

# Neonatal Anemia

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## ABSTRACT

Neonatal anemia is a public health problem of global concern and has significant associations with many short- and long-term morbidities. Many etiological factors ranging from perinatal physiologic transition, hematological maturation, illnesses, and iatrogenic reasons such as the phlebotomies necessary for laboratory evaluation may be involved, and there is a need for careful clinical decisions. In premature infants, the management of anemia also has to factor in the unique hematological transition seen during development, co-morbidities associated with preterm birth, the severity of illness severity, and all the iatrogenic factors. Untreated severe anemia is known to negatively impact long-term growth and neurodevelopment outcomes, making early diagnosis and treatment imperative. Additionally, there is a lack of consensus about the threshold and timing of packed red blood cell transfusions, and we need further consideration in view of various associated complications. Therefore, clinicians need to focus on preventable causes of anemia such as nutritional deficiencies, chronic illness, and excessive phlebotomy losses. In this article, we attempt to summarize the pathophysiology, etiologies, clinical management, and the opportunities in research in the field of neonatal anemia.

**Keywords:** Erythropoiesis, Hemoglobin, Hematocrit, Packed red blood cell transfusion.

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## INTRODUCTION

Neonatal anemia is a major, globally recognized public health problem that is associated with short- and long-term morbidities.<sup>1-4</sup> It is defined as hemoglobin or hematocrit that is at least two standard deviations below the mean at a particular gestational and/or chronological age, secondary to a reduction in red blood cell (RBC) mass from multiple etiologies.<sup>4,5</sup> Preventable causes of neonatal anemia, especially in term newborns, continue to persist with even greater prevalence in developing and low socioeconomic countries.<sup>4,6,7</sup> The hematocrit can be low because of factors such as iron deficiency, malnutrition, and infections that might be affecting either the mother or the infant in the pre- and postnatal periods.<sup>8</sup> In preterm infants, anemia can become even more severe and complex depending on gestational age and the severity of concomitant illnesses. Up to 80% of extremely preterm and 50% of preterm infants born at <32 weeks' gestational age may need one or more packed red blood cell (pRBC) transfusions.<sup>9-11</sup> And the decision for pRBC transfusions in these infants becomes highly complicated not only because of the associated risks, but also because the thresholds may need to be adjusted vis-à-vis specific diagnoses, the overall severity of illness, and the expected physiological nadirs at those corrected gestational ages.<sup>12-16</sup> In this review, we have summarized the pathophysiology, etiologies, clinical management, and future opportunities in research in the field of neonatal anemia.

## Epidemiology and Etiology

The World Health Organization (WHO) has estimated that greater than one-third of the world's population is anemic. Approximately one-third of all women of reproductive age have low hemoglobin levels, and the rates of anemia are much higher rates in low socioeconomic populations with limited resources and healthcare infrastructure.<sup>4</sup> Current data suggest that severe maternal anemia during the first trimester of pregnancy is associated with a slight increase in preterm birth, and with a non-statistically significant trend towards increased low birth weights.<sup>17,18</sup> Although the exact

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incidence of neonatal anemia is not well-determined, Lee et al. reported that of term infants born to adolescent people, 21% were anemic (Hb <13.0 gm/dL) and 25% had low iron stores (ferritin <76 µg/L).<sup>19</sup>

The etiology of anemia in a newborn is multifactorial, with prenatal factors like maternal malnutrition, iron-deficiency anemia, and infections being the most common.<sup>20</sup> Iron-deficiency anemia affects nearly half of all pregnant women in developing countries and can be easily corrected by supplementation leading to improved neonatal outcomes.<sup>21-23</sup> Each 10 mg increase in iron dose/day is associated with ~15 gm increase in birth weight and a 3% reduction in the risk of low birth weight, with a linear correlation between an increase in mean prenatal hemoglobin and birth weight (each 1 gm/L increase in Hb increased birth weight by 14 gm).<sup>24</sup> Iron supplementation is also important in lactating mothers who are exclusively breastfeeding, for these women and their infants. Chronic fetal hypoxia and placental insufficiency can reduce the transfer of iron stores to the fetus, especially in small-for-gestational age (SGA) infants and infants born to diabetic mothers.<sup>25</sup>

The severity of iron-deficiency anemia can worsen with many concomitant illnesses. Maternal parvo B19 infection, especially when it occurs in the first trimester, can increase the severity of fetal anemia leading to high-output cardiac failure.<sup>26</sup> Excessive

**Table 1:** Neonatal anemia classification based on red cell morphology

| <i>Microcytic anemia</i><br>MCV <90                                                                                         | <i>Normocytic normochromic anemia</i><br>MCV 100–130                                                                             | <i>Macrocytic anemia</i><br>MCV >130                                                                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Iron deficiency<br>Thalassemia<br>Sideroblastic anemia<br>Inborn errors of metabolism of iron metabolism<br>Chronic disease | Acute blood loss<br>Infections<br>Renal failure<br>Liver failure<br>Early phase of iron deficiency anemia<br>Hemolytic disorders | Vitamin B12 deficiency<br>Folic acid deficiency<br>Obstructive jaundice<br>Hypothyroidism<br>PNH<br>Down syndrome<br>Diamond blackfan anemia<br>Myelodysplastic syndromes |

