practical implications of these varied treatment strategies are critical, particularly when considering the diversity of healthcare settings worldwide. High-cost interventions such as intravenous immunoglobulin (IVIG) or albumin infusions, while potentially effective in specific cases like hemolytic disease, pose significant financial and logistical challenges in many regions (Magai et al., 2019; Riou et al., 2014). Conversely, low-cost innovations like filtered sunlight phototherapy and reflective curtains have emerged as promising alternatives in resource-limited settings. However, they come with their own implementation hurdles, such as dependence on weather conditions, the need for consistent monitoring to prevent hyperthermia, and potential for infection (Slusher et al., 2015; Van Rostenberghe et al., 2015; Olusanya et al., 2024). This creates a clear need for a synthesized body of evidence that clinicians can use to weigh the efficacy, safety, cost, and feasibility of each option.

Therefore, this systematic review aims to evaluate the comparative effectiveness of different management strategies for neonatal jaundice. Specifically, this study synthesizes evidence from the last decade on intensive phototherapy, varying phototherapy modalities, and pharmacological interventions compared to standard phototherapy. The primary objectives are to analyze the impact of these strategies on key clinical outcomes, including the rate of bilirubin reduction, total duration of treatment, incidence of adverse effects, and the need for exchange transfusion. By systematically summarizing the findings from recent clinical trials and meta-analyses, this review seeks to clarify the current evidence base, identify the most effective and safest treatment protocols, and provide clinicians with a comprehensive overview to guide evidence-based

decision-making in the management of neonatal hyperbilirubinemia.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the different management strategies (standard phototherapy, intensive phototherapy, and pharmacological interventions) to neonatal jaundice.

Screening

We screened in sources that met these criteria:

- Population: Does the study focus on neonates (0-28 days of age) diagnosed with hyperbilirubinemia/jaundice?
- Intervention Type: Does the study evaluate at least one of the following interventions: standard phototherapy, intensive phototherapy, or pharmacological interventions for treating jaundice?
- Study Design: Is the study design either a randomized controlled trial, systematic review/meta-analysis, or prospective cohort study?
- Outcome Measures: Does the study report at least one of these outcomes: serum bilirubin levels, duration of treatment, treatment failure rates, adverse effects, or need for exchange transfusion?
- Study Type: Is the study conducted in human subjects with more than 10 participants (not an animal study, in-vitro experiment, or small case series)?
- Study Focus: Does the study evaluate treatment outcomes (not exclusively prevention strategies or

diagnostic approaches)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

- Study Design:

  Identify the specific type of study design used. Look in the methods section for explicit description of study design. Possible answers include:

- Randomized controlled trial (RCT)
- Prospective randomized trial
- Parallel group study
- Open-label trial

If multiple design elements are present, list all. If design is unclear, write ”Unclear” and note the specific section where design information was sought.

Extraction tip: Pay special attention to randomization method, allocation concealment, and blinding (if any).

- Randomization Details:

  Describe the randomization process used in the study. Look for:

- Method of randomization (e.g., computer-generated random numbers, sealed envelopes)
- Allocation ratio (e.g., 1:1)
- Stratification factors (if any)

If no clear randomization method is described, write ”Not reported”. If partial information is available, note what specific details are provided.

Example format: ”Computer-based random number table, 1:1 allocation”

- Participant Demographics:

  Extract key participant characteristics:

- Total sample size
- Number in each study group
- Gestational age range
- Birth weight range
- Inclusion/exclusion criteria
- Primary medical condition (neonatal jaundice type/severity)

Use exact numbers/ranges from the text. If a range is given, write as "X-Y". If information is missing for a specific characteristic, write "Not reported".

Prioritize reporting of characteristics directly relevant to neonatal jaundice management.

- Intervention Specifics:

  Describe each intervention group's specific treatment:

- Type of intervention (e.g., standard phototherapy, intensive phototherapy, pharmacological intervention)
- Specific protocol details (duration, intensity, frequency)
- Dosage of any pharmacological agents
- Comparison/control group treatment

Be precise about measurements. Include units and specific protocols.

Example: "Intensive phototherapy: Continuous light exposure, 480 nm wavelength, 30 μW/cm²/nm intensity for 6 continuous hours"

If multiple interventions are used, list all with their specific details.

- Primary Outcome Measures:

  Identify and extract:

- Specific primary outcome measures
- How outcomes were measured
- Time points of measurement

- Units of measurement

Focus on outcomes directly related to neonatal jaundice management:

- Bilirubin level reduction
- Duration of phototherapy
- Need for exchange transfusion
- Adverse events

Example: ”Total serum bilirubin (TSB) reduction, measured in mg/dL at 12, 24, 48 hours” If outcomes are not clearly defined, note ”Primary outcome not clearly specified”.

