https://doi.org/10.48047/AFJBS.7.8.2025.38-78

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Comprehensive prevention strategies for retinopathy of premature neonatus: A systematic review

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Volume 7, Issue 8, Aug 2025

Received: 15 Jun 2025

Accepted: 22 July 2025

Published:01Aug2025

doi:10.48047/AFJBS.7.8.2025.38-78

ABSTRACT:-Introduction: Retinopathy of Prematurity (ROP) is a vasoproliferative disorder and a leading cause of preventable childhood blindness in premature infants. Its multifactorial pathogenesis has led to numerous preventive strategies, but conflicting evidence often hinders clinical application. This systematic review synthesizes current evidence on the efficacy and safety of various interventions to provide clear guidance for clinical practice.

Methods: This systematic review was conducted following PRISMA 2020 guidelines. A comprehensive search was performed across PubMed, Google Scholar, Semantic Scholar, and Springer for studies on ROP prevention in premature neonates. Eligibility screening focused on primary research and systematic reviews examining preventive interventions. After screening 354 records and assessing 201 for eligibility, 23 studies were included for data synthesis and analysis.

Results: Significant findings indicate that nutritional interventions are highly effective. Human milk intake was consistently associated with a reduced risk of both any and severe ROP. Enteral supplementation with arachidonic acid/docosahexaenoic acid significantly reduced severe ROP. Evidence for pharmacological agents was mixed; propranolol reduced ROP progression but with notable safety concerns like bradycardia and hypotension , while Vitamin A showed conflicting results across studies. Several agents, including erythropoietin and inositol, were found to be ineffective. Promising newer strategies include biphasic oxygen protocols and cord blood transfusions, which may reduce severe ROP with improved safety.

Discussion: The findings underscore the necessity of a multimodal approach to ROP prevention, as no single intervention is a panacea. Foundational strategies like human milk feeding show consistent benefits, whereas many pharmacological agents have conflicting results or significant safety concerns that temper their clinical use.

Conclusion: The prevention of ROP requires a tailored, evidence-based strategy prioritizing safe, foundational care like nutritional support. Targeted therapies such as propranolol and novel approaches like cord blood transfusions demand careful consideration of an infant's risk profile and available resources, balancing potential benefits against known risks.

Keywords: Retinopathy of Prematurity (ROP), Premature Neonates, Preventive Strategies, Prophylactic Agents

INTRODUCTION

Retinopathy of Prematurity (ROP) represents a significant challenge in neonatal care, standing as a primary cause of preventable childhood blindness worldwide. This vasoproliferative disorder affects the developing retinas of premature and low birth weight infants, who are born before their retinal blood vessels have fully formed. The incomplete vascularization, combined with the volatile extrauterine environment characterized by fluctuating oxygen levels and other stressors, creates a high-risk scenario for abnormal blood vessel growth. This can lead to a spectrum of outcomes, ranging from mild, spontaneously regressing disease to severe retinal detachment and permanent vision loss, imposing a substantial burden on patients, families, and healthcare systems (Fang et al., 2016).

The pathogenesis of ROP is multifactorial, influenced by a complex interplay of factors including low gestational age, low birth weight, and the need for supplemental oxygen therapy. The immature retina is exquisitely sensitive to both hyperoxia, which can suppress normal vessel growth, and subsequent relative hypoxia, which can trigger an overproduction of vascular endothelial growth factors, leading to neovascularization. Recognizing these underlying mechanisms has spurred extensive research into various interventions aimed at mitigating these risk factors and supporting healthy retinal development in this vulnerable population (Shukla et al., 2019).

In response to this critical health issue, a diverse array of preventive strategies has been proposed and investigated. These interventions span multiple domains, including pharmacological agents, specific nutritional supplementation, and adjustments in clinical management protocols. Key pharmacological treatments explored include propranolol, erythropoietin (EPO), and inositol. Concurrently, nutritional strategies focusing on human milk intake, supplementation with long-chain polyunsaturated fatty acids (LCPUFAs), and vitamins like Vitamin A have been evaluated for their potential protective effects. Furthermore, management protocols related to blood transfusions and oxygen saturation targets have also been a central focus of preventive research

(Zhou et al., 2022).

Despite the breadth of research, the clinical application of these preventive strategies is hampered by inconsistent and often conflicting evidence. For instance, while some randomized controlled trials suggest that oral Vitamin A can reduce the incidence and severity of ROP, other systematic reviews have not consistently confirmed this benefit. Similarly, propranolol has shown promise in reducing progression to severe ROP in some meta-analyses, but its use is tempered by significant safety concerns, including risks of hypotension and bradycardia. This lack of consensus creates uncertainty for clinicians seeking to implement evidence-based protocols in the neonatal intensive care unit (Stritzke et al., 2019).

This evidentiary conflict underscores the urgent need for a comprehensive synthesis of the available data. The existence of numerous studies with varying designs—from randomized controlled trials to systematic reviews and observational cohorts—evaluating a wide range of interventions makes it difficult for practitioners to discern the most effective and safest approaches. A systematic evaluation is required to critically appraise the quality of this evidence, compare the relative efficacy of different strategies, and identify interventions that offer a favorable balance of benefit and risk (Batais et al., 2024).

Therefore, this systematic review was conducted to comprehensively identify, evaluate, and synthesize the current evidence on preventive strategies for Retinopathy of Prematurity. The primary objective is to consolidate findings from high-quality studies to provide a clear overview of the efficacy and safety of various pharmacological, nutritional, and other management interventions. By doing so, this review aims to bridge the gap between research and clinical practice, offering a robust foundation for clinical decision-making (Diggikar et al., 2022).