**Table 2:** Neonatal anemia classification based on pathophysiology

| <i>Decreased production</i>                                                                                                                      |                                                                                                                                                                                      | <i>Increased destruction/loss</i>                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Intrinsic</i>                                                                                                                                 | <i>Extrinsic</i>                                                                                                                                                                     | <i>Hemolytic</i>                                                                                                                                                                                                                                                                                                                                                                                                           | <i>Non-hemolytic</i>                                                                                                                                                                                                                                                                                                                       |
| Anemia of prematurity<br>Chronic disease<br>Liver failure<br>Renal failure<br>Small for gestational age<br>Sideroblastic anemia<br>Drugs induced | Iron deficiency anemia<br>Vitamin B12 deficiency<br>Folic acid deficiency<br>Maternal malnutrition<br>Congenital/acquired infections<br>• Parvo B19<br>• CMV<br>• Herpes<br>• Others | Hemoglobinopathies<br>• Thalassemia's<br>• Sickle cell disease<br><br>Enzymopathies<br>• G-6-PD<br>• Pyruvate kinase deficiency<br><br>RBC membrane defects<br>• Hereditary spherocytosis<br>• Elliptocytosis<br>• Ovalocytosis<br><br>Disseminated intravascular coagulopathy<br>Infections (neonatal malaria)<br>Autoimmune hemolytic anemia<br>ABO/Rh incompatibility<br>Minor antigens incompatibility<br>Maternal ITP | Phlebotomy<br>NEC<br>Twin–twin transfusion<br>Peri-partum blood loss<br>• Placental abruption<br>• Placenta previa<br>• Precipitous delivery<br>• Obstetrical accidents involving the placenta<br>• Forceps delivery<br>• Cord avulsion<br>Birth trauma<br>• Subgaleal hemorrhage<br>cephalohematoma<br><br>Hemorrhagic disease of newborn |

peripartum maternal bleeding, possibly due to acute or chronic abruption, uterine rupture, feto-maternal hemorrhage, and/or cord accidents can lead to significant anemia at birth for both term and preterm infants. In developing nations, neonatal malaria is often seen in overcrowded areas.

**Subtypes of Neonatal Anemia**

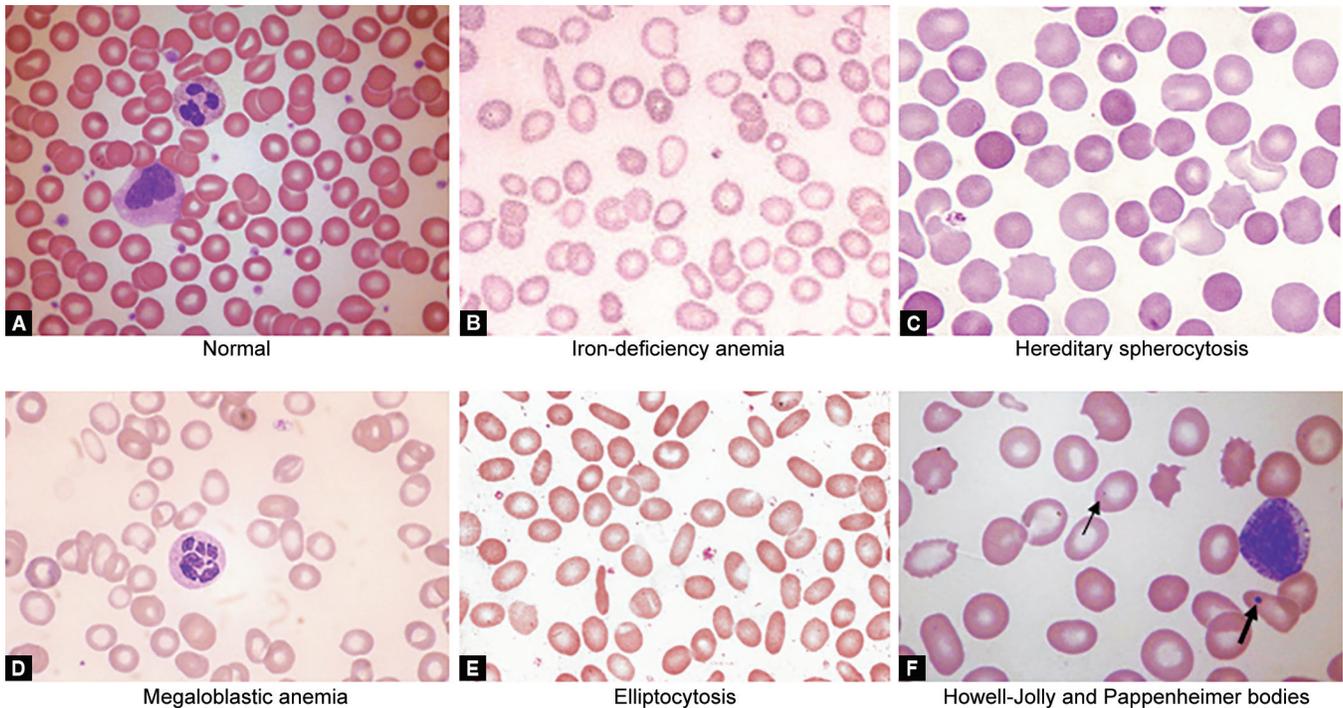
Anemia can be classified based on red cell morphology as microcytic hypochromic, normocytic normochromic, and macrocytic (Table 1). Some of these morphological changes can be as seen in Figure 1. Red blood cell indices and hemoglobin values vary by gestation and chronological age such that Hb and RBC count increase throughout gestation, whereas, RBC size and Hb content decrease. Anemia can also be classified based on pathophysiology as secondary to increased blood loss, decreased production, or increased destruction of red cells (Table 2). Management of anemia in term infants appears more straightforward compared to the preterm population. Anemia and blood transfusion practices in the preterm infants have a variable impact on neurodevelopmental outcomes with short-term gains from a liberal transfusion approach but detrimental long-term effects on brain development.<sup>20</sup>

**Embryology and Pathophysiologic Changes of Anemia**

During the third trimester of pregnancy, there is a transition of hematopoiesis from fetal liver to bone marrow. