Review

OPEN

Transfusion strategies for neonates: current perspectives

Muhammed A. Shafique, MBBS[a], Syeda Q. Abbas, MBBS[a], Ume Habiba, MBBS[a], Aira Mughal, MBBS[a],
Tagwa Kalool Fadlalla Ahmad, MBBS[b,*], Anfal Munir Chaudhary, MBBS[a]

Background: Blood transfusion intervention has been proven to be a crucial therapeutic aid for preterm infants with serious morbidities such as sepsis, intraventricular hemorrhage, and cardiopulmonary insufficiencies. However, blood transfusion practices have also been shown to cause significant adverse outcomes, which may negate the therapeutic effect of the intervention. To address the varying policies regarding the administration of blood products, healthcare professionals have adopted a consensus-based approach. The absence of a standard protocol has resulted in conflicting outcomes in previous clinical studies.
Objective: This study aimed to evaluate the effectiveness of blood transfusion practices in preterm infants by analyzing past clinical research and identifying the current trends that have emerged as a result of recent trials.
Results: Recent trials have demonstrated comparable trends in mortality rates and other primary outcomes, including retinopathy of prematurity, intraventricular hemorrhage, bronchopulmonary dysplasia, and brain injury, following transfusion of blood products in both groups. Nevertheless, employing restrictive thresholds rather than adopting a liberal approach can reduce these outcomes.
Conclusion: The current literature does not provide clear support for either technique as opposing and contradictory results are evident. However, there is a slight inclination toward the restrictive transfusion threshold due to recent trials, which warrants further in-depth investigation into this issue.

Keywords: guidelines, neonatal physiology, preterm infants, thresholds, transfusion practices

Introduction

The neonatal phase is distinguished by fast growth and development, as well as distinct physiological and hematological attributes that distinguish newborn babies from adults.[1] As a result, newborn transfusions require a specialized strategy that considers the complexities of the physiological and immunological systems[2]. Ensuring safe and successful transfusions requires careful balancing of criteria, such as gestational age, birth weight, hematological parameters, and possible hazards associated with transfusion-related problems[3]. Newborn transfusions may be required because of a variety of problems, including preterm birth difficulties, newborn anemia, hemolytic diseases, and congenital abnormalities. Each case necessitates a

HIGHLIGHTS

- There has been a contentious debate regarding transfusion approaches for neonates, particularly preterm ones. Over time, transfusion practices within this demographic have witnessed the application of both lenient strategies and corresponding guidelines.
- Nevertheless, recent trials have revealed that adopting higher thresholds for initiating transfusions is linked to increased mortality and morbidity. The most extensive recent trial conducted in the UK has reported similar findings.
- This article initially explores the distinctions in physiology between neonates and adults before delving into various types of transfusions and associated guidelines.

aDepartment of Medicine, Jinnah Sindh Medical University, Karachi, Pakistan and bDepartment of Medicine, Ahfad University for Women, Omdurman, Sudan

*Corresponding author. Address: Department of Medicine, Ahfad University for Women, JFVC+WF7, Omdurman, Sudan. Tel.: +249 969710718.
E-mail: tagwakaloolfaldalaahmed@gmail.com (T.F. Ahmad).

customized therapeutic strategy that maximizes possible benefits while minimizing the inherent hazards of blood transfusions[4].

Our objective was to investigate the diverse landscape of neonatal transfusions, encompassing challenges, advancements, and optimal strategies that underpin this critical aspect of neonatal care. By conducting an exhaustive analysis of the relevant literature, we aspire to offer valuable insights and evidence-based guidance to clinicians, researchers, and healthcare professionals, as they confront the intricacies of neonatal transfusion therapy.

Neonatal physiology

Understanding the fundamental physiology of newborns is crucial before discussing the various transfusion tactics used in this

population, as these differences in physiology account for the variations in transfusion patterns between neonates and adults. Because their bodies are still developing and it takes time for them to adjust from the intrauterine to the extrauterine environment, newborns are particularly susceptible to the effects of even small environmental changes. This paper will briefly discuss the physiology related to transfusion, specifically focusing on the physiological variations in newborn systems that make transfusion more challenging. However, it is beyond the scope of this paper to provide a comprehensive explanation of all physiology.

Cardiovascular system

The cardiovascular system of newborns develops swiftly, reaching adult levels within a few days of birth[5]. Shunts such as the ductus venosus and foramen ovale serve critical functions during fetal circulation but automatically shut down shortly after birth[6]. Fetal shunting lowers pulmonary blood flow, resulting in a reduction in oxygen delivery and the possibility of hypoxia[7]. As babies grow, their myocardium expands and their autonomic nervous system of the heart increases. Neonates have greater heart rates than adults, ranging from 120 to 160 beats per minute[8]. Their blood pressure is likewise lower, with an average systolic blood pressure of 60–70 mmHg[9]. Clotting factors do not cross the placenta in newborns. Vitamin K-dependent clotting factors are initially inadequate due to limited vitamin K reserves and undeveloped hepatocyte function[10].

Respiratory system

The respiratory system of newborns is characterized by unique features, including immature breathing control that results in sporadic breathing. Their airways are smaller, highly compliant, and prone to collapse, resulting in higher airway resistance[11]. Additionally, they have a higher metabolic oxygen demand and a smaller Functional Residual Capacity (FRC), making them more susceptible to rapid desaturation. Unfavorable rib configuration and inefficient respiratory muscles further contribute to this rapid desaturation[12]. Newborns have a considerably faster breathing rate compared to adults, typically ranging between 30 and 60 breaths per minute[13]. Surfactant plays a crucial role in the maturation of the neonatal respiratory system[14]. It reduces surface tension, stabilizes small alveoli, improves overall alveolar inflation, and lessens the hydrostatic force that can cause pulmonary edema. Respiratory distress syndrome is a clinical disorder that arises due to inadequate surfactant production in newborns[15].

Renal system

The renal system of newborns undergoes significant changes within the first 2–3 days after birth, entering a diuretic phase characterized by relatively high urine production. During this period, newborns generally have lower body weight and total body water compared to other stages[16]. Newborns experience a doubling of glomerular filtration rate during the first 2 weeks of life. The rapid increase in mean arterial pressure, renal blood flow, glomerular permeability, and filtration surface area contribute to this surge in glomerular filtration rate[17]. In terms of renal concentration and dilution, at birth, the maximum concentrating ability is relatively low, although term neonates can produce urine with a dilution similar to that of adults (25–35 mOsm/L). For preterm neonates, the maximum concentrating capacity is limited to 500 mOsm/L for a longer duration[18]. Concerning acid–base metabolism, neonates have a lower threshold for proximal tubular bicarbonate reabsorption compared to adults.[19] As the glomerular filtration rate increases, there is a gradual rise in bicarbonate reabsorption[20]. However, in neonates with congenital conditions, these typical physiological trends may be disrupted. In such cases, it becomes essential to closely monitor and measure urine flow, as well as urine and serum electrolyte concentrations, to manage fluid and electrolyte balance effectively[21].

Gastrointestinal system

Newborns do not have a completely formed gastrointestinal system. It is more difficult for them to digest and absorb nutrients because of their reduced release of digestive enzymes[22]. Additionally, they have decreased intestinal motility, which might make it harder for them to eat and cause digestive problems[23]. The trophic effect of enteral nutrition, which lasts for the first 24 h after birth, predominantly causes a growth spurt in the gastrointestinal tract[24]. Nursing newborns may be challenging; they could also have reflux, in which the stomach contents return to the esophagus[25]. Another gastrointestinal condition that typically affects premature infants is necrotizing enterocolitis (NEC). It is characterized by tissue death and intestinal inflammation[26].