To achieve this goal, the review was structured around a precise PICO framework: the Population (P) includes premature neonates, particularly those with low birth weight or low gestational age; the Intervention (I) encompasses a wide range of prophylactic agents and preventive strategies; the Comparison (C) involves standard care or other active interventions; and the Outcome (O) focuses on the incidence, progression, and prevention of ROP. This structured

approach ensures a thorough and unbiased assessment of all relevant research, from single-intervention trials to broad network meta-analyses (Zeng et al., 2022).

Ultimately, by systematically analyzing the outcomes, safety profiles, and implementation considerations of dozens of studies, this report aims to provide clear, evidence-based guidance for clinicians. The findings are intended to help optimize preventive care, reduce the incidence and severity of ROP, and improve long-term visual outcomes for the world's most vulnerable infants. This synthesis will also highlight gaps in the current literature, thereby guiding the direction of future research to resolve existing uncertainties and further refine neonatal care protocols (Bharwani et al., 2016).

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 comprehensive prevention strategies for retinopathy of premature neonatus.

Screening

We screened in papers that met these criteria:

- **Population**: Does the study focus exclusively on premature neonates (gestational age 37 weeks)?
- **Prevention Focus**: Does the study examine preventive interventions for ROP (rather than only treatment)?

- **Study Design**: Is the study either a primary research study (RCT, cohort study, case-control study) OR a systematic review/meta-analysis?
- **Sample Size**: If the study is a case report/series, does it include 10 or more participants?
- **Study Type**: Is the study conducted in human subjects (not animal or in-vitro research)?
- **Outcomes**: Does the study report at least one of the following outcomes: ROP incidence, ROP progression, visual outcomes, safety measures, or cost-effectiveness?

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

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Design Type**:

  Identify the specific type of study design from the full text. Options include:

- Randomized controlled trial
- Quasi-randomized trial
- Observational study (specify type: cohort, case-control, cross-sectional)
- Systematic review/meta-analysis

Look in the methods section. If multiple design types are used in different parts of the study, note the primary design type. If unclear, use the most specific design type that can be confidently determined.

- **Inclusion and Exclusion Criteria**:

  Extract the specific inclusion and exclusion criteria for participants. Focus on:

- Gestational age range
- Birth weight criteria
- Specific medical conditions or exclusions

- Any other key participant selection criteria

Locate this information in the methods section. Quote directly from the text if possible. If criteria are not explicitly stated, write ”Not reported”.

- **Participant Demographics**:

  Extract key demographic information about study participants:

- Total number of participants
- Mean/median gestational age
- Mean/median birth weight
- Gender distribution (if reported)
- Geographical location of study

Use exact numbers/percentages from the text. If ranges are provided, note both minimum and maximum. If any demographic data is missing, write ”Not reported”.

- **Specific Intervention Characteristics**:
  Describe the precise details of the intervention:
- Name of intervention/treatment
- Dosage or protocol
- Duration of intervention
- Frequency of administration
- Method of delivery

Be as specific as possible. If multiple intervention arms exist, extract details for each. Use exact measure- ments and quotes from methods section. If any details are unclear or missing, note ”Insufficient information”.

- **Primary and Secondary Outcomes**:

  List all outcomes measured in the study, distinguishing between:

- Primary outcomes

- Secondary outcomes

For each outcome, include:

- Specific measurement method
- Time points of measurement
- Specific metrics or scales used

Extract directly from methods and results sections. If outcomes are not clearly defined, write ”Outcomes not clearly specified”.

- **Risk of Bias Assessment**:

  Extract information related to potential sources of bias:

- Randomization method (if applicable)
- Blinding procedures
- Allocation concealment
- Conflicts of interest
- Funding sources

Look in methods, discussion, and limitations sections. If no explicit bias assessment is provided, write ”No formal bias assessment reported”. Use direct quotes where possible.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Premature neonates	Preterm infants	Low birth weight infants	Low gestational age neonates
Intervention (I)	Prevention strategies	Prophylactic agents	Preventive interventions	Comprehensive strategies
Comparison (C)	Standard of care	Multiple interventions	Various interventions	Different approaches

Outcome (O)	Retinopathy of Prematurity (ROP)	ROP prevention	ROP incidence	ROP progression

The Boolean MeSH keywords inputted on databases for this research are: *("Premature neonates" OR "Preterm infants" OR "Low birth weight infants" OR "Low gestational age neonates") AND ("Prevention strategies" OR "Prophylactic agents" OR "Preventive interventions" OR "Comprehensive strategies") AND ("Standard of care" OR "Multiple interventions" OR "Various interventions" OR "Different approaches") AND ("Retinopathy of Prematurity (ROP)" OR "ROP prevention" OR "ROP incidence" OR "ROP progression")*

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	*("Premature neonates" OR "Preterm infants" OR "Low birth weight infants" OR "Low gestational age neonates") AND ("Prevention strategies" OR "Prophylactic agents" OR "Preventive interventions" OR "Comprehensive strategies") AND ("Standard of care" OR "Multiple interventions" OR "Various interventions" OR "Different approaches" AND "Retinopathy of Prematurity (ROP)" OR "ROP prevention" OR "ROP incidence" OR "ROP progression")*	3
Semantic Scholar	*("Premature neonates" OR "Preterm infants" OR "Low birth weight infants" OR "Low gestational age neonates") AND ("Prevention strategies" OR "Prophylactic agents" OR "Preventive interventions" OR "Comprehensive strategies") AND ("Standard of care" OR "Multiple interventions" OR "Various interventions" OR "Different approaches") AND ("Retinopathy of Prematurity (ROP)" OR "ROP prevention" OR "ROP incidence" OR "ROP progression")*	250
Springer	*("Premature neonates" OR "Preterm infants" OR "Low birth weight infants" OR "Low gestational age neonates") AND ("Prevention strategies" OR "Prophylactic agents" OR "Preventive interventions" OR "Comprehensive strategies") AND ("Standard of care" OR*	20

