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REVIEW ARTICLE

Anemia of prematurity: a narrative review

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Abstract

Anemia of prematurity is a condition that is prevalent in neonatal intensive care units, especially among extremely low birth weight infants. Despite extensive practice and research, several preventive and therapeutic strategies remain controversial, giving rise to significant differences among centers. Preventive strategies include delayed cord clamping, umbilical cord milking, autologous and allogeneic cord blood transfusion, and reducing iatrogenic blood loss through innovative methods like microsample devices. The effectiveness of erythropoiesis-stimulating agents in reducing transfusions remains limited. Red blood cell transfusions, while beneficial, carry risks. Defining transfusion thresholds based on hemoglobin levels remains a challenge, with practices varying globally. Recent trials advocate for a restrictive transfusion approach, reducing the number of transfusions with no significant adverse effects. Near Infrared Spectroscopy evaluates tissue oxygenation, potentially aiding transfusion decisions based on individualized physiological markers of anemia. This review provides a summary of the latest literature on anemia of prematurity, emphasizing aspects related to pathophysiology, preventive measures, and therapeutic interventions to assist clinicians in managing this condition.

Keywords: Anemia. Hemoglobin. Preterm infants. Red blood cell transfusion.

Anemia da prematuridade: revisão narrativa

Resumo

A anemia da prematuridade é uma condição prevalente nas unidades de cuidados intensivos neonatais, especialmente em recém-nascidos prematuros com extremo baixo peso ao nascimento. Apesar da ampla prática e investigação, várias estratégias preventivas e terapêuticas permanecem controversas, resultando em diferenças significativas na prática clínica entre os diversos centros. As estratégias preventivas incluem a clampagem tardia do cordão umbilical, a expressão do cordão umbilical, as transfusões autóloga e alogénica de sangue do cordão e a redução da perda sanguínea iatrogénica através do uso de micro-amostras. A eficácia dos agentes estimuladores da eritropoiese na redução do número de transfusões permanece limitada. As transfusões de glóbulos vermelhos, apesar de benéficas, acarretam riscos. Definir os limiares de transfusão com base nos níveis de hemoglobina continua a ser um desafio, com práticas variadas a nível global. Ensaios recentes defendem uma abordagem de transfusão restritiva, demonstrando redução das transfusões sem efeitos adversos significativos. A espectroscopia próxima de Infravermelhos mostra-se promissora na avaliação da oxigenação dos tecidos, podendo auxiliar nas decisões de transfusão com base em marcadores fisiológicos de anemia individualizados. Esta revisão apresenta um resumo da literatura mais recente sobre a anemia da prematuridade, enfatizando aspetos relacionados com a fisiopatologia, medidas preventivas e intervenções terapêuticas, com o objetivo de auxiliar os clínicos no manejo desta condição.

Palavras-chave: Anemia. Hemoglobina. Recém-nascido pré-termo. Transfusão de glóbulos rubros.

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Keypoints

What is known

- Anemia of prematurity is a condition that is prevalent in neonatal intensive care units, particularly among extremely low birth weight infants.
- Red blood cell transfusions are the primary treatment for anemia of prematurity, yet global practices vary as there is no universal hemoglobin threshold.
- The use of erythropoiesis-stimulating agents is not currently recommended due to the limited benefits.

What is added

- Preventive strategies include delayed cord clamping, umbilical cord milking, minimizing iatrogenic blood loss with microsampling, and autologous/allogeneic cord blood transfusion.
- A restrictive transfusion strategy leads to a decrease in transfusions with no significant adverse effects.
- Near Infrared Spectroscopy is being studied as a potential adjunct for determining transfusion needs, based on individualized physiological markers of anemia.

Introduction

Neonatal anemia, characterized by hemoglobin (Hb) or hematocrit (Hct) concentrations more than two standard deviations below the mean for the postnatal age, is often observed in neonatal intensive care units (NICUs). Neonates, particularly extremely low birth weight (ELBW at < 1000 g) infants, are one of the most commonly transfused groups, with approximately 90% receiving at least one red blood cell (RBC) transfusion during their NICU stay, resulting, in some cases, in a cumulative replacement of 100-200% of their estimated total circulating volume at birth[1-3].

Most RBC transfusions in the NICU occur in the context of medically stable preterm infants who have developed chronic anemia, referred to as "anemia of prematurity" (AOP)[4]. The primary goal is to enhance oxygen delivery to vital organs. Despite widespread practice and a century of research and clinical advancements, the indications for RBC transfusion in neonates remain controversial due to the absence of uniformly accepted physiological or evidence-based criteria[5]. Moreover, there is a lack of conclusive data on the long-term effects of RBC transfusions[5]. As a result, neonatologists worldwide exhibit considerable variation in practices related to neonatal transfusions, often relying on expert opinion rather than a scientifically-robust evidence base[4,6].

The aim of this paper is to provide a comprehensive review and update of the pathophysiology, preventive strategies, and management of AOP according to the most recent literature.

Pathophysiology of AOP

After birth, all infants undergo a gradual decline in Hb, resulting in varying degrees of anemia. In healthy term infants, the nadir Hb value seldom drops below 10 g/dL between six and 12 weeks of age (Table 1)[7]. This physiological anemia of infancy is a well-tolerated benign phenomenon, reflecting several principles: a progressive shift from fetal Hb (HbF), characterized by higher oxygen affinity, to adult Hb (HbA) between 34 to 36 weeks' gestation and three to four months post-term; a shorter lifespan of RBC in newborns compared to adults (approximately 40 to 60 days versus 120 days); a postnatal rise in intra-erythrocyte 2,3-diphosphoglycerate, facilitating oxygen release from Hb; adaptive cardiovascular mechanisms compensating for the reduced oxygen-carrying capacity of anemia; and a transitional decrease in plasma erythropoietin relative to the degree of anemia, with a reduction in erythropoiesis compared to adults[3,4,8-10].

In preterm infants, this decline occurs earlier than in term infants, reaching a nadir at an average Hb concentration of 7-8 g/dL by a postnatal age of four to six weeks (Table 1)[7]. The severity is more pronounced, accompanied by clinical symptoms and signs of anemia such as tachycardia, tachypnea, higher oxygen requirements, increased frequency of apnea, bradycardia, pallor, and poor weight gain[4,11,12]. Due to these symptomatic manifestations and their consequences, anemia is not considered a benign event in preterm infants. The degree and severity are determined by gestational age and a combination of multiple physiological and non-physiological factors[13].

Physiological factors

Among the physiological factors contributing to AOP is the presence of low plasma erythropoietin (EPO) levels in response to anemia, attributed to decreased EPO production and accelerated catabolism[3]. Additionally, EPO is predominantly produced in the liver during the fetal and early preterm period, which is less sensitive to anemia and tissue hypoxia compared to the kidney, resulting in a relatively attenuated response to falling hemoglobin levels[8,9,12].

Another contributing factor relates to HbF, which constitutes 70-80% of the total Hb content in term newborns and can reach up to 97% in preterm infants[14]. Under similar conditions, the release of oxygen to tissues

Table 1. Hemoglobin: normal levels at birth and postnatal nadir

	Hb at birth (g/dL)	Hb nadir (g/dL)	Age at which Hb nadir is reached (weeks)
Term newborn	17 (14-20)	9.5-11	6-12
Preterm newborn 1.2-2.5 kg	16.4 (13, 5-19)	8-10	5-10
Preterm newborn < 1.2 kg	16 (13-18)	6.5-9	4-8

Hb: hemoglobin.
Adapted from Sánchez-Gabriel M. Anemia y policitemia neonatal. Protocolos de la Sociedad Española de Neonatología, SENeo 2023, 301-305.

is more challenging in preterm newborns[14]. Accelerated catabolism, a shortened lifespan of red blood cells (surviving only 35 to 50 days in the most premature infants, compared to 90 days and 120 days in term infants and adults, respectively), higher extrauterine growth and blood volume increase, and insufficient iron storage, are additional physiological factors contributing to AOP[13].