Immune system

Neonates, being born with an underdeveloped immune system, are more vulnerable to infections[27]. The process of birth itself exposes them to a wide range of diseases they have never encountered before, making them particularly susceptible to infections compared to adults[28]. Early in life, their immune response is somewhat restrained, partly due to the immunosuppressive environment of the womb. The susceptibility of neonates to infectious pathogens can be attributed to several factors. Their immune system is still growing, and they lack immunological memory, which means they have not encountered and built defenses against various pathogens[29]. Their exposure to a microbial-rich environment further increases the risk of infections. Both the innate and adaptive immune responses in newborns depend on factors such as the frequency of precursor cells, the amount of antigen exposure, and the mode of exposure[30]. Within the first 3 months of life, the cellular immune system of newborns undergoes rapid development, influenced by a multitude of factors[31]. Maternal cytokines, exposure to antigens, and the frequency of precursor lymphocytes and antigen-presenting cells all play vital roles in shaping the development of neonatal immunity[32].

Keeping in mind the aforementioned distinctions between the physiologies of a newborn and an adult, the transfusion of red blood cells (RBCs), white blood cells (WBCs), and platelets in the neonatal population and the complications associated with them have been briefly described in the following sections.

Table 1

Overview of platelet trials.

References	Objective	Methodology	Selection criteria	Threshold	Patient population	Result
PlaNeT-1[52]	To investigate the causes of bleeding and to describe the patterns of clinical bleeding in infants with severe thrombocytopenia.	The research admission criterion for severe newborn thrombocytopenia was a platelet count of $<60 \times 10^9$/L. Platelet count, GA, birth weight, gender, postnatal age, clinical diseases linked to thrombocytopenia, and the degree of any prior intraventricular hemorrhage (IVH; Papile grading 1–4) were among the baseline data collected. Data on platelet count, hemorrhage, platelet administration, and cause for transfusion were prospectively recorded over the course of the trial and for at least 7 days following enrollment. Data gathering persisted until the platelet count reached $\geq 60 \times 10^9$/L and remained at that level for a minimum of 2 days in the absence of transfusion assistance.	(1) Inclusion criteria: severe newborn thrombocytopenia (SNT) is defined as a platelet count below 60×10^9 platelets per liter of blood. (2) Exclusion criteria: newborns receiving a surgery, those receiving an exchange transfusion, those lacking clinical data, and those with abnormal platelet counts.	(1) Neonatal thrombocytopenia (platelet count $<150 \times 10^9$/L) (2) Severe thrombocytopenia (ST and platelet count $<60 \times 10^9$/L).	$n = 169$ neonates with severe thrombocytopenia.	Bleeding was observed in the majority of newborns with ST (138/169; 82%). (1) $n = 123$ neonates with minor bleeding. (2) $n = 15$ with major bleeding.
PlaNeT-2[79]	Analyzing the treatment effect heterogeneity to see whether any particular groups of neonates benefit from a low-platelet-count threshold for transfusion.	Neonates with severe thrombocytopenia, defined as a platelet count of 50×10^9/L, were compared to a prophylactic platelet transfusion threshold of 25×10^9/L. A composite of significant bleeding and/or death within 28 days following randomization was the main outcome. From June 2011 to August 2017, 43 neonatal intensive care centers in the UK, the Netherlands, and Ireland randomly assigned newborns.	(1) Inclusion criteria: preterm neonates with severe thrombocytopenia.	Severe thrombocytopenia: 50×10^9/L. (1) High threshold group: 50×10^9/L. (2) Low-threshold group: 25×10^9/L.	(1) $n = 653$ (2) Avg GA: 26.7 weeks and (3) Median postnatal age: 7.5 days.	The 25×10^9/L barrier was advantageous compared to the 50×10^9/L criterion in all categories of predicted baseline risk.
Andrew et al.[97]	Investigating if administering platelet concentrates early would decrease the occurrence, the extent, or both of cerebral bleeding.	(1) Patient population. (2) Clinical information gathering: a daily hemoglobin level, precise infusion quantities for packed red blood cells, fresh frozen plasma, and platelet concentrates, and blood withdrawal for testing were all crucial. (3) Platelet transfusion: blood group-matched platelet concentrates were given to infants randomly allocated to the treatment group for about an hour at a dosage of 10 ml/kg. (4) Laboratory monitoring: using an automated newborn equipment that had previously been verified, a bleeding-time study was conducted.	(1) Inclusion criteria: prematurity, birth weight between 500 and 1500 g, gestational age <33 weeks, and a platelet count $<150 \times 10^9$/L in the first 72 h of life. (2) Exclusion criteria: included the attending neonatologist's evaluation that the newborn would most certainly die within the first 72 h, an initial platelet count of 50×10^9/L, parental denial of permission, and the presence of periventricular leukomalacia at the initial examination.	(1) Severe thrombocytopenia (ST and platelet count $<50 \times 10^9$/L). (2) Moderate thrombocytopenia (platelet counts 50 to 100×10^9/L).	(1) $n = 152$. (2) GA <33 weeks. (3) Birth weight 500–1500 g, and platelets $<150 \times 10^9$/L.	Prophylactic platelet concentrate infusions do not reduce the incidence or duration of ICH by more than 25% in preterm newborns with moderate thrombocytopenia. (No difference 28% vs. 26%, $P = 0.73$).

| Curley et al. [98] | Comparison of mortality and bleeding rates between high and low prophylactic platelet transfusion thresholds in neonates. | In this multicenter trial, infants with severe thrombocytopenia who were born before 34 weeks of pregnancy were randomized to receive a platelet transfusion at either the high-threshold group (50 000 platelets/mm^3) or the low-threshold group (25 000 platelets/mm^3). Using a validated bleeding assessment instrument, bleeding was prospectively recorded. | (1) Inclusion criteria: a gestational age at delivery of fewer than 34 weeks, a platelet count of <50 000/mm^3, and no severe intraventricular hemorrhage (2) Exclusion criteria: a serious or life-threatening congenital deformity, substantial bleeding within the preceding 72 h, fetal cerebral hemorrhage, immune thrombocytopenia. | (1) High threshold group: 50 000/ mm^3 (2) Low-threshold group: 25 000/mm^3. | (1) n=660. (2) GA <34 weeks and platelets <50 × 10^9 . L (3) Median birth weight, 740 g. | Worse with higher platelet transfusion threshold. OR 1.57 (95% CI 1.06–2.32), P=0.02. |

CI, confidence interval; GA, gestational age; IVH, intraventricular hemorrhage; OR, odds ratio; SNT, severe newborn thrombocytopenia; ST, severe thrombocytopenia.

RBC transfusion

RBCs are beneficial for anemia, extremely low birth weight (ELBW), preterm infants, and those who have experienced acute blood loss from placental abruption or fetal–maternal hemorrhage. It effectively increases blood hemoglobin (Hb) levels and enhances tissue oxygenation[33]. Neonatal patients, characterized by underdeveloped hematopoietic systems and small blood volumes, constitute one of the most frequently transfused populations[1].

Notably, 90% of ELBW newborns and 58% of preterm infants born before 32 weeks of gestation are expected to undergo RBC transfusions[34]. While accurately estimating an infant's blood transfusion requirement is imperative, relying solely on isolated Hb readings can be challenging. Transfusion decisions currently consider clinical symptoms, Hb/hematocrit (Htc) values, and the infant's cardiorespiratory condition[35]. For optimization, researchers have explored non-invasive technologies, such as near-infrared spectroscopy (NIRS). NIRS exhibits potential in tracking oxygen saturation in the intestines and splanchnic regions, aiding in the determination of the proper transfusion threshold[36]. Moreover, both NIRS and sonographic perfusion tests have demonstrated promising results in identifying preterm neonates at risk of anemia[37].

Over time, various approaches to RBC transfusions have been developed. Common strategies include iron supplements, erythropoietin, darbepoetin, delayed cord clamping, and minimizing phlebotomy losses[38–40]. Despite numerous attempts to establish clinical guidelines for RBC transfusion in preterm infants, challenges persist, including concerns regarding long-term consequences. Ongoing research aims to clarify the ideal transfusion protocol in neonatal critical care units[41].

Platelet transfusion

Thrombocytopenia, characterized by low platelet counts (150 000 platelets/L)[42], is prevalent in neonates, with a frequency of 1–2% in healthy infants and 20–35% in those with health problems. Thrombocytopenia becomes more likely as gestational age decreases, reaching as high as 70% in extremely preterm babies[43]. Intrauterine infection, placental insufficiency, neonatal sepsis, severe medication effects, or immune-related issues are all possible causes. Premature newborns have lower normal platelet counts, ranging from 100 000 to 150 000/L[44,45].