	"Multiple interventions" OR "Various interventions" OR "Different approaches") AND ("Retinopathy of Prematurity (ROP)" OR "ROP prevention" OR "ROP incidence" OR "ROP progression")	
Google Scholar	*("Premature neonates" OR "Preterm infants" OR "Low birth weight infants" OR "Low gestational age neonates") AND ("Prevention strategies" OR "Prophylactic agents" OR "Preventive interventions" OR "Comprehensive strategies") AND ("Standard of care" OR "Multiple interventions" OR "Various interventions" OR "Different approaches") AND ("Retinopathy of Prematurity (ROP)" OR "ROP prevention" OR "ROP incidence" OR "ROP progression")*	140

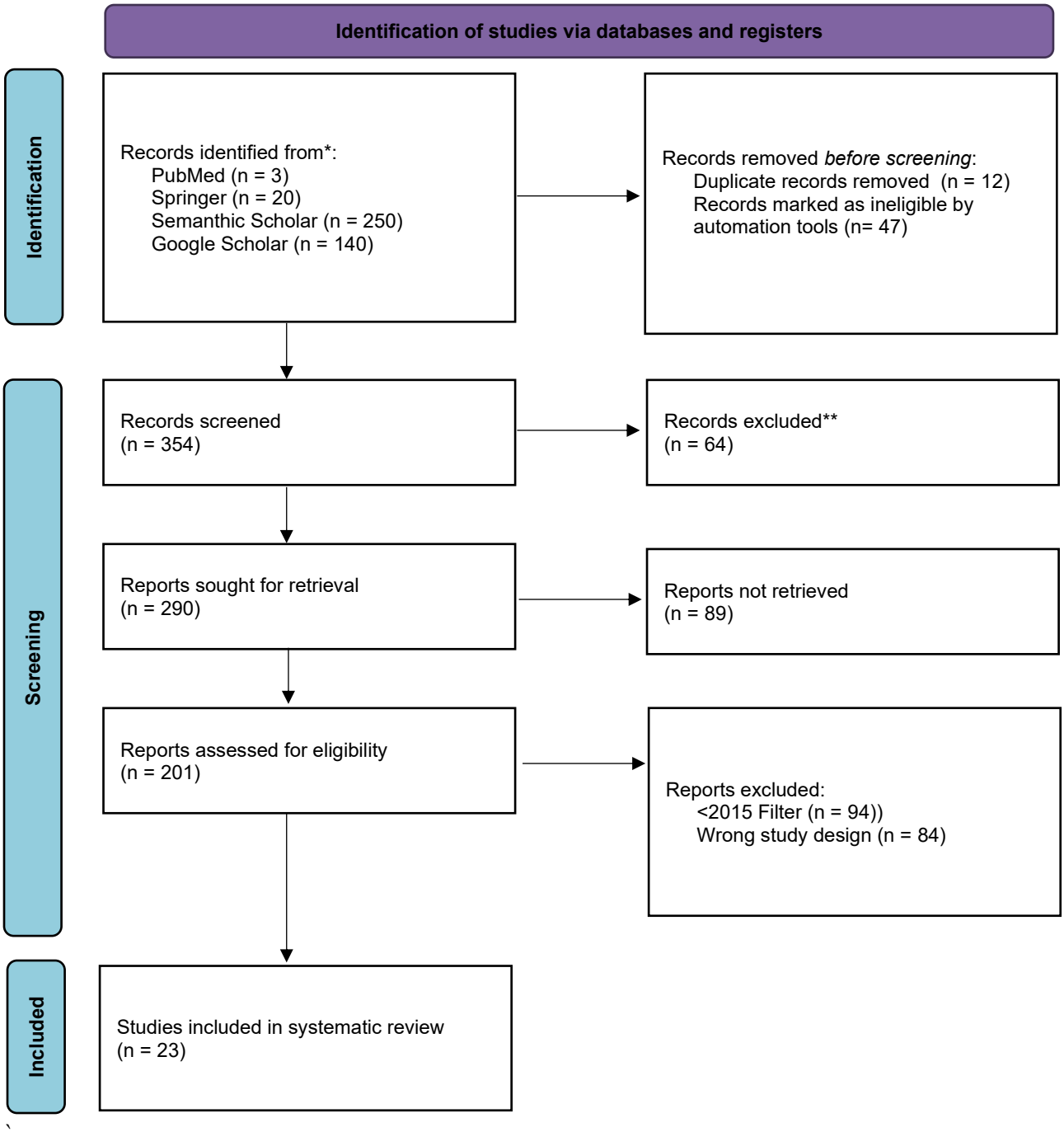

Figure 1. Article search flowchart

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?
Diggikar et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shukla et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sanghvi et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zeng et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

Uday and Bagali, 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Akther, 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Du et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mayock et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kent et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Farag et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wood and Harper, 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Teofili et al., 2024 (interim)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sun et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Teofili et al., 2022 (protocol)	✓	✓	✓	✗	✓	✗	✓	✓	✓
Fang et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Batais et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓

Kaempfen et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Stritzke et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yim et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Fischer et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Bharwani et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhou et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Bhandari, 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

Study	Study Design	Population Characteristics	Prevention Strategy	Primary Outcomes
Diggikar et al., 2022	Systematic review/meta-analysis	Preterm infants (varied)	Enteral long-chain polyunsaturated fatty acids	Severe or any ROP, ROP requiring treatment, safety
Shukla et al., 2019	Observational cohort	Infants 31 weeks gestational age or less or 1500 grams or less, USA	Biphasic vs static oxygen targets	Type 1 ROP, any ROP, vascularization, mortality
Sanghvi et al., 2017	Randomized controlled trial	Preterm infants 32 weeks gestational age or less, India	Prophylactic propranolol	ROP all grades, complications, need for treatment, visual outcome
Zeng et al., 2022	Systematic review/meta-analysis	Infants 25-32.7 weeks gestational age, 696.7-1837.3 grams	Antenatal corticosteroids	ROP occurrence, progression