Non-physiological factors

Frequent laboratory blood tests required for hematological, biochemical, and other parameter monitoring, are a significant iatrogenic contributor to AOP[3]. Very low birth weight infants (VLBW at < 1500 g) commonly experience routine blood losses of approximately 11-22 ml/kg per week (~ 15-30% of an infant's total blood volume) during the first six weeks of life[3,4,8]. Also, various non-physiological conditions can exacerbate the development of neonatal anemia, including blood loss, hemolysis, infection/sepsis, cardiorespiratory disease, and nutrient deficiencies necessary for erythropoiesis (iron, folate, protein, vitamins E and B12)[2-4]. Generally, the severity of AOP is inversely proportional to gestational age and birth weight, with younger and smaller infants requiring more RBC transfusions during their NICU stay[2,4,8].

Anemia at birth is universally considered pathological for both term and preterm infants, requiring further investigations if the cause is not identified antenatally or at delivery[15]. The pathological causes of anemia are outlined in table 2[4,15].

Laboratory monitoring

The diagnostic approach for AOP typically involves a comprehensive evaluation, including the family and maternal medical history, details about the pregnancy, delivery, and postpartum period, a physical examination, and laboratory tests[2].

For laboratory diagnosis, a complete blood count is essential[2]. Newborns' Hb or Hct levels should be assessed based on reference values appropriate for the gestational age and the site of sampling[12]. Hct or Hb concentration should be monitored weekly, or according to the clinical status, in ELBW infants during the first weeks of life[1,2,12]. Subsequently, weekly routine monitoring of Hct or Hb in healthy growing preterm infants is unnecessary. However, the serum Hb value must be known before hospital discharge[12]. Additional laboratory assessments may include reticulocytes, red cell indices, a peripheral blood smear, and indices of hemolysis (total and indirect bilirubin, lactate dehydrogenase, direct and indirect Coombs test, and haptoglobin), conducted stepwise and utilizing the smallest possible volume of blood[1].

Preventive strategies

Several practices have been employed to prevent and mitigate the degree of AOP, with the most relevant strategies outlined below (Table 3).

Non-pharmacological interventions

Delayed umbilical cord clamping. Interest in delaying umbilical cord clamping (DCC) during birth has surged in recent years as a potential method to enhance the transfer of blood from the placenta to the newborn, consequently reducing the need for subsequent RBC transfusions[16]. A recent meta-analysis conducted by Cochrane, encompassing data from 15 randomized trials involving a total of 738 infants born between 24 and 36 weeks of gestation, revealed that DCC for at least 30 seconds, as opposed to immediate clamping, appears to be correlated with a reduced necessity for transfusions, improved circulatory stability, decreased occurrences of intraventricular hemorrhage (IVH), and a lower risk of necrotizing enterocolitis (NEC)[16,17]. Subsequent to this, another meta-analysis pooling data from 27 clinical trials involving 2,834 preterm infants validated that clamping the cord at 30 seconds or more after birth was linked to a decrease in hospital mortality rates and a reduced need for transfusions[18]. A recent randomized trial

Table 2. Pathological causes of anemia in infants

Blood loss	Bone marrow disorders	Increased RBC destruction
Feto-maternal hemorrhage Twin-to-twin transfusion syndrome Umbilical cord rupture Abruptio placenta Intra- and extra-cranial hemorrhages (e.g. intra- and periventricular, subgaleal) Phlebotomies	Fanconi anemia Diamond-Blackfan syndrome Transient erythroblastopenia of childhood Congenital infections (e.g. TORCH) Nutritional deficiencies (e.g. vitamin B12, folate, iron)	Alloimmune hemolytic disease of newborn Inherited RBC enzyme abnormality Inherited RBC membrane defects Haemoglobinopathies Disseminated intravascular coagulopathy Metabolic disorders

Adapted from Saito-Benz M, Flanagan P, Berry MJ. Management of anaemia in pre-term infants. Br J Haematol. 2020, 188: 354-366.