The incidence of neonatal bleeding increases with decreasing gestational age[46]. Intraventricular hemorrhage (IVH) is the most common and severe type of bleeding, typically occurring during the first 3 days following delivery[47]. IVH is now associated with cardiorespiratory alterations rather than hematological abnormalities[48,49]. Platelet transfusion is an essential component of the suggested therapy[50]. Consequently, despite minimal evidence of usefulness, prophylactic platelet transfusions are widely used to avoid bleeding in cases of isolated thrombocytopenia[51]. In this study, we provide an overview of four trials related to platelet transfusions in preterm neonates, which are all listed in Table 1.

Shafique et al. Annals of Medicine & Surgery (2024)

Annals of Medicine & Surgery

Insights from the recent trials

PlaNeT-1

This study examined the clinical bleeding patterns in neonates with severe thrombocytopenia, defined as a platelet count $<60 \times 10^{-9}$ and analyzed the associated factors. The study included 169 neonates from seven tertiary-level neonatal units and recorded instances of hemorrhage. The study employed regression analysis to evaluate the relationship between bleeding, platelet count, and baseline characteristics. The findings indicated that 82% of neonates with severe thrombocytopenia experienced bleeding, with 123 minor and 15 major cases. Most minor bleeding events occurred in the renal tract (40% hematuria), endotracheal tube (21%), nasogastric tube (10%), and skin (15%). The study identified gestational age below 34 weeks, onset of severe thrombocytopenia within 10 days of birth, and NEC as strong predictors of increased bleeding events. Interestingly, lower platelet count was not found to be a robust predictor of increased bleeding. This underscores the importance of considering clinical factors in assessing the risk of bleeding[52].

PlaNeT-2

The PlaNeT-2 trial, which is the most recent and compelling evidence to date, focused on prophylactic platelet transfusion thresholds for preterm neonates and yielded surprising results. This study found that a threshold of 25×10^9/L was associated with a significant benefit over a threshold of 50×10^9/L for major bleeding and/or mortality, with a 7% absolute risk reduction. Researchers developed a predictive model for the baseline risk in all 653 neonates and established quartiles based on the predicted baseline risk. The absolute risk difference between the 50×10^9/L and 25×10^9/L threshold groups was evaluated within these quartiles. The results showed that the 25×10^9/L threshold was associated with absolute risk reduction in all risk groups, ranging from 4.9% in the lowest risk group to 12.3% in the highest risk group. These findings suggest that a prophylactic platelet count threshold of 25×10^9/L can be beneficial for all preterm neonates regardless of their predicted baseline risk of major bleeding and/or mortality.

WBC transfusion

The incidence of leukopenia and neutropenia in preterm neonates approximates to 1.3%, and with the predominance of sepsis as the major causative agent, the mortality rate rises to 70% in cases with ELBW infants (1000 g)[53]. The situation is aggravated by an inherently lower total leukocyte count in preterm neonates relative to their full-term counterparts, thereby necessitating the application of transfusion practices in many clinical institutions[54]; however, the current thresholds being employed are proving to be futile in other capacities. In a randomized controlled trial involving 101 preterm neonates, the mortality rate was 43.5%, of which the exchange transfusion (ET) group contributed 36%, whereas the control group had a mortality rate of 51%. The ET group failed to effectively treat neonatal sepsis and its associated tachycardia, neurodevelopmental anomalies, respiratory insufficiency, and fever. Even though the leukocyte count was raised from 4750/mm³ to the 'standard' 10 630/mm³, the desired outcomes were not achieved[55]. Similarly, a retrospective study with six infants suffering from antibiotic-resistant sepsis received polymorphonuclear leukocyte infusions (PMNs), with a mortality rate of 50%; however, the causes were unrelated to the intervention[56].

It is worth noting that in both studies, neutropenia and leukopenia were corrected, and the patients that survived made full recovery and suffered from no side effects or recurrence of sepsis in the following year. While the current thresholds may not seem to fully treat other complications of neonatal sepsis, the primary objective of raising the WBC count without posing any additional threat to the patient's life validates the continuous use of such interventions.

Volume and threshold

The appropriate volume of RBC transfusion in newborns remains a topic of ongoing investigation. Current guidelines in the United Kingdom recommend a cautious approach, suggesting volumes of 15 ml/kg for newborns without bleeding[57]. However, recent studies propose that higher transfusion volumes, around 20 ml/kg, may be beneficial without causing respiratory issues and could potentially reduce the need for frequent transfusions[1]. Nevertheless, caution is warranted, as volumes exceeding 20 ml/kg could lead to volume overload in patients without active bleeding[58]. A brief overview of the current guidelines is shown in Tables 2 and 3.

For all neonatal patients, the use of leukodepleted RBCs is universally recommended to minimize the risk of adverse reactions[59]. In the case of preterm newborns weighing less than 1500 g, additional precautionary measures such as irradiation of RBCs are advised[60]. Research findings from the age of RBCs in premature Infants Trial indicate that using fresher RBCs, as opposed to RBCs stored for longer durations, does not significantly improve outcomes in preterm newborns[61]. As a result, hospitals should implement policies to limit exposure to multiple blood donors, whenever possible. One approach to achieve this is the use of 'paedipacks', which are multiple aliquots for pediatric transfusions derived from a single adult blood donation, effectively reducing the number of donors and potential risks associated with multiple exposures[62].

In summary, the quest to determine the optimal RBC transfusion volume for newborns continues, and guidelines are evolving accordingly to ensure the safest and most effective approach for neonatal patients. Combining the use of leukodepleted RBCs and implementing strategies to minimize donor exposure can contribute to enhanced transfusion practices in this vulnerable population.

Table 2

Overview of the international guidelines and thresholds for hemoglobin transfusion.

	British Committee for Standards in Haematology (2016)[99]	Australian National Blood Authority (2016)[100]	Canadian Blood Services (2017)[101]
24 h	< 10 g/dl		
1 Week	< 10 g/dl	10–12 g/dl	10 g/dl
2 Weeks	< 7.5 g/dl	8.5–11 g/dl	8.5 g/dl
3 Weeks	< 7.5 g/dl	7–10 g/dl	7.5 g/dl

Overview of the international guidelines and thresholds for platelet transfusion.

	British Committee for Standards in Haematology (2016)	Australian National Blood Authority (2016)	Canadian Blood Services (2017)	Dutch Guidelines Quality Council (2019)[102]
Prophylactic in stable infant	25×10^9/L	$10–20 \times 10^9$/L	20×10^9/L	25×10^9/L
Bleeding or invasive procedure	50×10^9/L	50×10^9/L	50×10^9/L	50×10^9/L

Complications

Distinct physiological variations in this population result in unique metabolic challenges that are not commonly encountered in other groups. The administration of blood products in terms of type, dosage, infusion rate, monitoring, triggers, and the complexity of the processes involved, such as warming and infusion through rate monitoring devices, can introduce a new set of potential errors and complications. Furthermore, the specific blood components and indications for transfusion may differ significantly in this particular group of patients.

Hyperkalemia

Plasma potassium (K^+) levels rise during whole blood (WB) and RBC storage due to intracellular K^+ leakage produced by the suppression of the membrane Na^+/K^+ ATPase pump. At day 35, a unit of CPDA-1 WB had ~25 mEq/L of K^+, whereas RBCs contain roughly 75–100 mEq/L, resulting in ~8 mEq of K^+ per unit. This higher K^+ level would not be a problem for low-volume transfusions (10–20 ml/kg), given the infant's daily K^+ need is typically ~1–3 mEq/kg/day[63]. However, serious hyperkalemia can arise with large-volume transfusions or if the kidneys of infants are unable to eliminate K^+ properly[64]. A faster rate or use of central lines that deliver a high K^+ load directly to the heart can potentially lead to arrhythmias, including cardiac arrest[55], making it essential to monitor K^+ levels and cautiously administer transfusions in such situations.