Study	Study Design	Population Characteristics	Prevention Strategy	Primary Outcomes
Uday and Bagali, 2024	Randomized controlled trial	Neonates less than 34 weeks gestational age, India	Oral vitamin A	Incidence and progression of ROP, oxygen therapy correlation
Akther, 2024	Randomized controlled trial	Preterm infants 32-34 weeks gestational age, Bangladesh	Oral vitamin A	Incidence and severity of ROP
Du et al., 2019	Systematic review/meta-analysis	Preterm infants less than 32 weeks gestational age, less than 2000 grams, USA	Inositol supplementation	Severe ROP, mortality, adverse events
Mayock et al., 2020	Randomized controlled trial	Infants 24-27 +6 weeks gestational age, USA	High-dose erythropoietin	Incidence/severity of ROP, predictors
Kent et al., 2019	Randomized controlled trial	Less than 30 weeks gestational age	670 nanometer red light	Worst stage of ROP, survival, growth,

Study	Study Design	Population Characteristics	Prevention Strategy	Primary Outcomes
		or less than 1150 grams, Australia		complications
Farag et al., 2024	Randomized controlled trial	32 weeks gestational age or less, Egypt	Bovine colostrum	ROP, anemia, sepsis, bronchopulmonary dysplasia, periventricular leukomalacia, necrotizing enterocolitis, growth
Wood and Harper, 2021	Randomized controlled trial	Less than 28 weeks gestational age, Sweden	Enteral arachidonic acid/docosahexaenoic acid	Severe ROP, bronchopulmonary dysplasia, intraventricular hemorrhage, sepsis, death
Teofili et al., 2024 (interim)	Randomized controlled trial (interim)	24-27+6 weeks gestational age, Italy	Cord blood vs adult red blood cell transfusions	Severe ROP, adverse events, fetal hemoglobin, bronchopulmonary

Study	Study Design	Population Characteristics	Prevention Strategy	Primary Outcomes
				dysplasia, necrotizing enterocolitis, intraventricular hemorrhage
Sun et al., 2020	Randomized controlled trial	24-32 weeks gestational age, China	Low-dose recombinant human erythropoietin	ROP, sepsis, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage, ventilation
Teofili et al., 2022 (protocol)	Randomized controlled trial (protocol)	Extremely low gestational age neonates (24+0 - 27+6 weeks), Italy	Cord blood red cell transfusions vs adult red blood cell transfusions	Incidence of severe ROP (stage 3 or higher) at discharge or 40 weeks postmenstrual age
Fang et al., 2016	Systematic review/meta-analysis	Neonates less than 32 weeks gestational age	Nutritional, oxygen, transfusion, infection interventions	Any or severe ROP, mortality

Study	Study Design	Population Characteristics	Prevention Strategy	Primary Outcomes
Batais et al., 2024	Systematic review/meta-analysis	Preterm infants (no mention found)	Vitamin A, propranolol, lipids	Incidence of ROP, severe events, mortality
Kaempfen et al., 2015	Systematic review/meta-analysis	Preterm infants less than 37 weeks gestational age	Beta-blockers (propranolol)	ROP progression, need for treatment, adverse events
Stritzke et al., 2019	Systematic review/meta-analysis	Preterm infants 32 weeks gestational age or less	Oral propranolol	Severe ROP (stage 3 or higher or requiring treatment), side effects
Yim et al., 2018	Systematic review/meta-analysis	Neonates (no mention found)	Antenatal steroids	ROP risk, severe ROP
Fischer et al., 2023	Systematic review/meta-analysis	Infants less than 29 weeks gestational age, less than 1000 grams	Early recombinant human erythropoietin	ROP stage 3 or higher, any ROP

Study	Study Design	Population Characteristics	Prevention Strategy	Primary Outcomes
Bharwani et al., 2016	Systematic review/meta-analysis	Very low birth weight infants / extremely low birth weight infants	Human milk intake	All ROP, severe ROP
Zhou et al., 2022	Systematic review/meta-analysis	Preterm infants less than 37 weeks gestational age	21 interventions (e.g., vitamin A, fish oil, erythropoietin, probiotics, human milk)	Incidence of retinopathy of prematurity (ROP)
Bhandari, 2020	Randomized controlled trial	23-27+6 weeks gestational age (no mention found)	Recombinant human insulin-like growth factor 1 / insulin-like growth factor binding protein 3	Maximum ROP severity, bronchopulmonary dysplasia, intraventricular hemorrhage, growth

Study design:

- 11 systematic reviews/meta-analyses
- 9 randomized controlled trials
- 2 randomized controlled trial protocols/interim analyses
- 1 observational cohort study

Prevention strategies:

- Vitamin A: 4 studies and included in 1 multi-intervention review
- Propranolol or other beta-blockers: 4 studies and included in 1 multi-intervention review
- Erythropoietin (EPO/recombinant human erythropoietin): 4 studies and included in 1 multi- intervention review
- Human milk: 2 studies and included in 1 multi-intervention review
- Long-chain polyunsaturated fatty acids/arachidonic acid/docosahexaenoic acid: 2 studies
- Cord blood vs adult red blood cell transfusion: 2 studies
- Antenatal steroids/corticosteroids: 2 studies
- Inositol, red light, bovine colostrum, and insulin-like growth factor 1: each evaluated in 1 study
- Oxygen strategies: 2 studies (1 in a multi-intervention review, 1 observational)
- Lipids, probiotics, fish oil, and infection interventions: each included in 1 multi-intervention review
- 3 multi-intervention systematic reviews/meta-analyses