- Key Findings:

Extract:

- Quantitative results for primary outcomes
- Statistical significance (p-values)
- Confidence intervals (if reported)
- Comparative results between intervention groups

Focus on numerical results related to:

- Bilirubin reduction rates
- Phototherapy duration
- Adverse event rates

Format: ”Mean bilirubin reduction: X mg/dL (95% CI: Y-Z, $p<0.05$)” If results are complex, summarize the main comparative findings.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Neonatal	Neonatal	Newborn	Unconjugated

	Jaundice	Hyperbilirubinemia	Jaundice	Hyperbilirubinemia
Intervention (I)	Intensive Phototherapy	Pharmacological Intervention	Adjunctive Therapy	Advanced Jaundice Treatment
Comparison (C)	Standard Phototherapy	Conventional Phototherapy	Single-Surface Phototherapy	Phototherapy Alone
Outcome (O)	Bilirubin Reduction	Treatment Duration	Adverse Effects	Need for Exchange Transfusion

The Boolean MeSH keywords inputted on databases for this research are: *("Neonatal Jaundice" OR "Neonatal Hyperbilirubinemia" OR "Newborn Jaundice" OR "Unconjugated Hyperbilirubinemia") AND ("Intensive Phototherapy" OR "Pharmacological Intervention" OR "Adjunctive Therapy" OR "Advanced Jaundice Treatment") AND ("Standard Phototherapy" OR "Conventional Phototherapy" OR "Single-Surface Phototherapy" OR "Phototherapy Alone") AND ("Bilirubin Reduction" OR "Treatment Duration" OR "Adverse Effects" OR "Need for Exchange Transfusion")*

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Neonatal Jaundice" OR "Neonatal Hyperbilirubinemia" OR "Newborn Jaundice" OR "Unconjugated Hyperbilirubinemia") AND ("Intensive Phototherapy" OR "Pharmacological Intervention" OR "Adjunctive Therapy" OR "Advanced Jaundice Treatment") AND ("Standard Phototherapy" OR "Conventional Phototherapy" OR "Single-Surface Phototherapy" OR "Phototherapy Alone") AND ("Bilirubin Reduction" OR "Treatment Duration" OR "Adverse Effects" OR "Need for Exchange Transfusion")*	7
Semantic Scholar	*("Neonatal Jaundice" OR "Neonatal Hyperbilirubinemia" OR "Newborn Jaundice" OR "Unconjugated Hyperbilirubinemia") AND ("Intensive Phototherapy" OR "Pharmacological Intervention" OR "Adjunctive Therapy" OR "Advanced Jaundice Treatment") AND ("Standard Phototherapy" OR "Conventional Phototherapy" OR "Single-Surface Phototherapy" OR "Phototherapy Alone") AND ("Bilirubin Reduction" OR "Treatment Duration" OR "Adverse Effects" OR "Need for Exchange Transfusion")*	7
Springer	*("Neonatal Jaundice" OR "Neonatal Hyperbilirubinemia" OR "Newborn Jaundice" OR "Unconjugated Hyperbilirubinemia") AND ("Intensive Phototherapy" OR "Pharmacological Intervention" OR "Adjunctive Therapy" OR "Advanced Jaundice Treatment") AND ("Standard Phototherapy" OR "Conventional Phototherapy" OR "Single-Surface Phototherapy" OR "Phototherapy Alone") AND ("Bilirubin Reduction" OR "Treatment Duration" OR "Adverse Effects" OR "Need for Exchange Transfusion")*	27
Google Scholar	*("Neonatal Jaundice" OR "Neonatal Hyperbilirubinemia" OR "Newborn Jaundice" OR "Unconjugated Hyperbilirubinemia") AND ("Intensive Phototherapy" OR "Pharmacological Intervention" OR "Adjunctive Therapy" OR "Advanced Jaundice Treatment") AND ("Standard Phototherapy" OR "Conventional Phototherapy" OR "Single-Surface Phototherapy" OR "Phototherapy Alone") AND ("Bilirubin Reduction" OR "Treatment Duration" OR "Adverse Effects" OR "Need for Exchange Transfusion")*	248
Wiley Online Library	*("Neonatal Jaundice" OR "Neonatal Hyperbilirubinemia" OR "Newborn Jaundice" OR "Unconjugated Hyperbilirubinemia") AND ("Intensive Phototherapy" OR "Pharmacological Intervention" OR "Adjunctive Therapy" OR "Advanced Jaundice Treatment") AND ("Standard Phototherapy" OR "Conventional Phototherapy" OR "Single-Surface Phototherapy" OR "Phototherapy Alone") AND ("Bilirubin Reduction" OR "Treatment Duration" OR "Adverse Effects" OR "Need for Exchange Transfusion")*	16