In neonatal settings, it is advisable to refrain from utilizing irradiated blood beyond 24 h of storage[56]. Particular attention must be paid to prevent mechanical lysis of cells during the infusion process. To mitigate the potential risks associated with radiant warmers or phototherapy lights, it is recommended to shield blood transfusion tubing with aluminum foil. While inline potassium adsorption filters or washing have demonstrated efficacy in removing extracellular K^+ from RBC units, their routine implementation may not always be feasible in practical clinical scenarios[53,65]. Thus, careful consideration should be exercised when determining their application.

Hypothermia

The increased vulnerability of infants to hypothermia can be attributed to several factors, including reduced body fat, underdeveloped epidermal barrier, and higher surface area-to-weight ratio. Certain groups of infants are at a higher risk, such as those undergoing extracorporeal membrane oxygenation (ECMO), ETs, cardiac surgery, or trauma. Additionally, it has been observed that transfusing blood products at room temperature can further contribute to a decrease in the infant's core body temperature by ~0.7–2.5°C[54,66].

It is highly recommended to use blood warmers specifically designed for blood administration purposes[67]. Among the available technologies, counter-current technology for warming has been identified as the most effective method for ensuring safe and efficient blood warming during transfusions[68].

Glucose homeostasis

Both hypoglycemia and hyperglycemia are associated with blood transfusions in neonates. It is possible that the infants at risk of developing these conditions are also the ones more likely to receive a transfusion[69]. Neonates exhibit reduced glycogen stores and mucosal G-6-phosphatase levels, which contribute to glucose fluctuations. Additionally, glucose concentrations in stored blood units are known to decline over time[70]. Following transfusion, glucose levels have been reported to decrease, often without noticeable symptoms. However, mild symptoms can be observed in infants, particularly in those undergoing ET[71]. Studies have shown the incidence of hypoglycemia in infants with erythroblastosis fetalis to range from 2% to 20%[66].

It is imperative to identify and monitor infants who are at a risk of developing complications during blood transfusion. To ensure safe administration, blood products should be transfused through a separate intravenous line while being cautious to administer maintenance fluids at a slower rate to prevent fluid overload. If the infusion rate is reduced, it may be necessary to adjust the glucose concentration of the fluid to maintain appropriate glucose levels in the infant's bloodstream[1].

2,3-Diphosphoglycerate

During storage of RBCs, the concentration of 2,3-diphosphoglycerate rapidly decreases. This leads to a leftward shift in the Hb–oxygen dissociation curve, resulting in reduced oxygen release from RBCs to the tissues[72]. Regeneration of 2,3-diphosphoglycerate typically takes between 3 and 8 h after the transfusion of one unit of RBCs[73]. Infants under the age of 4 months cannot compensate as efficiently as older patients, who can respond to the resulting hypoxia by increasing their heart rate[74]. This highlights the importance of careful monitoring and consideration of oxygenation in young infants after RBC transfusion.

Advantages of current guidelines

Preterm infants often suffer from anemia and thrombocytopenia, and the majority of them require at least one blood transfusion within the first few weeks of life. To prevent these conditions, it is essential to implement effective measures such as delayed cord

Shafique et al. Annals of Medicine & Surgery (2024)

Annals of Medicine & Surgery

clamping and minimizing iatrogenic blood loss. Although older guidelines were developed based on available trials at the time, they have some advantages. A liberal transfusion threshold can significantly increase Hb levels and reduce the time on ventilator or CPAP for preterm infants. Additionally, it may decrease the time on supplemental oxygen and improve Htc levels. Both liberal and restrictive transfusion thresholds are safe and effective strategies for RBC transfusion in anemic preterm infants, but the liberal strategy may be more effective in reducing the need for respiratory support. However, liberal thresholds are also associated with greater morbidity and mortality, despite being more efficacious. At that time, the major concern was the safety profile rather than the efficacy.

Guidelines for RBC transfusion

RBC transfusions are expected to be administered to 90% of ELBW newborns and 58% of preterm children born before 32 weeks of gestation[75] for medical reasons. RBC transfusions may benefit these populations in the management of anemia, enhancement of oxygenation, reinforcement of cardiovascular stability (premature infants frequently have immature cardiovascular systems, making them more vulnerable to variations in blood pressure and cardiac output), enhanced weight gain and growth, avoidance of apneas, and enhancement of growth parameters[33].

The choice between restrictive and liberal blood transfusion methods for preterm infants has been a topic of investigation and debate within the medical profession, with the decision between the two options depending on the specific clinical circumstances and desired outcomes. Restrictive transfusion practices may be harmful to preterm infants, as evidenced by the higher incidence of periventricular leukomalacia and frequent episodes of apnea in the restrictive group than in the liberal group, according to the results of a randomized control trial mentioned in Table 4[76]. Similar rates of patent ductus arteriosus (PDA), IVH, and retinopathy of prematurity (ROP) were observed in both the liberal and restrictive transfusion groups in a different study. To prevent chronic liver disease in very low birth weight (VLBW) infants, the study recommended stringent criteria for limiting the total volume of transfusion to less than 30 ml[77]. In a different randomized control trial, the low-threshold group had rates of 74.0%, and the high-threshold group had rates of 69.7% for the primary outcome [ROP, BPD (bronchopulmonary dysplasia), brain injury]; however, there were no significant differences in the secondary outcome (Hb level, number of RBC transfusions, serum ferritin) between the two groups[78]. Table 4 provides an overview of trials related to RBC transfusions.

Platelet transfusion guidelines

Recent studies suggest that newborns with elevated predicted baseline risks are at a similar risk of harm at a higher transfusion threshold than those with lower predicted baseline risks, despite recommendations in certain protocols that suggest a platelet transfusion threshold of $> 25 \times 10^9$/L for neonates with higher baseline risks. It is important to note that other factors such as gestational age, past significant bleeding incidents, and assigned treatment were independently associated with the outcomes. Several prediction models have consistently demonstrated the predictive role of gestational age in bleeding and mortality, which aligns with the findings of the PlaNeT-2 trial. This study revealed a surprising overall advantage of a preventative platelet transfusion threshold of 25×10^9/L compared to 50×10^9/L in reducing the risk of major bleeding and/or death in preterm newborns. Additionally, there is a noticeable decrease in risk across all risk categories[79]. Premature infants are often prone to developing isolated thrombocytopenia, a condition characterized by low platelet levels in the blood that can result in bleeding. Prophylactic platelet transfusions are frequently performed to prevent this complication. This approach has several benefits, including supporting hemostasis, reducing the likelihood of transfusion triggers, and lowering the risk of bleeding and/or mortality, particularly when a low platelet transfusion threshold is used. Recent studies, including the PlaNeT trial, have reported similar results, challenging the current outdated guidelines and recommendations governing the use of platelet transfusions in this vulnerable population. Therefore, it is imperative to conduct immediate and innovative trials to address this issue, while controlling for other confounding factors. The results of these trials warrant a thorough re-evaluation of the current guidelines and recommendations to ensure optimal patient care.

WBC transfusion guidelines

Previous medical research has not demonstrated significant advantages of using leukocyte concentrates in neonatal transfusion procedures. Conversely, current guidelines recommend leukodepletion of all cellular products, except for those containing granulocytes (WBCs $<1 \times 10^6$/unit), as they effectively prevent non-hemolytic fever reactions, reduce the risk of alloimmunization, and decrease the likelihood of cytomegalovirus (CMV) transmission[41]. While granulocyte concentrates have been suggested as a potential therapeutic option for neonates suffering from severe neutropenia resulting from antibiotic-resistant sepsis, the optimal dose remains unclear. However, some studies have recommended administering $1-2 \times 10^9$ granulocytes per kilogram of body weight. It is important to ensure that the granulocyte concentrate is ABO-compatible with the recipient, as it is heavily contaminated with RBCs. Additionally, the concentrate must be RhD-compatible (i.e. RhD-negative for RhD-negative females) and irradiated to a minimum dose of 25 Gy before administration. Ideally, the concentrate should also be CMV seronegative. Although the optimal duration of therapy is not well established, multiple daily infusions of the appropriate dose have been associated with improved outcomes[80].