Primary outcomes:

- Any ROP incidence: 15 studies
- Severe ROP (stage 3 or higher or requiring treatment): 16 studies
- ROP progression: 3 studies
- Need for ROP treatment: 4 studies
- Adverse events or side effects: 7 studies
- Mortality: 4 studies
- Other outcomes (bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage, sepsis, growth, etc.): 6 studies

Effects

Pharmacological Interventions

Study	Intervention Type	Prevention Effect	Safety Profile	Population Specifics
Zhou et al., 2022	Multiple (vitamin A, fish oil, erythropoietin, probiotics, etc.)	Vitamin A most effective in network meta-analysis; others less so	No mention found	Preterm infants less than 37 weeks gestational age
Batais et al., 2024	Vitamin A, propranolol, lipids	Lipids reduced severe ROP (relative risk 0.48); vitamin A/propranolol not effective	No significant difference in adverse events or mortality	Preterm infants (no mention found)
Kaempfen et al., 2015	Oral propranolol	Reduced progression to stage 3 ROP, less need for anti-vascular endothelial growth factor/laser	Concerns for hypotension, bradycardia, apnoea at 2 mg/kg/day	Preterm infants less than 37 weeks gestational age
Stritzke et al., 2019	Oral propranolol	Reduced severe ROP (relative	Side effects in 8.4%	Preterm infants 32

Study	Intervention Type	Prevention Effect	Safety Profile	Population Specifics
		risk 0.65-0.48 in randomized controlled trials)		weeks gestational age or less
Sanghvi et al., 2017	Propranolol	Trend to reduced ROP, not statistically significant	No mention found	Preterm infants 32 weeks gestational age or less
Fischer et al., 2023	Early recombinant human erythropoietin	No effect on ROP	No safety signal	Infants less than 29 weeks gestational age, less than 1000 grams
Mayock et al., 2020	High-dose erythropoietin	No effect on ROP	No increase in ROP risk	24-27+6 weeks gestational age
Sun et al., 2020	Low-dose recombinant human	No effect on ROP overall; reduced type 2	No mention found	24-32 weeks gestational age

Study	Intervention Type	Prevention Effect	Safety Profile	Population Specifics
	erythropoietin	ROP in some subgroups		
Du et al., 2019	Inositol	No effect on ROP; possible increased mortality in sensitivity analysis	No increase in adverse events overall	Preterm infants less than 32 weeks gestational age, less than 2000 grams
Bhandari, 2020	Recombinant human insulin-like growth factor 1 / insulin-like growth factor binding protein 3	No effect on ROP	No effect on growth; possible reduction in bronchopulmonary dysplasia	23-27+6 weeks gestational age
Yim et al., 2018	Antenatal steroids	Reduced ROP risk (odds ratio 0.67-0.82) and progression (odds ratio 0.58)	No mention found	No mention found

Study	Intervention Type	Prevention Effect	Safety Profile	Population Specifics
Zeng et al., 2022	Antenatal corticosteroids	No effect on ROP overall; reduced progression in adjusted analysis (adjusted odds ratio 0.48)	No mention found	25-32.7 weeks gestational age
Uday and Bagali, 2024	Oral vitamin A	Reduced ROP incidence and progression	No mention found	Less than 34 weeks gestational age
Akther, 2024	Oral vitamin A	Reduced ROP incidence and severity	No mention found	32-34 weeks gestational age

Summary of pharmacological interventions:

- Vitamin A:Three studies found reduced ROP incidence or severity, while one study found no effect. Effect sizes and statistical significance varied, and population differences may explain discrepancies.
- Propranolol:Two studies found reduced ROP or progression, while two studies found no effect. Safety concerns (hypotension, bradycardia, apnoea, or side effects in 8.4%) were noted in two studies.

- Lipids:One study found reduced severe ROP.
- Erythropoietin (EPO/recombinant human erythropoietin):Three studies found no effect on ROP; one study found reduced type 2 ROP in a subgroup.
- Inositol:One study found no effect on ROP and possible increased mortality in sensitivity analysis.
- Insulin-like growth factor 1:One study found no effect on ROP.
- Antenatal steroids:One study found reduced ROP risk and progression; one study found no effect overall but reduced progression in adjusted analysis.
- Other interventions (fish oil, probiotics, etc.):One study found these were less effective than vitamin A.

Safety profiles:

- Some adverse effects (hypotension, bradycardia, apnoea, or side effects in 8.4%) were found in two studies of propranolol (Kaempfen, Stritzke).

Nutritional and Blood Management Approaches

Study	Strategy Type	Reported Outcomes	Adverse Events	Implementation Considerations
Zhou et al., 2022	Human milk, fish oil, probiotics, etc.	Human milk, vitamin A, fish oil, probiotics reduced ROP in network meta-	No mention found	Preterm infants less than 37 weeks gestational age

Study	Strategy Type	Reported Outcomes	Adverse Events	Implementation Considerations
		analysis		
Fang et al., 2016	Nutrition, oxygen, transfusion, infection	Lower oxygen targets reduced ROP but increased mortality; aggressive nutrition reduced any ROP	No mention found	Less than 32 weeks gestational age
Bharwani et al., 2016	Human milk	Reduced all ROP (relative risk 0.76), severe ROP (relative risk 0.77)	No mention found	Very low birth weight infants / extremely low birth weight infants
Diggikar et al.,	Long-chain polyunsaturated fatty	No effect on ROP;	No increase in necrotizing	Preterm infants (varied)