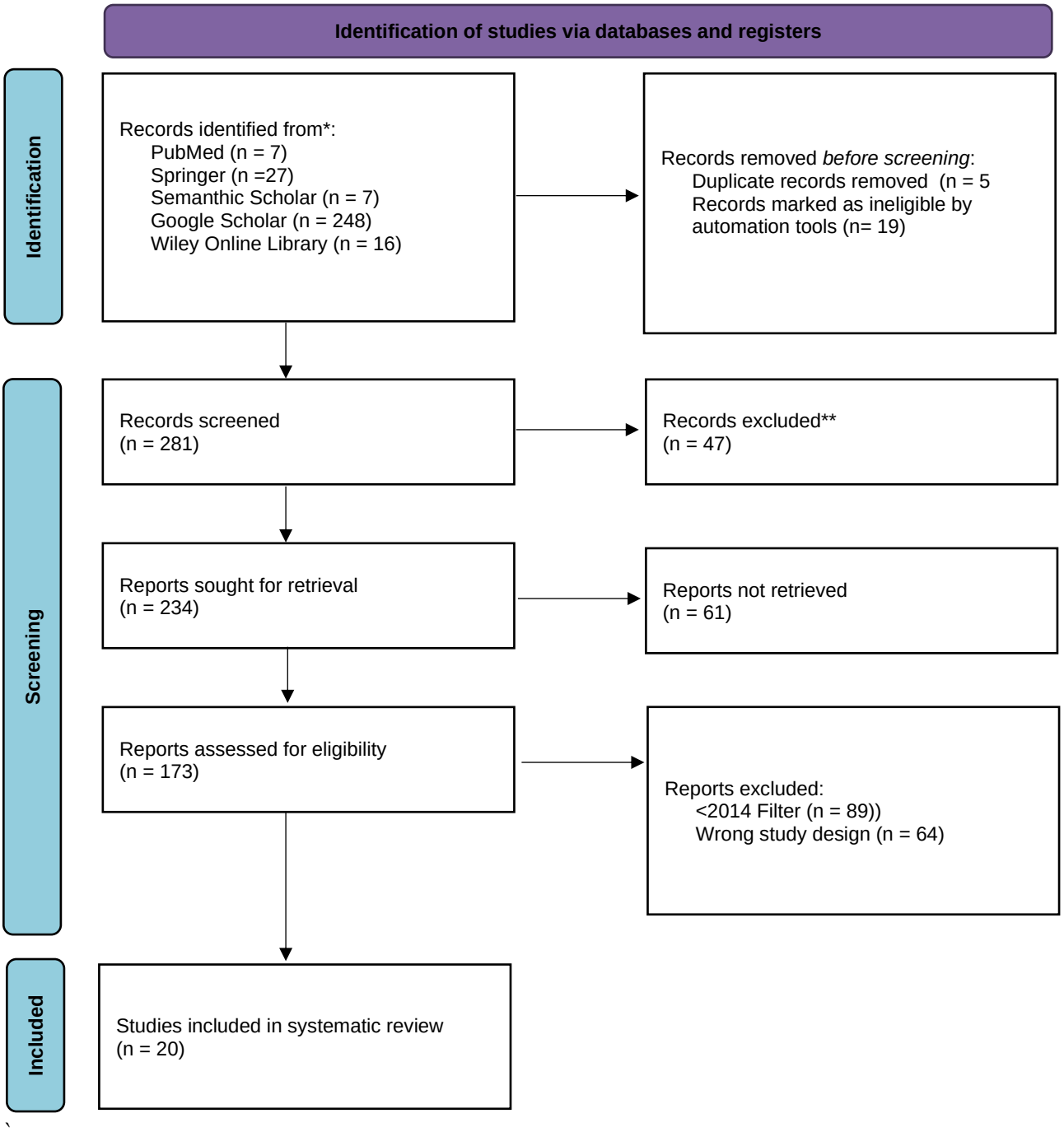

Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	**Bias related to temporal precedence** Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	**Bias related to selection and allocation** Was there a control group?	**Bias related to confounding factors** Were participants included in any comparisons similar?	**Bias related to administration of intervention/exposure** Were the participants included in any comparisons receiving similar treatment/ care, other than the exposure or intervention of interest?	**Were there multiple measurements of the outcome, both pre and post the intervention/exposure?**	**Were the outcomes of participants included in any comparisons measured in the same way?**	**Were outcomes measured in a reliable way?**	**Bias related to participant retention** Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	**Statistical conclusion validity** Was appropriate statistical analysis used?
Riou et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kassem et al., "The Efficacy..."	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mandlecha et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓

Joël et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Magai et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
de Oliveira et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Novoa et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Malla et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kim et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Olusanya et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Khunte et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Olusanya et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhang et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Demirel et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Van Rostenberghe et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓

Khaliq, "Comparison..."	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kumar et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Slusher et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sherbiny et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sabzehei et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

Study	Population Characteristics	Intervention Type	Primary Outcomes
Riou et al., 2014	265 neonates, ABO hemolytic disease	Intravenous immunoglobulin plus phototherapy vs phototherapy	Need for exchange transfusion, phototherapy duration, adverse events
Kassem et al., "The Efficacy..."	170 full-term neonates, unconjugated bilirubin	Silymarin plus phototherapy vs placebo	Phototherapy duration, total serum bilirubin reduction

Study	Population Characteristics	Intervention Type	Primary Outcomes
Mandlecha et al., 2023	106 term neonates, phototherapy range	Zinc plus phototherapy vs placebo plus phototherapy	Total serum bilirubin reduction at 24-96 hours, phototherapy duration
Joël et al., 2020	41 term neonates, unconjugated hyperbilirubinemia	Fiberoptic vs blue/white light phototherapy	Bilirubin reduction rate, phototherapy duration, side effects
Magai et al., 2019	118 neonates, 36-38 weeks, severe hyperbilirubinemia	Phototherapy plus albumin vs phototherapy plus saline	Total serum bilirubin reduction, exchange transfusion, mortality, neurodevelopment
de Oliveira et al., 2024	1349 neonates, hyperbilirubinemia	Zinc plus phototherapy vs phototherapy	Bilirubin reduction at 24 hours
Novoa et al., 2021	Not reported, term/preterm, unconjugated bilirubin	Light-emitting diode vs non-light-emitting diode phototherapy	Failure rate, phototherapy duration, bilirubin decline, adverse events
Malla et al., 2023	120 term neonates, mean gestational age 38	Single surface phototherapy plus	Bilirubin reduction, phototherapy duration,