In the early 2000s, a meta-analysis was conducted, which revealed that there were no statistically significant differences in terms of morbidity or mortality between neonates who were treated with granulocyte concentrates and those who were treated with the 'standard' method of care[81]. Thus, considering the potential serious side effects (transmission of infections), it is current practice to use recombinant granulocyte growth factors (recombinant granulocyte colony-stimulating factor and recombinant granulocyte–monocyte colony-stimulating factor) as an alternative[80].

Conclusion

Newborn infants possess unique physiological and hematological characteristics that require specialized approaches for blood transfusions. This study highlights the importance of individualized therapeutic strategies that consider factors such as

Table 4

Overview of RBC trials.

References	Objective	Sample size	Inclusion criteria	Primary outcome	Results
Bell et al.[76]	To ascertain whether restrictive guidelines regarding red blood cell (RBC) transfusions for preterm infants can decrease the quantity of transfusions without causing negative effects.	100	100 hospitalized preterm infants with birth weights of 500–1300 g were enrolled in a randomized clinical trial. Infants were excluded if they had alloimmune hemolytic disease, congenital heart disease (including significant patent ductus arteriosus), other major birth defect requiring surgery, or a chromosomal abnormality.	Infants in the liberal transfusion group received more RBC transfusions. However, the number of donors to whom the infants were exposed was not significantly different. Infants in the restrictive transfusion group were more likely to have intraparenchymal brain hemorrhage or periventricular leukomalacia, and they had more frequent episodes of apnea, including both mild and severe episodes.	Although both transfusion programs were well tolerated, the finding of more frequent major adverse neurologic events in the restrictive RBC transfusion group suggests that the practice of restrictive transfusions may be harmful to preterm infants.
Chen et al.[82]	To determine the impact of blood transfusions on the outcomes of preterm infants with extremely low body weights using two distinct transfusion criteria.	36	NICU-admitted premature newborns weighing <1500 g who did not have a major birth defect or chromosomal abnormality were included in the study.	Infants in the liberal group received a larger PRBC transfusion volume compared with the restrictive group over 30 days (41.7 ± 20.1 vs. 27.2 ± 15.9 ml, $P = 0.029$). There were no significant differences in the proportion of patients with respiratory distress syndrome, patent ductus arteriosus, severe intraventricular hemorrhage, ROP, or CLD between the two groups.	Both criteria of PRBC transfusion had similar clinical outcomes, although liberal transfusion resulted in a greater amount of blood transfused and a low reticulocyte count at 30 days of age. We suggest restrictive criteria for minimizing the overall amount of transfusion to <30 ml may be a better way of preventing CLD in VLBW infants.
Kirpalani et al.[78]	To determine whether extremely low birth weight infants (ELBW) transfused at lower hemoglobin thresholds versus higher thresholds have different rates of survival or morbidity at discharge.	451	At the time of enrollment, the babies had to be 48 h old, have a gestational age of 31 weeks, and weigh 1000 g at birth. Exclusion criteria included having cyanotic heart disease, congenital anemia, acute shock, transfusion after 6 h of life, known parental resistance to transfusions, a family history of hemolytic illness and anemia, or a situation in which the attending physician planned to use erythropoietin.	Rates of the primary outcome (ROP, BPD, brain injury) were 74.0% in the low-threshold group and 69.7% in the high. There were no statistically significant differences between groups in any secondary outcome (Hb level, number of RBC transfusion, rate of growth, and serum ferritin).	In extremely low birth weight infants, maintaining a higher hemoglobin level results in more infants receiving transfusions but confers little evidence of benefit.
Liao et al.[83]	To analyze the related risk factors in blood transfusions for extremely low birth weight infants and extreme preterm infants.	36/24	Gestational age <28 weeks; birth weight <1000 g.	Higher rates of blood transfusion would result from a smaller birth weight, a longer hospital stay, a younger gestational age, and a larger blood collection within 2 weeks of delivery.	Blood transfusion in extremely low birth weight infants and extreme preterm infants is associated with an increased risk of apnea, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, and patent ductus arteriosus.
Duan et al.[84]	To investigate the association of anemia with the development of bronchopulmonary dysplasia (BPD) in preterm infants.	71/1721	Gestational age (GA) <32 weeks.	The rate of early anemia in BPD patients was higher than non-BPD patients. Low Hct levels were closely related to BPD in preterm infants.	Early anemia (≤ 14 days) is a significant risk factor for BPD.
Ghirardello et al.[85]	To evaluate the association between red blood cell (RBC) transfusions on the risk of death, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC) in very low birth weight (VLBW) infants.	269/372	Birth weight <100 g.	Transfusions were associated with the risk of developing the composite outcome, independently from other conditions; this risk correlated with several transfusions > 3.	An association was observed between RBC transfusions in the first 28 days of life and the risk of developing the composite outcome of death, ROP, BPD, or NEC in a cohort of VLBW infants.
Cai et al.[86]	To create and validate a BPD risk prediction model, as well as to assess the risk factors for bronchopulmonary dysplasia (BPD) in very low birth weight infants (VLBWIs).	63/388	Gestational age <32 weeks; birth weight <1500 g.	Neonatal asphyxia, the positive rate of sputum culture, neonatal sepsis, neonatal respiratory distress syndrome (NRDS), blood transfusions (≥ 3), patent ductus arteriosus (PDA), the time of invasive mechanical ventilation, the duration of	The risk prediction model has a good predictive effect for the risk of BPD in VLBWIs, and can provide a reference for preventive treatment and nursing intervention.

Table 4

(Continued)

References	Objective	Sample size	Inclusion criteria	Primary outcome	Results
				oxygen therapy, and the time of parenteral nutrition were the independent risk factors of BPD. Verification of prediction model showed a sensitivity of 92.9% and a specificity of 76%, demonstrating that the effects of this model were satisfactory.	
Gao *et al.*[87]	To investigate the association between ultrasound findings and preterm infants with bronchopulmonary dysplasia (BPD).	32/49	Gestational age ≤ 28 weeks or birth weight ≤ 1500 g.	Between June 2018 and June 2019, the incidence of BPD was 39.5% among the 81 preterm newborns recruited. There were 46 male and 35 female newborns, with a gestational age of 29.71 ± 2.27 weeks and a birth weight of 1189.5 ± 184.5 g on average. The average hospitalization day for BPD patients was 58.8 days.	Lung ultrasonography scores enable monitoring of lung aeration and function in extremely preterm newborns, and gestational age-adjusted values, beginning on the seventh day of life, strongly predict the likelihood of BPD.
Park *et al.*[88]	The iron status of extremely low birth weight newborns receiving numerous erythrocyte transfusions during hospitalization in the neonatal intensive care unit (NICU) was investigated.	10/36	Gestational age (weeks): 30 ± 2 and birth weight (g) <1500 g.	One-fourth of the women were iron deficient, and more than half were anemic; nonetheless, no children were born with anemia or iron deficiency. The babies' mean blood levels at discharge was 328.8 ± 328.0 ng/ml (range: 33.8–1510.0 ng/ml). During their stay in the NICU, no newborns were iron-deficient. Erythrocyte transfusions were given to 38 of the VLBW neonates. ROP, BPD, necrotizing enterocolitis, and intraventricular hemorrhage occurred at rates of 24%, 24%, 0%, and 2%, respectively.	Very low birth weight neonates that received several erythrocyte transfusions had high iron reserves, and non-transfused newborns may also be at risk of iron overload during NICU hospitalization.
Lardon-Fernandez *et al.*[89]	To investigate the epidemiological variables and morbidity related to the development of BPD in a group of VLBW premature babies.	60/69	Preterm infants with birth weight ≤ 1500 g.	The BPD prevalence in the sample was most frequent for the mild grade (28.4%) followed by moderate (11.2%) and severe (6%).	Respiratory assistance, feeding, and various forms of medication were all risk factors for the development of BPD. Furthermore, individuals with BPD experienced more related morbidity than those who did not acquire BPD.
Go *et al.*[90]	To investigate the prenatal variables that influence RDW and to determine whether RDW might be a possible biomarker for BPD.	85/91	GA <30 weeks.	Small for gestational age (SGA), chorioamnionitis (CAM), hypertensive disorders of pregnancy (HDP), gestational age, and birth weight were significantly associated with RDW at birth. SGA, BPD, and red blood cell (RBC) transfusion before days of life (DOL 14) were associated with RDW at DOL 14. BPD and RBC transfusion before DOL 14 were associated with RDW at DOL 28. Compared with non-BPD infants, mean RDW at birth DOL 14 and DOL 28 were significantly higher in BPD infants. Multivariate analysis revealed that RDW at DOL 28 was significantly higher in BPD infants.	We conclude that RDW at DOL 28 might be used as a biomarker to predict BPD severity. The mechanism by which RDW at DOL 28 is linked to the pathophysiology of BPD requires more investigation.
Sharma *et al.*[91]	To identify risk factors for moderate/severe BPD in an era of widespread availability of NIV in the DR.	155/108	Gestational age 23–27 weeks.	On logistic regression, birth weight, gender, oxygen concentration, cumulative duration of oxygen and MV, surfactant, and blood transfusions predicted moderate/severe BPD. Duration of oxygen and MV	Early failures of non-invasive ventilation (NIV) represent opportunities for improvement of NIV techniques and of non-invasive surfactant to avoid intubation in the first 48 h. Furthermore, these risk