Table 3. Evidence level for preventive strategies for anemia of prematurity

Strategy	Quality of evidence	Strength of recommendation	Recommendation of the Standards Committee of the SENeo
Delayed cord clamping	1A	High/substantial A	Recommended for routine clinical practice
Initial cord/placental blood tests	2B	Moderate/moderate B	Recommended for routine clinical practice
Reducing phlebotomy losses	1B	Moderate/substantial B	Recommended for routine clinical practice
Erythropoietin	1A	Moderate/moderate B	Further research is required to recommend its clinical use

Adapted from Sánchez-Gabriel M. Anemia y policitemia neonatal. Protocolos de la Sociedad Española de Neonatología, SENeo 2023, 301-305.

comparing early clamping (within 10 seconds) and delayed clamping (at least 60 seconds) in 1,566 preterm neonates indicated no significant differences in the primary outcome of death or major morbidities[19]. However, fewer infants in the DCC group required subsequent RBC transfusions by 36 weeks of postmenstrual age[19]. Consequently, DCC is increasingly acknowledged as a standard practice during preterm delivery[4].

The optimal duration for DCC remains uncertain, although the 2021 European Resuscitation Council Guidelines recommend, when immediate resuscitation or stabilization isn't imperative, DCC for a minimum of 60 seconds, ideally after the aeration of the lungs[20]. Limited follow-up studies indicate that DCC may lead to enhanced neurodevelopmental outcomes in the initial year of life[19,21]. Concerns regarding polycythemia and jaundice necessitating significant intervention do not seem to be supported by evidence from randomized trials[20,21].

Umbilical cord milking. Umbilical cord milking (UCM) involves manually moving blood from the unclamped umbilical cord to the infant, typically carried out three to five times before clamping, aiming to facilitate an autotransfusion of blood into a preterm neonate[17]. DCC is not recommended in cases where placental blood flow is compromised due to conditions like placental abruption, cord prolapse, vasa previa, cord avulsion, or maternal hemorrhage[20]. In such situations, UCM is considered as an alternative method[19]. However, this remains a controversial topic, with some authors expressing concerns about potential fluctuations in systemic blood pressure and cerebral blood flow[17].

In a randomized trial comparing UCM to immediate cord clamping in 256 newborns born before 34 weeks of gestation, UCM showed higher levels of Hb and Hct, reduced occurrences of anemia in early infancy and at six months postpartum, fewer RBC transfusions during hospitalization, and improved iron stores compared to immediate cord clamping[22]. Other meta-analyses have indicated that UCM during preterm birth was relatively safe and associated with reduced exposure to RBC transfusions and a lower incidence of complications such as IVH, NEC, and mortality[23]. As per the 2021 European Resuscitation Council Guideline, when DCC is not feasible, cord milking in infants above 28 weeks of gestation should be considered[20]. Although the available data is limited, some authors strongly advocate that UCM should no longer be viewed as an experimental technique; rather, it should be recognized as an established intervention ensuring that premature neonates above 28 weeks of gestation receive an adequate placental transfusion at birth[17,20].

Autologous and allogenic cord blood transfusion. An alternative to DCC and UCM is the use of autologous blood

from the placenta immediately following delivery for later transfusion to the same patient[24]. Although there are challenges associated with this practice as relatively small volumes are collected (~ 10-30 ml/kg), this strategy is attractive because it reduces an infant's exposure to life-threatening viral infections associated with iatrogenic blood products while conserving limited blood resources[24-26]. Alternatively, allogeneic cord blood transfusion effectively reduces exposure to adult donor RBC and may have a role in neonatal transfusion practice in the future[27].

Minimizing iatrogenic blood loss. Reducing iatrogenic blood loss is crucial in managing AOP. A significant contributor to this issue is the blood drawn for laboratory testing. However, adjustments in practice can help minimize phlebotomy-related blood losses[17]. Another method involves employing microsample point-of-care devices[17,25]. These devices have shown a 43% reduction in the mean volume of RBC transfusions among ELBW infants[28]. They achieve this by reducing unnecessary laboratory testing, optimizing the frequency, and using collection tubes with minimal volumes[28].

Moreover, umbilical cord blood serves as a valuable resource for conducting neonatal blood typing, screening, complete blood count with differential, and blood culture assessments[29]. Utilizing 'in-line' umbilical arterial catheter devices offers another avenue[8,17,29]. These devices make it possible to analyze blood gas, Hct, and electrolytes without drawing blood directly from the infant; instead, they return dead-space blood draws to the infant[17,29].