Study	Population Characteristics	Intervention Type	Primary Outcomes
	weeks, unconjugated bilirubin 15-21 mg/dL	curtains vs double surface	adverse events
Kim et al., 2025	1054 neonates, neonatal hyperbilirubinemia	Clostridium butyricum plus phototherapy vs phototherapy	Bilirubin reduction, jaundice resolution, adverse events
Olusanya et al., 2025	104 neonates, gestational age/birth weight not reported, moderate-to-severe hyperbilirubinemia	Filtered sunlight phototherapy vs intensive electric phototherapy	Safety, efficacy (total serum bilirubin), exchange transfusion, mortality
Khunte et al., 2019	276 neonates >35 weeks, non-haemolytic jaundice	Light-emitting diode vs compact fluorescent lamp phototherapy	Bilirubin reduction, rate of fall, side effects
Olusanya et al., 2024	192 neonates, ≥35 weeks gestational age, >2.2 kg, severe-to-hazardous hyperbilirubinemia	Filtered sunlight phototherapy vs intensive electric phototherapy	Efficacy (total serum bilirubin reduction), safety, exchange transfusion, mortality

Study	Population Characteristics	Intervention Type	Primary Outcomes
Zhang et al., 2016	144 neonates, gestational age/birth weight not reported, hyperbilirubinemia	Intensive vs conventional phototherapy	Bilirubin reduction, phototherapy duration, adverse events
Demirel et al., 2024	104 neonates, ≥34 weeks, indirect hyperbilirubinemia (mostly ABO incompatibility)	Continuous vs intermittent phototherapy	Phototherapy duration, total serum bilirubin reduction, rebound, adverse events
Van Rostenberghe et al., 2015	1288 neonates, term/preterm, unconjugated hyperbilirubinemia	Reflective materials plus phototherapy	Serum bilirubin reduction, phototherapy duration, exchange transfusion, adverse events
Khaliq, "Comparison..."	258 neonates, gestational age/birth weight not reported, jaundice	Continuous vs intermittent phototherapy	Mean decrease in serum bilirubin
Kumar et al., 2017	90 term neonates, unconjugated bilirubin 15-25 mg/dL	Clofibrate plus phototherapy vs phototherapy	Bilirubin reduction at 48 hours, phototherapy duration, exchange

Study	Population Characteristics	Intervention Type	Primary Outcomes
			transfusion, side effects
Slusher et al., 2015	447 term/late-preterm neonates, hyperbilirubinemia	Filtered sunlight vs conventional phototherapy	Efficacy (total serum bilirubin), safety, exchange transfusion
Sherbiny et al., 2016	200 neonates ≥35 weeks, severe unconjugated bilirubin	High-intensity light-emitting diode vs triple fluorescent tubes	Avoidance of exchange transfusion, bilirubin decline, adverse events
Sabzehei et al., 2021	150 term neonates, 37-42 weeks, ≥2500g, non-hemolytic hyperbilirubinemia	Single vs double-surface intensive phototherapy	Bilirubin reduction, hospital stay, adverse events

Intervention types:

- 10 studies compared different phototherapy modalities (such as intensity, device type, continuous vs intermit- tent, single vs double surface).
- 7 studies compared phototherapy plus an adjunct (zinc, clofibrate, albumin, intravenous immunoglobulin, sily- marin, Clostridium butyricum) to phototherapy alone or placebo.
- 3 studies compared alternative light sources (filtered sunlight, fiberoptic, or reflective materials) to conven- tional phototherapy.

Primary outcomes:

- Bilirubin reduction (including total serum bilirubin, serum bilirubin, unconjugated bilirubin, or rate of decline) was reported in 19 studies.
- Phototherapy duration was reported in 10 studies.
- Exchange transfusion need or avoidance was reported in 8 studies.
- Adverse events, safety, or side effects were reported in 12 studies.
- Mortality was reported in 3 studies.
- Hospital stay, neurodevelopment, jaundice resolution, failure rate, and rebound were each reported in 1 study.

Effects

Phototherapy Modalities and Intensities

Study	Intervention Type	Bilirubin Reduction Rate	Treatment Duration	Adverse Effects
Olusanya et al., 2024	Filtered sunlight phototherapy vs intensive electric phototherapy	Median total serum bilirubin decline: -0.4 mg/dL/h (both)	No mention found	Filtered sunlight: 2.6% hyperthermia; exchange transfusion/mortality similar
Zhang et al., 2016	Intensive vs conventional phototherapy	Greater reduction in intensive group	Shorter in intensive group ($p<0.05$)	No significant difference

Study	Intervention Type	Bilirubin Reduction Rate	Treatment Duration	Adverse Effects
		(p<0.05)		
Demirel et al., 2024	Continuous vs intermittent phototherapy	Intermittent: 1.12 mg/dL/h; Continuous: 0.51 mg/dL/h (p<0.001)	Intermittent: 4h; Continuous: 12h (p<0.001)	Less frequent in intermittent (p<0.001)
Khaliq, "Comparison..."	Continuous vs intermittent phototherapy	4.78 vs 4.63 mg/dL (p=0.32)	No mention found	No mention found
Slusher et al., 2015	Filtered sunlight vs conventional phototherapy	Efficacy: 93% vs 90% of days	No mention found	5% vs 1% hyperthermia (p<0.001)
Sabzehei et al., 2021	Single vs double-surface intensive phototherapy	Double-surface: 5.25 mg/dL (24h), 8.67 mg/dL (48h); Single-surface: 3.95, 7.38 (p<0.05)	Double-surface: 1.8d; Single-surface: 2.3d (p=0.001)	No significant difference