				were shown to be the most important predictors for moderate/severe BPD.	factors may allow earlier identification of infants most likely to benefit from interventions to prevent or decrease severity of BPD.
Lee *et al.*[92]	To analyze the relationship between RBC transfusion and short-term outcomes in very low birth weight (VLBW) infants.	109/141	Birth weight <1500 g.	Univariate analysis revealed that all short-term outcomes except early-onset sepsis and patent ductus arteriosus were associated with RBC transfusion. In multivariate analysis adjusted for gestational age, birth weight and Apgar score at 1 min, RBC transfusion was significantly correlated with BPD.	RBC transfusion is significantly associated with adverse clinical outcomes such as necrotizing enterocolitis (NEC) and bronchopulmonary dysplasia (BPD) in VLBW infants.
Patel *et al.*[93]	To evaluate the association between the cumulative dose of enteral iron supplementation, total volume of RBCs transfused, and risk of bronchopulmonary dysplasia (BPD) in VLBW infants.	240/358	Birth weight <1500 g.	In multivariable analyses, a greater cumulative dose of supplemental enteral iron exposure was associated with an increased risk of BPD. Similarly, a greater volume of RBCs transfused was associated with a higher risk of BPD.	The cumulative dose of supplemental enteral iron exposure and total volume of RBC transfusion are both independently associated with an increased risk of BPD in VLBW infants.
Raffa *et al.*[94]	Association between blood transfusions and the development and severity of retinopathy of prematurity (ROP).	5/106	Gestational age <30 weeks; birth weight <1500 g.	Compared to non-transfused infants, those who were transfused had a lower GA, a lower BW, a longer stay in the NICU, and received significantly more artificial ventilation. These infants also had a higher number of comorbidities, including sepsis and intraventricular hemorrhage. The number and volume of RBCs at day 30 were significantly higher in infants with any stage of ROP than in those without ROP.	A higher frequency and volume of RBC transfusion were associated with an increased risk of ROP development.
Jassem-Bobowicz *et al.*[95]	To develop a multifactorial model that allows the prediction of bronchopulmonary dysplasia (BPD) in preterm newborns.	127/151	Gestational age <32 weeks.	The significant risk factors for BPD in the multivariate analysis were gestational age, number of red blood cell concentrate transfusions, number of surfactant administrations, and hemodynamically significant patent ductus arteriosus. The combination of these factors determined the risk of developing BPD, with an AUC value of 0.932. A multifactorial predictive model based on these factors, weighted by their odds ratios, identified four categories of newborns with mean BPD risks of 9%, 59%, 82%, and 100%.	A multifactorial model based on easily available clinical factors can predict BPD risk in preterm newborns and inform potential preventive measures.
Tao *et al.*[96]	To investigate the predictors of bronchopulmonary dysplasia in neonates with respiratory distress syndrome (RDS).	102/523	Neonates with respiratory distress syndrome (RDS).	Bivariate analysis and multivariate logistic-regression analyses revealed that birth weight, gestational age under 32 weeks, duration of oxygen therapy over 10 days, asphyxia, patent ductus arteriosus, transfusion of red blood cells (packed red blood cells), and surfactant use were significantly associated with the development of BPD.	Birth weight, gestational age <32 weeks, total duration of oxygen therapy > 10 days, asphyxia, patent ductus arteriosus, need for red blood cell infusion, and the use of pulmonary surfactant were important predictors of BPD in neonates with RDS.

CLD, chronic liver disease.

Shafique et al. Annals of Medicine & Surgery (2024)

Annals of Medicine & Surgery

gestational age, birth weight, and hematological parameters. The distinct physiology of newborns, including their cardiovascular, respiratory, and renal systems, highlights the differences between neonates and adults that affect transfusion practices. Recent trials with rigorous designs and control of confounding factors have raised questions regarding the effectiveness of liberal transfusion strategies for preterm infants. These findings call for further investigation and the development of appropriate guidelines for this population group.

Ethical approval

As we are submitting a review article, we do not require ethical approval from any department.

Consent

This study does not include any individual patient, so no consent will be required.

Sources of funding

The authors received no extramural funding for the study.

Author contribution

M.A.S.: supervision and analysis; A.M.C., U.H., S.Q.A., and T. K.F.A.: literature search and screening; A.M.: data extraction. The initial draft was prepared by S.Q.A. and U.H. The final revision of the draft was done by M.A.S.

Conflicts of interest disclosure

The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
2. Unique identifying number or registration ID: not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): not applicable.

Guarantor

All authors take responsibility for the work, access to data, and decision to publish.

Data availability statement

Not applicable.

Provenance and peer review

Not applicable.

Acknowledgement

Not applicable.