Pharmacological intervention

Erythropoiesis-stimulating agents. The impaired production of EPO in AOP has prompted the exploration of erythropoiesis-stimulating agents (ESAs), particularly recombinant human EPO (rhEPO), as a potential therapy[12]. Research has extensively investigated the role of rhEPO, indicating its ability to enhance both erythropoiesis and the reticulocyte count in a dose-dependent manner[30]. However, its effectiveness in significantly reducing transfusions and blood donor exposure for infants, regardless of early initiation (less than eight days of life) or later administration (after the first two weeks of life), remains limited[8,12,30].

Initial studies, including the Cochrane review on early rhEPO therapy, demonstrated marginal benefits in reducing transfusions but suggested an increased risk of severe (stage ≥ 3) retinopathy of prematurity (ROP)[30,31]. As a result, early rhEPO therapy was not recommended based on these findings[31]. Subsequent meta-analyses, including more trials with ESAs initiated before eight days of age, showed a slight reduction in RBC transfusions and donor exposure[32]. However, the clinical significance of these findings remains modest. Importantly, the updated review confirmed the safety of early ESA administration with no significant difference in the rate of severe ROP[32]. Additionally, the rate of significant neonatal morbidity, including NEC, IVH, and periventricular leukomalacia, appeared lower in the ESA-treated group. Nevertheless, differing results from major trials and substantial heterogeneity in analyses suggest the necessity for more trials before drawing definitive conclusions[32].

A recent double-blind randomized controlled trial (RCT) administering high-dose EPO within 24 hours of birth in extremely preterm infants (< 28 weeks gestational age) exhibited fewer transfusions and a decreased cumulative transfused volume[33]. A significant proportion of infants in the EPO group remained transfusion-free at 12 weeks of age compared to the placebo group. However, the trial found no differences in primary outcomes such as death or severe neurodevelopmental impairment at 22-26 months of corrected gestational age. Moreover, rates of ROP, NEC, IVH, or bronchopulmonary dysplasia (BPD) did not differ significantly between the groups[33]. Similarly, evidence supporting the late administration of ESAs is inconclusive, demonstrating minimal clinical benefits and conflicting safety profiles[34]. While it may reduce the need for one or more RBC transfusions, the total volume of RBC transfused per infant remains unchanged. Moreover, donor exposure isn't effectively avoided, as most studies included infants who received RBC transfusions before entering the trial[34].

In summary, based on current findings, the International Guidelines do not recommend the early or late administration of rhEPO[32-34].

Iron supplementation. Premature infants have lower iron levels at birth compared to full-term infants since the significant transfer of iron occurs mainly during the third trimester of gestation[35]. Consequently, the iron reserves in preterm infants are often depleted by the age of two to three months[35]. The standard practice in NICUs worldwide involves enteral supplementation of iron for preterm infants, typically initiated once they can tolerate enteral feeds (> 100 ml/kg)[36,37]. This supplementation generally involves administering 2-3 mg/kg/day of iron throughout the first year of life[36-38]. While iron supplementation does not prevent AOP, using iron-fortified formula instead of non-fortified formula offers more iron substrate when erythropoiesis is stimulated[36-37]. This strategy helps in reducing iron-deficiency anemia, a condition for which preterm infants are at a higher risk during their first year of life[12,35-38].

RBC transfusions to treat AOP

RBC transfusions continue to be the primary treatment for AOP, typically recommended when the severity of the anemia leads to symptoms or affects the delivery of oxygen[1,3]. However, significant controversy surrounds the potential advantages and risks associated with RBC transfusions in preterm infants, as well as the ideal transfusion thresholds for this specific population[4,12,39].

Potential benefits and risks

RBC transfusions are commonly administered in the context of AOP to enhance cardiorespiratory stability and promote weight gain[25,40]. Generally, they provide benefits by elevating circulating Hb levels, leading to improved tissue oxygenation, reduced cardiac output, and enhanced weight gain[40]. However, these transfusions also carry well-recognized risks, which can be categorized as follows: the transmission of infections (viral, bacterial, and parasitic), adverse effects due to leukocytes (including immunomodulation, graft-versus-host disease, transfusion-related acute lung injury, and alloimmunization), acute volume or electrolyte disturbances, increased exposure to donors, and rare blood group incompatibilities (often due to transfusion errors)[12,41]. While all transfusion-transmitted infections pose risks to newborns, cytomegalovirus (CMV) infection can be particularly serious for extremely immature infants[42,43]. The adoption of universal leukoreduction in NICUs has contributed to reducing the risk of CMV infection[42,43]. Rare conditions such as transfusion-related acute lung injury and transfusion-associated circulatory overload may go unnoticed, particularly in critically ill ELBW newborns exhibiting respiratory symptoms[44].