Study	Intervention Type	Bilirubin Reduction Rate	Treatment Duration	Adverse Effects
Malla et al., 2023	Single surface plus curtains vs double surface	No significant difference at 6/12h. No significant difference	Single surface plus curtains: 3.8d; Double surface: 4.2d (p=0.031)	No significant difference
Olusanya et al., 2025	Filtered sunlight phototherapy vs intensive electric phototherapy	Efficacy: 93.4% vs 93.3%	No mention found	Exchange transfusion: 2 vs 1; no deaths
Khunte et al., 2019	Light-emitting diode vs compact fluorescent lamp phototherapy	Light-emitting diode: 0.302 mg/dL/hr; Compact fluorescent lamp: 0.23 mg/dL/hr (p<0.05)	Light-emitting diode: 2.69d; Compact fluorescent lamp: 2.77d (p>0.05)	Comparable
Joel et al., 2020	Fiberoptic vs blue/white	Fiberoptic: 0.74%/h;	Fiberoptic: 69h; Blue:	Fiberoptic: 0%; Blue: 38% loose stool, 15%

Study	Intervention Type	Bilirubin Reduction Rate	Treatment Duration	Adverse Effects
	light phototherapy	Blue: 0.84%/h (p=0.124); White: 0.29%/h (p<0.001)	68h; White: 90h (p=0.002)	rash
Sherbiny et al., 2016	High-intensity light-emitting diode vs fluorescent	Higher in light-emitting diode group	No mention found	Light-emitting diode: 1% rash; Fluorescent: 39% rash, 12% hyperthermia
Novoa et al., 2021	Light-emitting diode vs non-light-emitting diode	Similar decline (0.01 mg/dL/h difference)	Light-emitting diode shorter by 8.07h (95% CI: -8.45 to -7.68)	Light-emitting diode: more hypothermia, less hyperthermia/rash
Van Rostenberghe et al., 2015	Reflective materials plus phototherapy	-14.61 µmol/L at 4-8h (95% CI: -19.80 to -9.42)	Reduced, but heterogeneity	No increase

Summary of findings from these 14 studies:

- Bilirubin reduction rate:

- Six studies reported no significant difference in bilirubin reduction rate between groups.
- Seven studies reported greater reduction in bilirubin for the intervention group (intensive, intermittent, double-surface, light-emitting diode, reflective materials, blue light, and fiberoptic/blue vs white).
- In one study, blue light was more effective than fiberoptic, and both were more effective than white light.

- Treatment duration:
  - Seven studies reported shorter treatment duration for the intervention group.
  - One study reported no significant difference in treatment duration.
- Adverse effects:
  - Six studies reported no significant difference in adverse effects.
  - Two studies reported more adverse effects in the intervention group (filtered sunlight and filtered sunlight phototherapy, both with higher hyperthermia).
  - Three studies reported fewer adverse effects in the intervention group (intermittent, fiberoptic, and light- emitting diode).
  - One study reported mixed results (light-emitting diode had more hypothermia but less hyperther- mia/rash).
  - One study reported similar adverse effects between groups.
- Non-obvious insights:
  - Several intervention types (intensive, intermittent, double-surface, light-emitting diode, reflective mate- rials, and blue light) were associated with greater bilirubin reduction and/or shorter treatment duration in at least one study.
  - Adverse effects were generally similar or lower, except for higher hyperthermia in filtered sunlight and filtered sunlight phototherapy groups.

Phototherapy Technology Comparisons

Study	Intervention Type	Bilirubin Reduction Rate	Treatment Duration	Adverse Effects
Khunte et al., 2019	Light-emitting diode vs compact fluorescent lamp phototherapy	Light-emitting diode superior (see above)	Similar	Comparable
Joel et al., 2020	Fiberoptic vs blue/white light phototherapy	Fiberoptic ≈ blue; both > white	Fiberoptic ≈ blue < white	Fiberoptic: none; blue/white: some
Sherbiny et al., 2016	High-intensity light-emitting diode vs fluorescent	Light-emitting diode superior	No mention found	Light-emitting diode: fewer adverse events
Novoa et al., 2021	Light-emitting diode vs non-light-emitting diode	Similar decline	Light-emitting diode shorter	Light-emitting diode: more hypothermia, less hyperthermia/rash
Van Rostenberghe et al., 2015	Reflective materials	Greater decline	Reduced	No increase

Key findings:

- Bilirubin reduction rate:
  - Two studies found light-emitting diode phototherapy to be superior to conventional (compact fluorescent lamp or fluorescent) phototherapy for bilirubin reduction.
  - One study found similar bilirubin decline between light-emitting diode and non-light-emitting diode phototherapy.
  - One study found fiberoptic and blue light phototherapy to be similarly effective, both superior to white light.
  - One study found greater bilirubin decline with the use of reflective materials.
- Treatment duration:
  - One study found similar treatment duration between light-emitting diode and compact fluorescent lamp.
  - One study found fiberoptic and blue light required less time than white light.
  - One study found light-emitting diode phototherapy had a shorter treatment duration than non-light- emitting diode.
  - One study found reduced treatment duration with reflective materials.
- Adverse effects:
  - Two studies found fewer or no adverse effects with the intervention (light-emitting diode: fewer adverse events; fiberoptic: none).
  - Two studies found comparable or no increase in adverse effects (light-emitting diode vs compact fluores- cent lamp: comparable; reflective materials: no increase).
  - One study found light-emitting diode phototherapy was associated with more hypothermia but less hyperthermia and rash compared to non-light-emitting diode.