References

[1] Kim DH. Transfusion practice in neonates. Korean J Pediatr 2018;61: 265–70.
[2] Venkatesh V, Khan R, Curley A, et al. How we decide when a neonate needs a transfusion. Br J Haematol 2013;160:421–33.
[3] Murray NA, Roberts IA. Neonatal transfusion practice. Arch Dis Child Fetal Neonatal Ed 2004;89:F101–7.
[4] Colombatti R, Sainati L, Trevisanuto D. Anemia and transfusion in the neonate. Semin Fetal Neonatal Med 2016;21:2–9.
[5] Hines MH. Neonatal cardiovascular physiology. Semin Pediatr Surg 2013;22:174–8.
[6] Friedman AH, Fahey JT. The transition from fetal to neonatal circulation: normal responses and implications for infants with heart disease. Semin Perinatol 1993;17:106–21.
[7] Askin DF. Fetal-to-neonatal transition--what is normal and what is not? Neonatal Netw 2009;28:e33–40.
[8] Jaeggi E, Öhman A. Fetal and neonatal arrhythmias. Clin Perinatol 2016;43:99–112.
[9] Sottas CE, Cumin D, Anderson BJ. Blood pressure and heart rates in neonates and preschool children: an analysis from 10 years of electronic recording. Paediatr Anaesth 2016;26:1064–70.
[10] Malia RG, Preston FE, Mitchell VE. Evidence against vitamin K deficiency in normal neonates. Thromb Haemost 1980;44:159–60.
[11] Stocks J. Respiratory physiology during early life. Monaldi Arch Chest Dis 1999;54:358–64.
[12] Gonzalez LP, Pignaton W, Kusano PS, et al. Anesthesia-related mortality in pediatric patients: a systematic review. Clinics (Sao Paulo) 2012; 67:381–7.
[13] Davis RP, Mychaliska GB. Neonatal pulmonary physiology. Semin Pediatr Surg 2013;22:179–84.
[14] Daniels CB, Orgeig S. Pulmonary surfactant: the key to the evolution of air breathing. News Physiol Sci 2003;18:151–7.
[15] Nkadi PO, Merritt TA, Pillers DA. An overview of pulmonary surfactant in the neonate: genetics, metabolism, and the role of surfactant in health and disease. Mol Genet Metab 2009;97:95–101.
[16] Doherty TM, Hu A, Salik I. Physiology, Neonatal. StatPearls Publishing; 2023.
[17] Guignard JP, Torrado A, Da Cunha O, et al. Glomerular filtration rate in the first three weeks of life. J Pediatr 1975;87:268–72.
[18] Davis BB, Zenser TV. Evaluation of renal concentrating and diluting ability. Clin Lab Med 1993;13:131–4.
[19] Baum M, Quigley R. Maturation of proximal tubular acidification. Pediatr Nephrol 1993;7:785–91.
[20] Sulemanji M, Vakili K. Neonatal renal physiology. Semin Pediatr Surg 2013;22:195–8.
[21] Bhatia J. Fluid and electrolyte management in the very low birth weight neonate. J Perinatol 2006;26(Suppl 1):S19–21.
[22] Indrio F, Neu J, Pettoello-Mantovani M, et al. Development of the gastrointestinal tract in newborns as a challenge for an appropriate nutrition: a narrative review. Nutrients 2022;14:1405.
[23] Jacobi SK, Odle J. Nutritional factors influencing intestinal health of the neonate. Adv Nutr 2012;3:687–96.
[24] Trahair JF. Is fetal enteral nutrition important for normal gastrointestinal growth? A discussion. JPEN J Parenter Enteral Nutr 1993;17: 82–5.
[25] Dahlen HG, Foster JP, Psaila K, et al. Gastro-oesophageal reflux: a mixed methods study of infants admitted to hospital in the first 12 months following birth in NSW (2000–2011). BMC Pediatr 2018; 18:30.
[26] MohanKumar K, Kaza N, Jagadeeswaran R, et al. Gut mucosal injury in neonates is marked by macrophage infiltration in contrast to pleomorphic infiltrates in adult: evidence from an animal model. Am J Physiol Gastrointest Liver Physiol 2012;303:G93–102.
[27] McKenney WM. Understanding the neonatal immune system: high risk for infection. Crit Care Nurse 2001;21:35–47.
[28] Brook B, Harbeson D, Ben-Othman R, et al. Newborn susceptibility to infection vs. disease depends on complex in vivo interactions of host and pathogen. Semin Immunopathol 2017;39:615–25.

[29] Gollwitzer ES, Marsland BJ. Impact of early-life exposures on immune maturation and susceptibility to disease. Trends Immunol 2015;36: 684–96.

[30] Tsafaras GP, Ntontsi P, Xanthou G. Advantages and limitations of the neonatal immune system. Front Pediatr 2020;8:5.

[31] Olin A, Henckel E, Chen Y, et al. Stereotypic immune system development in newborn children. Cell 2018;174:1277–92.e14.

[32] Basha S, Surendran N, Pichichero M. Immune responses in neonates. Expert Rev Clin Immunol 2014;10:1171–84.

[33] Howarth C, Banerjee J, Aladangady N. Red blood cell transfusion in preterm infants: current evidence and controversies. Neonatology 2018; 114:7–16.

[34] Wang YC, Chan OW, Chiang MC, et al. Red blood cell transfusion and clinical outcomes in extremely low birth weight preterm infants. Pediatr Neonatol 2017;58:216–2.

[35] Markham C, Small S, Hovmand P, et al. Transfusion decision making in pediatric critical illness. Pediatr Clin North Am 2017;64:991–1015.

[36] Bailey SM, Mally PV. Review of splanchnic oximetry in clinical medicine. J Biomed Opt 2016;21:091306.

[37] Harer MW, Adegboro CO, Richard LJ, et al. Non-invasive continuous renal tissue oxygenation monitoring to identify preterm neonates at risk for acute kidney injury. Pediatr Nephrol 2021;36:1617–25.

[38] Aher SM, Ohlsson A. Early versus late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2020;2:CD004865.

[39] Ohls RK, Christensen RD, Kamath-Rayne BD, et al. A randomized, masked, placebo-controlled study of darbepoetin alfa in preterm infants. Pediatrics 2013;132:e119–27.

[40] Lemyre B, Sample M, Lacaze-Masmonteil T. Minimizing blood loss and the need for transfusions in very premature infants. Paediatr Child Health 2015;20:451–62.

[41] Girelli G, Antoncecchi S, Casadei AM, et al. Recommendations for transfusion therapy in neonatology. Blood Transfus 2015;13:484–97.

[42] Christensen R, Henry E, Wiedmeier S, et al. Thrombocytopenia among extremely low birth weight neonates: data from a multihospital healthcare system. J Perinatol 2006;26:348–53.

[43] Bonifacio L, Petrova A, Nanjundaswamy S, et al. Thrombocytopenia-related neonatal outcome in preterms. Indian J Pediatr 2007;74:269–74.

[44] Guida JD, Kunig AM, Leef KH, et al. Platelet count and sepsis in very low birth weight neonates: is there an organism-specific response? Pediatrics 2003;111:1411–5.

[45] Aballi AJ, Puapondh Y, Desposito F. Platelet counts in thriving premature infants. Pediatrics 1968;42:685–9.

[46] Walsh B. Neonatal and 5-year outcomes after birth at 30–34 weeks of gestation. Obstet Gynecol 2007;110:1171–2.

[47] Reddy PA, Sreenivasulu H, Shokrolahi M, et al. Navigating the complexities of intraventricular hemorrhage in preterm infants: an updated review. Cureus 2023;15:e38985.

[48] Cecchetti G, Binda A, Piperno A, et al. Cardiac alterations in 36 consecutive patients with idiopathic haemochromatosis: polygraphic and echocardiographic evaluation. Eur Heart J 1991;12:224–30.

[49] Dykes FD, Lazzara A, Ahmann P, et al. Intraventricular hemorrhage: a prospective evaluation of etiopathogenesis. Pediatrics 1980;66:42–9.

[50] Murray N, Howarth L, McCloy M, et al. Platelet transfusion in the management of severe thrombocytopenia in neonatal intensive care unit patients. Transfus Med 2002;12:35–41.

[51] Stanworth SJ. Thrombocytopenia, bleeding, and use of platelet transfusions in sick neonates. Hematology Am Soc Hematol Educ Program 2012;2012:512–6.

[52] Muthukumar P, Venkatesh V, Curley A, et al. Severe thrombocytopenia and patterns of bleeding in neonates: results from a prospective observational study and implications for use of platelet transfusions. Transfus Med 2012;22:338–43.

[53] Balasubramanyam P, Basavarajegowda A, Hanumanthappa N, et al. Irradiating stored blood and storing irradiated blood: is it different? – A study of serial changes in biochemical parameters of red blood cell units. Asian J Transfus Sci 2021;15:172–8.

[54] Laptook AR, Salhab W, Bhaskar B. Admission temperature of low birth weight infants: predictors and associated morbidities. Pediatrics 2007; 119:e643–9.

[55] Maclaine Pont J, Hack WW, Sobotka-Plojhar M, et al. 2 newborn infants with severe arrhythmia caused by hyperkalemia. Tijdschr Kindergeneeskd 1987;55:28–32.

[56] Eshghifar N, Maghsudlu M, Amini Kafi-Abad S. The effect of pre-storage irradiation blood on quality of red blood cells. Int J Hematol Oncol Stem Cell Res 2021;15:1–6.

[57] Strauss RG, Sacher RA, Blazina JF, et al. Commentary on small-volume red cell transfusions for neonatal patients. Transfusion 1990;30: 565–70.

[58] Fanaroff JM, Fanaroff AA. Blood pressure disorders in the neonate: hypotension and hypertension. Semin Fetal Neonatal Med 2006;11: 174–81.

[59] Fergusson D, Hébert PC, Lee SK, et al. Clinical outcomes following institution of universal leukoreduction of blood transfusions for premature infants. JAMA 2003;289:1950–6.