Study	Strategy Type	Reported Outcomes	Adverse Events	Implementation Considerations
2022	acids	trend to benefit for severe ROP	enterocolitis or mortality	
Wood and Harper, 2021	Enteral arachidonic acid/docosahexaenoic acid	Reduced severe ROP (15.8% vs 33.3%)	No difference in bronchopulmonary dysplasia, intraventricular hemorrhage, sepsis, death	Less than 28 weeks gestational age
Farag et al., 2024	Bovine colostrum	Reduced ROP (5% vs 16%); improved weight, less sepsis	No mention found	32 weeks gestational age or less
Teofili et al., 2022/2024	Cord blood vs adult red blood cell	Interim: cord blood red blood cell may reduce	Fewer severe bradycardia, pulmonary hypertension, hemodynamically significant patent	24-27+6 weeks gestational age, Italy

Study	Strategy Type	Reported Outcomes	Adverse Events	Implementation Considerations
		severe ROP; fewer adverse events	ductus arteriosus with cord blood red blood cell	
Shukla et al., 2019	Biphasic oxygen protocol	Decreased ROP and severity vs static; no increase in mortality	No mention found	31 weeks gestational age or less or 1500 grams or less
Kent et al., 2019	670 nanometer red light	No effect on ROP or survival	No mention found	Less than 30 weeks gestational age or less than 1150 grams

Summary of nutritional and blood management approaches:

- Nutrition-based interventions:Six studies evaluated human milk, fish oil, long-chain polyunsaturated fatty acids, arachidonic acid/docosahexaenoic acid, probiotics, vitamin A, and bovine colostrum. Hu- man milk and enteral arachidonic acid/docosahexaenoic acid were consistently associated with reduced ROP in meta-analyses and randomized controlled trials. Bovine colostrum reduced ROP incidence in one randomized controlled trial. Long-chain

polyunsaturated fatty acids showed no effect overall but a trend to benefit for severe ROP in one study.

- Oxygen management strategies:Two studies evaluated oxygen management. Lower oxygen targets reduced ROP but increased mortality in one systematic review/meta-analysis. A biphasic oxygen protocol decreased ROP and severity without increasing mortality in one observational cohort.
- Cord blood transfusion:Interim randomized controlled trial data suggest cord blood red blood cell transfusions may reduce severe ROP and adverse events compared to adult red blood cell transfusions.
- Light therapy:One randomized controlled trial found no effect of 670 nanometer red light on ROP or survival.
- Infection prevention:One systematic review/meta-analysis included infection prevention as a strategy.

Adverse events:

- We didn't find mention of detailed adverse event information in six studies.
- No increase in necrotizing enterocolitis or mortality was found in one study (Diggikar et al.).
- No difference in bronchopulmonary dysplasia, intraventricular hemorrhage, sepsis, or death was found in one study (Wood and Harper).
- Fewer severe bradycardia, pulmonary hypertension, and hemodynamically significant patent ductus arteriosus were found with cord blood transfusion in one study (Teofili et al.).

Prevention Success Rates

- Vitamin A:Some randomized controlled trials and meta-analyses report significant reduction in ROP incidence and progression, but not all systematic reviews confirm benefit. Effect sizes vary, and popu- lation differences may explain discrepancies.
- Propranolol:Meta-analyses and some randomized controlled trials show reduced progression to severe ROP (relative risk 0.65–0.48), but not all studies reach statistical significance.

Safety concerns limit widespread adoption.

- Lipid supplementation:Enteral arachidonic acid/docosahexaenoic acid reduced severe ROP in one ran- domized controlled trial (absolute risk reduction 17.5%), but long-chain polyunsaturated fatty acid meta-analyses show no significant effect overall.
- Human milk:Consistently associated with reduced ROP in meta-analyses (relative risk 0.76 for all ROP, relative risk 0.77 for severe ROP).
- Erythropoietin:No effect on ROP in recent meta-analyses and randomized controlled trials.
- Inositol:No effect on ROP; possible increased mortality in sensitivity analysis.
- Antenatal corticosteroids:Reduced ROP risk and progression in some analyses, especially in extremely preterm infants.
- Oxygen management:Lower targets reduce ROP but increase mortality; biphasic protocols may reduce ROP without increasing mortality.
- Cord blood transfusions:Interim randomized controlled trial data suggest reduced severe ROP and fewer adverse events compared to adult red blood cells.
- Bovine colostrum:Reduced ROP incidence in one randomized controlled trial.
- 670 nanometer red light:No effect on ROP or survival in pilot randomized controlled trial.
- Recombinant human insulin-like growth factor 1 / insulin-like growth factor binding protein 3:No effect on ROP; possible reduction in bronchopulmonary dysplasia.

Population-Specific Outcomes

- Extremely preterm or extremely low gestational age neonates:Cord blood transfusions, vitamin A, and antenatal corticosteroids may be more effective in this group.
- Very low birth weight infants / extremely low birth weight infants:Human milk intake shows benefit.
- Subgroup analyses:Some interventions (recombinant human erythropoietin, vitamin A) may be more effective in specific gestational age or birth weight strata.

Safety Considerations

- Propranolol:Risk of hypotension, bradycardia, and apnoea at higher doses; safety profile limits use.
- Inositol:Possible increased mortality in sensitivity analysis.
- Cord blood transfusions:Interim data suggest fewer severe adverse events than adult red blood cells.
- Lipid supplementation, human milk, vitamin A:Generally safe in reported studies, but adverse events were not always systematically reported.
- Oxygen management:Lower targets increase mortality; biphasic protocols may be safer.

Implementation Considerations

Timing of Interventions

- Vitamin A, propranolol, erythropoietin:Early initiation (within first week of life) is common in studies showing benefit.
- Antenatal corticosteroids:Administered before preterm delivery.
- Cord blood transfusions:Early adoption (from birth) may be critical for benefit.