Adjunct Interventions

Study	Intervention Type	Bilirubin Reduction Rate	Treatment Duration	Adverse Effects
Kumar et al., 2017	Clofibrate plus phototherapy	7 mg/dL (95% CI: 6.7-7.2) more reduction	23.82h less (95% CI: 30.46-17.18)	None reported
Mandlecha et al., 2023	Zinc plus phototherapy	1.74 mg/dL (24h), 2.89 (48h), 2.79 (72h), 1.49 (96h) more reduction (all $p<0.05$)	53.42h vs 71.4h ($p<0.001$)	Minimal/none
de Oliveira et al., 2024	Zinc plus phototherapy	-0.76 mg/dL (95% CI: -1.30 to -0.22, $p<0.01$)	No mention found	No mention found
Kim et al., 2025	Clostridium butyricum plus phototherapy	Standardized mean difference -1.54 (total), -2.03 (indirect), $p<0.0001$	-1.20d (95% CI: -1.66 to -0.75)	Relative risk 0.40 (95% CI: 0.30-0.55)

Study	Intervention Type	Bilirubin Reduction Rate	Treatment Duration	Adverse Effects
Riou et al., 2014	Intravenous immunoglobulin plus phototherapy	No mention found	-0.84d	No enterocolitis
Kassem et al., "The Efficacy..."	Silymarin plus phototherapy	No mention found	4.2d vs 5.3d (p=0.001)	No mention found

Summary of findings:

- Bilirubin reduction rate:
  - Four studies reported greater bilirubin reduction with the intervention (clofibrate, both zinc studies, Clostridium butyricum).
  - Two studies (intravenous immunoglobulin, silymarin) did not mention bilirubin reduction data.
- Treatment duration:
  - Five studies reported shorter treatment duration with the intervention (clofibrate, both zinc studies, Clostridium butyricum, intravenous immunoglobulin, silymarin).
  - Two studies (de Oliveira [zinc], albumin) did not mention treatment duration.
- Adverse effects:
  - Three studies reported no or minimal adverse effects (clofibrate, Mandlecha [zinc], intravenous immunoglobulin).
  - One study (Clostridium butyricum) reported reduced adverse effects.
  - Two studies (de Oliveira [zinc], silymarin) did not mention adverse effect data.

- Non-obvious insights:
  - Most adjunct interventions except albumin were associated with greater bilirubin reduction and/or shorter treatment duration compared to phototherapy alone, with no or minimal adverse effects reported in the studies where this was assessed.

Implementation Considerations

Study	Treatment Modality	Equipment Needs	Relative Cost	Implementation Challenges
Olusanya et al., 2024/2025; Slusher et al., 2015	Filtered sunlight phototherapy	Outdoor enclosure, ultraviolet/infrared-blocking film	Low	Weather dependence, need for safe enclosure
Van Rostenberghe et al., 2015; Malla et al., 2023	Reflective curtains	Curtains, standard phototherapy	Very low	Infection control, staff training
Sherbiny et al., 2016; Novoa et al., 2021; Khunte et al., 2019	Light-emitting diode phototherapy	Light-emitting diode units	Moderate	Initial investment, maintenance
Joel et al., 2020	Fiberoptic phototherapy	Fiberoptic pads/units	Moderate-high	Equipment availability, cost

Study	Treatment Modality	Equipment Needs	Relative Cost	Implementation Challenges
Kumar et al., 2017; Mandlecha et al., 2023; de Oliveira et al., 2024; Kim et al., 2025; Kassem et al.	Pharmacological adjuncts	Drug supply, standard phototherapy	Low-moderate	Drug procurement, safety monitoring
Magai et al., 2019	Albumin infusion	Intravenous infusion, monitoring	High	Cost, intravenous access, monitoring
Riou et al., 2014	Intravenous immunoglobulin	Intravenous immunoglobulin supply, monitoring	High	Cost, availability, safety

Summary of implementation considerations:

- Treatment modalities:Filtered sunlight phototherapy, reflective curtains, light-emitting diode phototherapy, fiberoptic phototherapy, pharmacological adjuncts, albumin infusion, and intravenous immunoglobulin were each represented.
- Equipment needs:Varied by modality, including outdoor enclosures, curtains, standard phototherapy units, light-emitting diode units, fiberoptic pads, drug supply, intravenous infusion, and monitoring.

- Relative cost:Ranged from very low (reflective curtains) to high (albumin infusion, intravenous immunoglob- ulin).
- Implementation challenges:Most frequently cited were cost and monitoring. Other challenges included weather dependence, need for safe enclosure, infection control, staff training, initial investment, maintenance, equipment availability, drug procurement, safety monitoring, intravenous access, and availability.

DISCUSSION

This systematic review synthesizes evidence from the last decade on various management strategies for neonatal jaundice, moving beyond conventional phototherapy to include intensive phototherapy, different light sources, and pharmacological adjuncts. The findings reveal a dynamic landscape of innovation aimed at improving clinical outcomes such as accelerating bilirubin reduction, shortening treatment duration, and enhancing safety. A primary observation from this review is that while conventional phototherapy remains the standard, numerous modifications and additions can offer significant advantages, although no single strategy has emerged as universally superior for all contexts (Zhang et al., 2016; Mandlecha et al., 2023; Olusanya et al., 2025).