In preterm infants, RBC transfusions have been associated with the development of conditions like BPD, ROP, NEC, and IVH, although a direct causal relationship has not been firmly established[44]. Some observational studies suggest an association between NEC and transfusions[45]. However, findings from randomized clinical trials do not consistently support this correlation[46,47]. In a prospective multicenter cohort study analyzing 1,430 transfusion exposures in VLBW infants, NEC appeared to be associated more with severe anemia (Hb ≤ 8 g/dL) rather than directly linked to RBC transfusion[46]. Most meta-analyses investigating these associations rely on observational and cohort studies, which carry the potential for confounding factors and biases. Hence, large prospective randomized trials are still necessary[46,47].

Selection of RBC products

Upon deciding to administer RBC transfusions, selecting the appropriate RBC product becomes crucial, taking into consideration the various efficacy and safety concerns aimed at mitigating potential risks[25]. Strategies in blood banking, such as stringent donor selection criteria, pathogen inactivation techniques, and infectious disease testing, have significantly reduced the likelihood of developing transfusion-transmitted diseases[25,41,42]. Moreover, specific practices in blood banking include using stored rather than fresh RBC to minimize donor exposure, opting for white blood cell (WBC)-reduced (leucodepleted) RBC to eliminate complications related to WBCs, and prescribing gamma-irradiated RBC to prevent graft-versus-host disease[4,25].

The risks associated with RBC transfusions have notably decreased due to the adoption of single-donor and small-volume pack units (pedipacks), which can be stored for up to 35 days[44]. These units have donor plasma replaced by anticoagulant additive solutions and utilize additives like mannitol and glucose[13]. Furthermore, using leucodepleted and gamma-irradiated RBC is universally recommended for transfusions in preterm infants[4,41].

Conventionally, transfusion volumes ranging from 10 to 20 mL/kg have been typical for newborns, yet evidence on the optimal volume remains limited[48]. A survey assessing transfusion practices in preterm infants across Europe revealed a median RBC transfusion volume of 15 mL/kg[49]. Several studies suggest that volumes of 20 mL/kg might offer benefits with no adverse respiratory effects, reducing the necessity for frequent transfusions[48]. However, transfusion volumes exceeding 20 mL/kg could elevate the risk of volume overload[41,48]. Transfusions should ideally be administered over two to four hours[12,41].

Transfusion thresholds for preterm infants

The variability in transfusion practices across different medical units is significant[49]. Most guidelines for RBC transfusions rely on Hb or Hct levels, in conjunction with the patient's clinical condition. These thresholds may differ based on postnatal age, oxygen requirements, and the type of respiratory support provided[4,12]. Predictors for a reduced need for subsequent RBC transfusions include higher birth weight and higher Hb levels at admission, while occurrences of sepsis are significantly associated with an increased need for additional transfusions[3,8].

Currently, there is no universally-accepted Hb threshold guiding RBC transfusion decisions. Consequently, clinicians base their decisions on clinical judgment and national or local guidelines[8,40]. The substantial variation in RBC transfusion thresholds across different regions and medical practices is outlined in table 4, comparing guidelines from various countries[11,40,48,50-52].

The observed diversity in transfusion thresholds highlights the absence of international and European consensus on transfusion criteria. Until recently, there has been a dearth of evidence regarding whether neonatal RBC transfusion therapy should follow a restrictive or liberal approach[49].

Restrictive versus liberal transfusions—evidence from clinical trials

Recent years have witnessed a transition in neonatal practice towards a more restrictive approach to RBC transfusions[53,54]. Several studies have examined restrictive transfusion guidelines to ascertain the safety of tolerating lower Hb levels[54]. This shift was initially prompted by concerns over exposure to blood products and multiple donors[54]. Subsequently, RCT began assessing whether restrictive or liberal transfusion practices impact short-term morbidities (e.g., BPD and ROP) and long-term neurodevelopmental outcomes[8].