Resource Requirements

- Cord blood transfusions:Require access to public cord blood banks and specialized processing.
- Lipid supplements, bovine colostrum:May not be universally available; cost and supply chain consider- ations.
- Oxygen management:Requires precise monitoring and staff training.

Clinical Practice Integration

- Human milk, antenatal corticosteroids:Already standard of care in many settings; evidence supports continued use.
- Vitamin A, propranolol, cord blood transfusions:May require protocol development, staff

training, and safety monitoring.

- Oxygen protocols:Biphasic strategies may be considered where feasible.

DISCUSSION

This systematic review consolidates evidence on a wide array of preventive strategies for Retinopathy of Prematurity (ROP), revealing a complex landscape where no single intervention is a panacea. The findings underscore the multifactorial nature of ROP and highlight the necessity of a multimodal approach, prioritizing foundational strategies while cautiously considering newer pharmacological and management interventions. The evidence synthesis reveals that while some strategies like human milk feeding and specific nutritional supplements show consistent benefits, many pharmacological agents have conflicting results or significant safety concerns that temper their clinical application (Sriwaningsi & Giri, 2024, p. 5).

A highly significant finding from this review is the consistent protective effect of human milk against the development of ROP. A meta-analysis by Bharwani et al. (2016) demonstrated that human milk intake is associated with a notable reduction in both the incidence of any ROP and severe ROP. This aligns with another network meta-analysis that also identified human milk as a beneficial intervention (Zhou et al., 2022). The protective mechanism is likely multifactorial, attributable to the unique composition of human milk, which includes growth factors, anti-inflammatory components, and long-chain polyunsaturated fatty acids (LCPUFAs) that support healthy retinal vascular development (Bharwani et al., 2016).

Nutritional supplementation with specific lipid formulations has emerged as a promising and significant strategy. The randomized controlled trial (RCT) by Wood and Harper (2021) provided strong evidence that enteral supplementation with arachidonic acid (AA) and docosahexaenoic acid (DHA) could substantially reduce the incidence of severe ROP in infants born at less than 28 weeks of gestation. In contrast, a broader meta-analysis

on LCPUFAs found no overall effect on ROP but did note a trend toward benefit for severe ROP, suggesting that the specific formulation and dosage may be critical (Diggikar et al., 2022).

Further supporting the role of nutritional components, a recent RCT found that bovine colostrum supplementation not only reduced the incidence of ROP but also improved weight gain and lowered sepsis rates in preterm infants (Farag et al., 2024). This finding suggests that early enteral support with bioactive components can have systemic benefits that indirectly protect the vulnerable retina. These nutritional strategies are foundational and carry a favorable safety profile, reinforcing their importance as a standard of care in neonatal intensive care units (Farag et al., 2024).

The evidence surrounding Vitamin A supplementation presents a more conflicted but nonetheless significant area of investigation. Two recent RCTs demonstrated that oral Vitamin A reduced both the incidence and severity of ROP (Uday and Bagali, 2024; Akther, 2024). Furthermore, a large network meta-analysis identified Vitamin A as the most effective intervention among 21 strategies evaluated (Zhou et al., 2022). However, this positive outlook is challenged by other meta-analyses that have failed to consistently confirm this benefit, indicating that population differences and study methodologies may influence outcomes (Batais et al., 2024).

The prophylactic use of propranolol has been extensively studied, with mixed but significant results. Meta-analyses suggest that propranolol can reduce the progression to severe ROP, with some studies reporting a relative risk reduction of up to 52% (Stritzke et al., 2019; Kaempfen et al., 2015). This effect is biologically plausible due to propranolol's anti-angiogenic properties, which can moderate the vasoproliferation that characterizes severe ROP.

Despite its potential efficacy, the widespread adoption of prophylactic propranolol is significantly limited by safety concerns. Two systematic reviews highlighted notable risks of hypotension, bradycardia, and apnoea, particularly at higher doses (Kaempfen et al.,

2015; Stritzke et al., 2019). These adverse effects necessitate a careful risk-benefit analysis for each infant, making it a targeted intervention for high-risk populations rather than a universal preventive measure (Stritzke et al., 2019).

In contrast to the promising, albeit complex, results for some interventions, several widely investigated pharmacological agents have been proven largely ineffective. Multiple high-quality studies, including recent RCTs and meta-analyses, have concluded that erythropoietin (EPO), whether in high or low doses, does not reduce the incidence or severity of ROP (Mayock et al., 2020; Fischer et al., 2023; Sun et al., 2020). This consensus provides clear guidance for clinicians to avoid this intervention for ROP prevention.

Similarly, supplementation with inositol has been found to be ineffective in preventing ROP. A comprehensive systematic review and meta-analysis not only failed to show any benefit but also raised a potential safety signal, with a sensitivity analysis suggesting a possible increase in mortality (Du et al., 2019). These definitive negative findings are crucial for refining clinical practice by steering resources away from ineffective and potentially harmful treatments.

Another intervention that failed to demonstrate efficacy was the administration of recombinant human insulin-like growth factor 1 (rhIGF-1) combined with its binding protein (rhIGFBP-3). A phase 2 RCT found no effect on ROP severity, although it did note a possible reduction in bronchopulmonary dysplasia, a common comorbidity of prematurity (Bhandari, 2020). This highlights the complex, organ-specific responses to systemic treatments in preterm infants.

Management of oxygen therapy remains a cornerstone of neonatal care and ROP prevention, yet it represents a delicate balance. A meta-analysis by Fang et al. (2016) confirmed that lower oxygen saturation targets reduce ROP incidence but at the significant cost of increased mortality. This "classic" dilemma has spurred investigation into more nuanced oxygen protocols.