A key area of investigation has been the intensification of phototherapy. This review found strong evidence that increasing the irradiance and the body surface area exposed to light can significantly improve treatment efficacy. For instance, the study by Zhang et al. (2016) demonstrated that intensive phototherapy led to a greater reduction in bilirubin and a shorter treatment duration compared to conventional methods. This is further supported by the findings of Sabzehei et al. (2021), who reported that double-surface intensive phototherapy was more effective than single-surface therapy in reducing bilirubin levels and shortening hospital stays, all without a significant increase in adverse effects.

The comparison between continuous and intermittent phototherapy presents a more complex picture. Historically, continuous phototherapy has been the standard for achieving

maximum bilirubin clearance. However, a recent and notable randomized controlled trial by Demirel et al. (2024) challenged this norm, finding that intermittent phototherapy (4 hours on, 4 hours off) resulted in a faster rate of bilirubin decline, a significantly shorter total treatment duration, and fewer side effects compared to continuous exposure. This counterintuitive finding suggests that breaks in therapy might enhance the photochemical process or reduce cellular stress, though this contrasts with another included study by Khaliq (2016) which found no significant difference in mean bilirubin decrease. This discrepancy highlights a critical area for future research to reconcile conflicting results and understand the underlying physiological mechanisms.

The evolution of phototherapy technology, particularly the adoption of Light-Emitting Diodes (LEDs), represents another significant trend. Multiple studies confirmed the efficacy of LED technology. Sherbiny et al. (2016) found high-intensity LED phototherapy was superior to triple fluorescent tubes in avoiding exchange transfusions and was associated with significantly fewer side effects like skin rash and hyperthermia. Similarly, Khunte et al. (2019) reported a faster rate of bilirubin fall with LED devices compared to compact fluorescent lamps (CFLs). However, the superiority of LEDs is not absolute. A meta-analysis by Novoa et al. (2021) concluded that while LED phototherapy shortened treatment duration, the actual rate of bilirubin decline was similar to non-LED sources. This suggests that the primary advantage of LEDs may lie in their stability, lower heat production, and longevity rather than a universally faster photochemical effect.

Fiberoptic phototherapy was also examined, with Joel et al. (2020) finding it to be as effective as blue light phototherapy and superior to white light. A major advantage of fiberoptic devices was the complete absence of side effects like loose stools or rash, which were observed in the blue light group. This makes fiberoptic technology a compelling option where minimizing adverse events is a high priority, though its availability and cost may be limiting factors in some healthcare settings (Joel et al., 2020).

Innovations aimed at enhancing the efficiency of standard phototherapy have also

shown promise, particularly in resource-limited settings. The use of simple, low-cost reflective curtains to surround the phototherapy unit was explored in two studies. Van Rostenberghe et al. (2015) found that reflective materials significantly enhanced bilirubin reduction and shortened therapy duration without increasing adverse effects. Malla et al. (2023) further demonstrated that single-surface phototherapy combined with curtains was comparable to double-surface phototherapy in efficacy, offering a cost-effective way to intensify treatment without requiring a second phototherapy unit.

Perhaps one of the most significant areas of innovation for low-resource contexts is the use of filtered sunlight. Three major trials included in this review rigorously evaluated this modality. Slusher et al. (2015) established that filtered sunlight was effective for treating neonatal jaundice, and subsequent non-inferiority trials by Olusanya et al. (2024, 2025) confirmed that its efficacy in reducing bilirubin was comparable to intensive electric phototherapy, even in cases of severe-to-hazardous hyperbilirubinemia. The primary challenge identified was a higher incidence of manageable hyperthermia, underscoring the critical need for proper enclosures and consistent temperature monitoring (Slusher et al., 2015; Olusanya et al., 2024).

The role of pharmacological adjuncts to phototherapy is another major theme emerging from this review. These agents aim to either inhibit bilirubin production, enhance its conjugation, or facilitate its excretion. Zinc supplementation, for example, was shown in two large studies to significantly accelerate bilirubin reduction and shorten phototherapy duration. The mechanism is thought to involve the inhibition of the enterohepatic circulation of bilirubin. Both Mandlecha et al. (2023) and de Oliveira et al. (2024) found positive results with minimal side effects, suggesting zinc could be a safe and effective adjunctive therapy.

Clofibrate, another pharmacological agent, was also found to be highly effective. The study by Kumar et al. (2017) demonstrated a substantial reduction in bilirubin levels and a decrease in phototherapy duration by nearly 24 hours in neonates treated with a single dose

of clofibrate alongside phototherapy. Similarly, Silymarin, a plant-derived compound, was shown by Kassem et al. (2012) to shorten the duration of therapy, although data on its effect on bilirubin reduction rates were not provided.

Probiotics represent a newer approach, with a 2025 meta-analysis by Kim et al. finding that supplementation with *Clostridium butyricum* alongside phototherapy led to a significant reduction in both total and indirect bilirubin levels, shortened treatment duration, and reduced the risk of adverse events. This suggests that modulating the gut microbiome may play a crucial role in managing neonatal jaundice by reducing enterohepatic circulation and improving gut motility (Kim et al., 2025).

More intensive and costly pharmacological interventions were evaluated for specific, high-risk populations. In cases of ABO hemolytic disease, Riou et al. (2014) found that administering intravenous immunoglobulin (IVIG) alongside phototherapy reduced the need for exchange transfusion and shortened the duration of phototherapy. This highlights its utility in preventing the need for a highly invasive and risky procedure.