[60] Spinella PC, Dressler A, Tucci M, et al. Survey of transfusion policies at US and Canadian children's hospitals in 2008 and 2009. Transfusion 2010;50:2328–35.

[61] Fergusson DA, Hébert P, Hogan DL, et al. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very-low-birth-weight infants: the ARIPI randomized trial. JAMA 2012;308:1443–51.

[62] Motta M, Testa M, Tripodi G, et al. Changes in neonatal transfusion practice after dissemination of neonatal recommendations. Pediatrics 2010;125:e810–7.

[63] Opoku-Okrah C, Acquah BK, Dogbe EE. Changes in potassium and sodium concentrations in stored blood. Pan Afr Med J 2015;20:236.

[64] Hall TL, Barnes A, Miller JR, et al. Neonatal mortality following transfusion of red cells with high plasma potassium levels. Transfusion 1993;33:606–9.

[65] Fujita H, Teratani M, Hazama Y, et al. Use of potassium adsorption filter for the removal of ammonia and potassium from red blood cell solution for neonates. Transfusion 2018;58:2383–7.

[66] Jackson JC. Adverse events associated with exchange transfusion in healthy and ill newborns. Pediatrics 1997;99:E7.

[67] Poder TG, Pruneau D, Dorval J, et al. Pressure infusion cuff and blood warmer during massive transfusion: an experimental study about hemolysis and hypothermia. PLoS One 2016;11:e0163429.

[68] Uhl L, Pacini D, Kruskall MS. A comparative study of blood warmer performance. Anesthesiology 1992;77:1022–8.

[69] Arsenault D, Brenn M, Kim S, et al. A.S.P.E.N. Clinical Guidelines: hyperglycemia and hypoglycemia in the neonate receiving parenteral nutrition. JPEN J Parenter Enteral Nutr 2012;36:81–95.

[70] Fowden AL, Mundy L, Ousey JC, et al. Tissue glycogen and glucose 6-phosphatase levels in fetal and newborn foals. J Reprod Fertil Suppl 1991;44:537–42.

[71] Schiff D, Aranda JV, Colle E, et al. Metabolic effects of exchange transfusion. II. Delayed hypoglycemia following exchange transfusion with citrated blood. J Pediatr 1971;79:589–93.

[72] Sharma S, Brugnara C, Betensky RA, et al. Reductions in red blood cell 2,3-diphosphoglycerate concentration during continuous renal replacment therapy. Clin J Am Soc Nephrol 2015;10:74–9.

[73] Beutler E, Wood L. The in vivo regeneration of red cell 2,3 diphosphoglyceric acid (DPG) after transfusion of stored blood. J Lab Clin Med 1969;74:300–4.

[74] James LS, Rowe RD. The pattern of response of pulmonary and systemic arterial pressures in newborn and older infants to short periods of hypoxia. J Pediatr 1957;51:5–11.

[75] Wang Y-C, Chan O-W, Chiang M-C, et al. Red blood cell transfusion and clinical outcomes in extremely low birth weight preterm infants. Pediatr Neonatol 2017;58:216–2.

[76] Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. Pediatrics 2005;115:1685–91.

[77] Chen HL, Tseng HI, Lu CC, et al. Effect of blood transfusions on the outcome of very low body weight preterm infants under two different transfusion criteria. Pediatr Neonatol 2009;50:110–6.

[78] Kirpalani H, Whyte RK, Andersen C, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. J Pediatr 2006;149:301–7.

[79] Fustolo-Gunnink SF, Fijnvandraat K, van Klaveren D, et al. Preterm neonates benefit from low prophylactic platelet transfusion threshold despite varying risk of bleeding or death. Blood 2019;134:2354–60.

[80] New HV, Berryman J, Bolton-Maggs PH, et al. Guidelines on transfusion for fetuses, neonates and older children. Br J Haematol 2016;175: 784–828.

Shafique et al. Annals of Medicine & Surgery (2024)

Annals of Medicine & Surgery

[81] Mohan P, Brocklehurst P. Granulocyte transfusions for neonates with confirmed or suspected sepsis and neutropaenia. Cochrane Database Syst Rev 2003;4:CD003956.

[82] Chen H-L, Tseng H-I, Lu C-C, et al. Effect of blood transfusions on the outcome of very low body weight preterm infants under two different transfusion criteria. Pediatr Neonatol 2009;50:110–6.

[83] Liao Z, Zhao X, Rao H, et al. Analysis of correlative risk factors for blood transfusion therapy for extremely low birth weight infants and extreme preterm infants. Am J Transl Res 2021;13:8179–5.

[84] Duan J, Kong X, Li Q, et al. Association between anemia and bronchopulmonary dysplasia in preterm infants. Sci Rep 2016;6:22717.

[85] Ghirardello S, Dusi E, Cortinovis I, et al. Effects of red blood cell transfusions on the risk of developing complications or death: an observational study of a cohort of very low birth weight infants. Am J Perinatol 2017;34:88–95.

[86] Cai H, Jiang L, Liu Y, et al. Development and verification of a risk prediction model for bronchopulmonary dysplasia in very low birth weight infants. Transl Pediatr 2021;10:2533–43.

[87] Gao S, Xiao T, Ju R, et al. The application value of lung ultrasound findings in preterm infants with bronchopulmonary dysplasia. Transl Pediatr 2020;9:93–100.

[88] Park SH, Kim HM. The iron status of very low birth weight infants receiving multiple erythrocyte transfusions during hospitalization in the neonatal intensive care unit. Pediatr Gastroenterol Hepatol Nutr 2015; 18:100–7.

[89] Lardon-Fernandez M, Uberos J, Molina-Oya M, et al. Epidemiological factors involved in the development of bronchopulmonary dysplasia in very low birth-weight preterm infants. Minerva Pediatr 2017;69:42–9.

[90] Go H, Ohto H, Nollet KE, et al. Red cell distribution width as a predictor for bronchopulmonary dysplasia in premature infants. Sci Rep 2021;11:7221.

[91] Sharma A, Xin Y, Chen X, et al. Early prediction of moderate to severe bronchopulmonary dysplasia in extremely premature infants. Pediatr Neonatol 2020;61:290–9.

[92] Lee EY, Kim SS, Park GY, et al. Effect of red blood cell transfusion on short-term outcomes in very low birth weight infants. Clin Exp Pediatr 2020;63:56–62.

[93] Patel RM, Knezevic A, Yang J, et al. Enteral iron supplementation, red blood cell transfusion, and risk of bronchopulmonary dysplasia in very-low-birth-weight infants. Transfusion 2019;59:1675–82.

[94] Raffa LH, Aljohani W. Evaluation of the effect of blood transfusion on retinopathy of prematurity at a tertiary care center in western Saudi Arabia. Cureus 2022;14:e24495.

[95] Jassem-Bobowicz JM, Klasa-Mazurkiewicz D, Żawrocki A, et al. Prediction model for bronchopulmonary dysplasia in preterm newborns. Children (Basel) 2021;8:886.

[96] Tao Y, Han X, Guo WL. Predictors of bronchopulmonary dysplasia in 625 neonates with respiratory distress syndrome. J Trop Pediatr 2022; 68:fmac037.

[97] Andrew M, Vegh P, Caco C, et al. A randomized, controlled trial of platelet transfusions in thrombocytopenic premature infants. J Pediatr 1993;123:285–91.

[98] Curley A, Stanworth SJ, Willoughby K, et al. Randomized trial of platelet-transfusion thresholds in neonates. N Engl J Med 2019;380:242–51.

[99] New HV, Berryman J, Bolton-Maggs PH, et al. Guidelines on transfusion for fetuses, neonates and older children. Br J Haematol 2016;175:784–828.

[100] Neonatal and Paediatrics Steering Committee, Neonatal and Paediatrics Expert Working Group. Patient Blood Management Guidelines: Module 6: Neonatal and Paediatrics, 2016.

[101] Lau W. Neonatal and pediatric transfusion. Transfus Today 2017;13:1–16.

[102] Lopriore E. Updates in red blood cell and platelet transfusions in preterm neonates. American journal of perinatology. 2019;36(S 02):S37–40.