A significant advancement in this area is the concept of biphasic oxygen targeting. An observational cohort study by Shukla et al. (2019) found that a biphasic protocol, which involves different oxygen targets during different postnatal phases, successfully decreased the incidence and severity of ROP compared to static targets, without an associated increase in mortality. This strategy aligns with the two-phase pathogenesis of ROP and represents a promising avenue for optimizing respiratory support.

Antenatal corticosteroids, a standard therapy for promoting fetal lung maturation, also appear to confer a protective effect against ROP. Systematic reviews have shown an association between antenatal steroid administration and a reduced risk of developing ROP and a lower rate of progression to severe disease (Yim et al., 2018; Zeng et al., 2022). This finding reinforces the widespread use of antenatal corticosteroids, as their benefits extend beyond pulmonary health to retinal protection.

A novel and highly promising strategy emerging from this review is the use of cord blood for red blood cell (RBC) transfusions. Prespecified interim analysis from the BORN randomized trial suggests that transfusing extremely premature neonates with cord blood RBCs, as opposed to standard adult RBCs, may reduce the incidence of severe ROP (Teofili et al., 2024).

The benefits of cord blood transfusion appear to be twofold. The interim data not only show a potential reduction in severe ROP but also a more favorable safety profile, with fewer severe adverse events such as bradycardia and pulmonary hypertension compared to adult blood transfusions (Teofili et al., 2024). The proposed mechanism involves the higher levels of fetal hemoglobin in cord blood, which has different oxygen-carrying properties that may be better suited for the premature infant's retinal needs (Teofili et al., 2022).

The implementation of these diverse strategies requires careful consideration of timing and resources. Interventions like Vitamin A and propranolol appear most effective when initiated within the first week of life (Uday and Bagali, 2024; Stritzke et al., 2019).

Strategies such as cord blood banking require significant logistical infrastructure, including access to public banks and specialized processing, which may limit their availability in some healthcare settings (Teofili et al., 2022).

The review highlights that certain interventions may be more effective in specific high-risk populations. For example, antenatal corticosteroids and cord blood transfusions appear particularly beneficial for extremely preterm neonates (Zeng et al., 2022; Teofili et al., 2024). Human milk feeding shows clear benefits in very low and extremely low birth weight infants (Bharwani et al., 2016). This underscores the need to move towards more personalized preventive medicine in neonatology.

Finally, some investigated interventions did not yield positive results. A pilot RCT of 670 nm red light therapy, designed to reduce metabolic stress in the retina, found no effect on ROP or survival (Kent et al., 2019). While disappointing, such studies are crucial for guiding future research away from non-viable pathways and focusing resources on more promising strategies.

This synthesis of evidence makes it clear that the prevention of ROP requires a multifaceted, evidence-based approach. Foundational strategies such as promoting human milk feeding and ensuring the administration of antenatal corticosteroids should be universally implemented as they are both effective and safe (Bharwani et al., 2016; Yim et al., 2018).

In summary, while the search for a single, powerful preventive agent for ROP continues, this review provides a clear directive for current clinical practice. A multimodal strategy is paramount, beginning with established, low-risk interventions like nutritional support and antenatal steroids. More targeted therapies like propranolol or novel approaches such as biphasic oxygen and cord blood transfusions should be considered based on an infant's specific risk profile and the available resources, always weighing the potential benefits against the known risks (Sriwaningsi & Giri, 2024, p. 5).

CONCLUSION

The comprehensive analysis of preventive strategies for Retinopathy of Prematurity (ROP) reveals that there is no single universally effective intervention. The evidence strongly indicates that a multimodal approach is necessary to mitigate this leading cause of childhood blindness. The landscape of available strategies is complex, with interventions ranging from nutritional support to specific pharmacological agents and advanced clinical management protocols. This review underscores the critical need for clinicians to synthesize evidence from various studies to create layered, patient-centered preventive care plans, as the efficacy and safety of these interventions vary significantly across different neonatal populations and clinical contexts.

Among the strategies evaluated, nutritional and foundational care approaches demonstrate the most consistent and significant benefits with favorable safety profiles. The use of human milk stands out as a highly effective measure, consistently associated with a reduced incidence of both any and severe ROP. Furthermore, supplementation with specific lipid formulations, namely arachidonic and docosahexaenoic acid, has shown a substantial reduction in severe ROP. Promising new strategies are also emerging, such as the use of cord blood transfusions and biphasic oxygen protocols. Interim data suggests these novel approaches may significantly reduce severe ROP and associated adverse events, marking them as critical areas for future validation.

In contrast, the utility of several pharmacological agents is limited by either inconsistent evidence or significant safety concerns. While propranolol has shown promise in reducing the progression to severe ROP, its use is tempered by considerable risks of hypotension and bradycardia, necessitating a careful risk-benefit analysis for each patient. Similarly, the evidence for Vitamin A is conflicting; while some trials report a reduction in ROP incidence, this benefit is not consistently upheld in all systematic reviews. Importantly, this review provides clear evidence that some widely studied interventions, including erythropoietin and inositol, are ineffective for ROP prevention and should not be a part of standard prophylactic care.

Ultimately, the prevention of ROP requires a tailored, evidence-based strategy that prioritizes safe, foundational care while judiciously applying more targeted interventions.

Clinicians are encouraged to focus on robust implementation of proven strategies like human milk feeding and antenatal corticosteroid administration. For other interventions, especially pharmacological ones like propranolol, a cautious and individualized approach is essential. Future research should concentrate on validating the efficacy and safety of promising new strategies and identifying which interventions are most effective for specific high-risk neonatal subgroups. This will allow for the continued refinement of clinical protocols to improve long-term visual outcomes for the world's most vulnerable infants.

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