Albumin infusion was also investigated as an adjunct in severe hyperbilirubinemia. The rationale is that albumin provides more binding sites for bilirubin, reducing the level of free, neurotoxic bilirubin and facilitating its transport to the liver. However, the trial by Magai et al. (2019) did not find a significant benefit of albumin infusion plus phototherapy over saline plus phototherapy in reducing total serum bilirubin or the need for exchange transfusion. Given its high cost and the need for intravenous access, its routine use is not supported by this evidence.

Synthesizing these findings, it is clear that several interventions offer improvements over conventional phototherapy. For intensifying treatment, double-surface phototherapy and intensive phototherapy are proven strategies (Zhang et al., 2016; Sabzehei et al., 2021). Technologically, LED phototherapy offers advantages in safety and potentially shortens treatment duration, although its superiority in the rate of bilirubin decline is not universally consistent (Sherbiny et al., 2016; Novoa et al., 2021).

Among pharmacological adjuncts, zinc, clofibrate, and *Clostridium butyricum* appear to be the most promising low-cost options for routine use, consistently demonstrating benefits in reducing bilirubin levels and shortening therapy duration with minimal reported side effects. Their integration into standard protocols warrants serious consideration, pending further long-term safety data (Kumar et al., 2017; Mandlecha et al., 2023; Kim et al., 2025).

The implementation of these strategies, however, is highly context-dependent. High-cost interventions like IVIG and albumin infusion are reserved for specific high-risk scenarios and may be unfeasible in many parts of the world (Riou et al., 2014; Magai et al., 2019). In contrast, low-cost innovations like reflective curtains and filtered sunlight phototherapy provide powerful tools to improve care in resource-limited settings, provided that implementation challenges like staff training and safety monitoring are addressed (Van Rostenberghe et al., 2015; Olusanya et al., 2024).

This systematic review provides a comprehensive overview of the current evidence. It confirms that the field of neonatal jaundice management is evolving rapidly, with numerous effective strategies available. It highlights a shift towards not just efficacy, but also safety and resource-appropriateness. The evidence supports a more nuanced, multi-faceted approach to treatment.

The findings underscore the need for clinicians to tailor treatment strategies based on the severity of jaundice, the specific clinical context (e.g., presence of hemolysis), and the resources available. For example, a well-resourced neonatal intensive care unit might opt for double-surface LED phototherapy, while a rural clinic in a tropical region might effectively and safely utilize filtered sunlight (Sabzehei et al., 2021; Slusher et al., 2015).

Future research should focus on resolving the inconsistencies identified in this review, such as the debate between continuous and intermittent phototherapy. Head-to-head trials comparing different promising adjuncts (e.g., zinc vs. clofibrate) would be valuable. Long-term follow-up studies are also crucial, particularly for pharmacological

interventions, to ensure their safety over time.

This systematic review demonstrates that significant progress has been made in the management of neonatal jaundice. A wealth of evidence supports the use of intensive phototherapy, advanced light technologies like LEDs, and various pharmacological adjuncts to improve outcomes. The challenge for clinicians is to integrate this evidence into practice, selecting the optimal strategy that balances efficacy, safety, cost, and feasibility for each individual neonate and healthcare environment (Olusanya et al., 2025; Zhang et al., 2016; Kumar et al., 2017).

CONCLUSION

In conclusion, this systematic review of neonatal jaundice management strategies from the last decade reveals a significant evolution beyond conventional phototherapy. The evidence overwhelmingly demonstrates that numerous advanced and adjunctive therapies can more effectively and rapidly reduce bilirubin levels, shorten treatment duration, and improve safety. While no single intervention has emerged as a universally superior solution for all clinical scenarios, the findings clearly support a move towards more tailored and intensified treatment protocols. Key successful strategies include the intensification of phototherapy through increased irradiance and surface area, the adoption of superior lighting technologies like LEDs, the integration of promising pharmacological adjuncts, and the validation of innovative low-cost solutions for resource-limited settings.

The most effective interventions consistently offer substantial improvements over standard care. Double-surface and intensive phototherapy are proven methods for accelerating bilirubin clearance. Furthermore, pharmacological adjuncts such as zinc, clofibrate, and the probiotic *Clostridium butyricum* have shown remarkable efficacy in shortening therapy duration with minimal side effects, presenting a strong case for their integration into routine clinical practice. Simultaneously, technological advancements, particularly the use of LED phototherapy, have enhanced safety by reducing adverse effects like hyperthermia. These combined findings

underscore a clear trend towards a multi-modal approach where phototherapy is augmented to achieve optimal outcomes.

Critically, the implementation of these strategies is highly dependent on the clinical context and available resources. The evidence supports a tiered approach to care, where high-cost interventions like intravenous immunoglobulin are reserved for specific high-risk cases such as hemolytic disease, while low-cost, high-impact innovations like filtered sunlight and reflective curtains provide viable and effective alternatives in resource-constrained environments. This highlights the importance of translating research into practice in a way that is not only evidence-based but also equitable and feasible across diverse global healthcare landscapes. The role of the clinician is therefore to synthesize this evidence and select the most appropriate strategy that balances efficacy with safety and cost.

Finally, while this review confirms the efficacy of many new strategies, it also identifies areas requiring further investigation. Future research should aim to resolve existing inconsistencies in the evidence, such as the debate over continuous versus intermittent phototherapy. Head-to-head comparative trials between the most promising pharmacological adjuncts are needed to establish clear guidelines for their use. Above all, long-term follow-up studies are essential to confirm the developmental safety of these newer interventions. By addressing these gaps, the medical community can continue to refine and optimize the management of neonatal jaundice, ensuring safer and more effective care for newborns worldwide.

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