Before 2020, clinical practice was partially guided by two significant RCT: the Premature Infants in Need of Transfusion (PINT) and the Iowa trials[55,56].

The PINT trial, involving 451 ELBW preterm infants, investigated mortality and morbidity at discharge as its primary outcome. It found no significant differences between ELBW infants receiving transfusions based on higher (liberal group) or lower (restrictive group) Hb thresholds. Consequently, the application of higher Hb thresholds increased transfusion frequency with no strong evidence of the benefits[41,55-57].

Concurrently, the Iowa study (n = 103, birth weight 500-1300 g) compared restrictive and liberal thresholds during a similar period to the PINT trial[56]. Although their restrictive thresholds mirrored those in the PINT trial, the liberal thresholds were notably higher (approximately 2 g/dL). Infants in the restrictive group were more likely to experience major neurological adverse events and increased frequency of apnea at NICU discharge[41,51,55-57].

The PINT study showed no statistically significant differences in combined death or disability at 18 months corrected gestational age. However, a post-hoc analysis favored high Hb thresholds regarding less severe Bayley II mental developmental index outcomes, impacting this primary outcome[49,55]. In a 2011 Cochrane Review analyzing the PINT and Iowa trials, the need for further studies to elucidate the long-term implications of restrictive versus liberal transfusion thresholds for V/ELBW infants was emphasized[4,58].

The scarcity of data suggesting that higher Hb thresholds could mitigate cognitive delay led to the development of two multicenter randomized trials: the Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants (ETTNO) trial and the Transfusion of Prematures (TOP) trial[6,59,60].

The ETTNO trial randomized 1,013 neonates across 36 European NICUs and the TOP trial included 1,692 neonates from 19 US centers. Their primary outcome was neurodevelopmental impairment at 24 (22-26) months corrected age or death before assessment. In both trials, no significant differences were observed in the primary outcomes or secondary outcomes like NEC, BPD, ROP, brain injury, and nosocomial infection[41,59-61].

The TOP trial did not indicate improvements in cognitive outcomes in infants assigned to higher Hb thresholds or other clinically-relevant outcomes during the initial hospital stay or at 22 – 26 months. Despite more frequent transfusions in the higher Hb threshold group, there was no difference in NEC rates[41,55].

Practitioners are advised to adhere to transfusion thresholds within the ranges of the ETTNO and TOP trials[59-60]. These trials suggest that Hb transfusion thresholds should not exceed 13 g/dL or fall below 11 g/dL for critically ill newborns in their first week of life or requiring significant respiratory support. For stable older infants with no critical illness and who do not require significant respiratory support, thresholds should not exceed 10 g/dL or drop below 7 g/dL. Most guidelines now recommend a restrictive transfusion strategy for preterm neonates. Anyone proposing thresholds beyond those studied should bear the burden of proving their safety[12,41,51].

The Spanish Society of Neonatology encourages units to adopt specific guidelines aligned with local clinical practices to minimize heterogeneity[41].

NIRS as a way to monitor anemia

Guidelines typically offer Hb thresholds for transfusion decisions; however, several unconsidered factors might also influence such decisions. These factors encompass a patient's transfusion history, reticulocyte counts, expected phlebotomy losses, nutritional status, concurrent illnesses, the severity of these, and the use of ESAs[61].

Table 4. Comparison of British, American, Australian, Canadian and Portuguese practice guidelines for RBC transfusion in newborn infants

Clinical status	BCSH guideline	American Red Cross practice guideline	Australian National Blood Authority guideline	Canadian Blood Services guideline	Portuguese guideline SPN
Anemia in the first 24h	Hb < 12 g/dL or Hct < 36%	-	No respiratory support: Hb 10-12 g/dL Respiratory support Hb 11-13 g/dL	On ECMO and congenital cyanotic heart disease Hb < 15 g/dL	-
Infants receiving intensive care. Severe cardiopulmonary disease (FiO2 > 0.35)	Hb < 12 g/dL or Hct < 36%	Hct 40-45%	Hb 11-13 g/dL	Hb < 12 g/dL	Hb ≤ 10 g/dL Htc ≤ 30%
Chronic oxygen dependency Moderate cardiopulmonary disease (CPAP or O2)	Hb < 11 g/dL	1Hct 30-35%	Hb 8.5-11 g/dL	Hb < 10 g/dL	Hb ≤ 8 g/dL Htc ≤ 25%
Late anemia, stable patient	Hb < 7 g/dL	Hct 20-25%	Hb 7-10 g/dL	Hb < 7 g/dL	Hb ≤ 7 g/dL Htc ≤ 20%

BCSH: British Committee for Standards in Haematology; SPN: Portuguese Neonatology Society; Hb: hemoglobin; Hct: hematocrit; ECMO: extracorporeal membrane oxygenation; CPAP: continuous positive airway pressure.
Adapted from Howarth C, Banerjee J, Aladangady N. Red blood cell transfusion in preterm infants: current evidence and controversies. Neonatology. 2018;114 (1):7-16 and Anemia of Prematurity Consensus, revised in 2013 by the Portuguese Neonatology Society

Near Infrared Spectroscopy (NIRS) presents as a potential avenue for guiding transfusion practices in the future[62,63]. NIRS serves as a physiological marker for tissue hypoxia and has been utilized clinically to monitor regional mixed venous oxygen saturation in the central nervous system[62,63]. NIRS enables the measurement of oxygen consumption, represented by the fractional total oxygen extraction (FTOE), which reflects the ratio of consumption to supply. Although NIRS is commonly employed to assess brain oxygenation, its applicability extends to other tissues such as peripheral and gut perfusion[64]. Several small observational studies and recent reviews have associated increasing anemia with decreasing cerebral oxygen saturation or a compensatory rise in cerebral oxygen extraction (cFTOE), suggesting that elevating cFTOE could potentially serve as a physiological indicator of worsening anemia[61,63,64].

A secondary analysis of the TOP trial revealed an improvement in tissue oxygenation in both brain and mesenteric regions following transfusion, regardless of the Hb threshold group[65]. Infants experiencing cerebral saturation below 50% exhibited a higher incidence of death or neurodevelopmental impairment at 22 to 26 months corrected age. These results suggest that cerebral NIRS could be a valuable target for enhancing survival with no neurodevelopmental impairment in infants facing various levels of anemia. A prospective investigation comparing the current Hb threshold-based transfusion practices with an individualized guideline based on cerebral NIRS measurements is warranted[61,63-65].

Conclusion

Anemia is prevalent among premature infants, particularly those born below 30 weeks of gestation, making RBC transfusion a crucial and common aspect of neonatal intensive care. Most RBC transfusions are administered to medically stable newborns to enhance their oxygen-carrying capacity during the critical phase of growth and development.

Despite the frequent use of transfusions in this population, there is an incomplete understanding of the potential benefits and drawbacks of these procedures. This has led to significant variations in approaches among clinicians, institutions, and countries.

Preventing AOP is vital, achievable by minimizing blood draws and utilizing capillary microsampling methods. Other preventive measures include DCC, UCM, and rhEPO therapy. However, the benefits of EPO usage remain limited[13].

Transfusion carries rare but established risks. The primary goal of ideal transfusion practices is to minimize unnecessary transfusions while ensuring that neonates who genuinely benefit from transfusions receive them appropriately. Most trials have used varying thresholds of anemia for transfusion, making systematic reviews and meta-analyses challenging to interpret. Clinical

trials consistently demonstrated that adopting a restrictive transfusion practice decreases exposure to transfusions without raising morbidity or mortality[55,56,59,60].

The integration of physiological biomarkers indicating tissue hypoxia into transfusion guidelines is a current area of research in neonatology. The use of NIRS to assess end-organ tissue oxygenation shows the potential for employing non-invasive methods to determine therapeutic thresholds[8,65].

In summary, the most effective approach for experts in this field is preventing anemia induced by prematurity through the implementation of protocols and the adoption of restrictive transfusion strategies. Each unit should endorse the specific guideline that aligns best with local clinical practices and promote strict adherence to it, aiming to minimize variability in clinical practice.

Authors' contribution

S.A. Santos: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Drafting the article; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. G. Rocha: Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published: Agreement to be accountable for the accuracy or integrity of the work. H. Soares: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were

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Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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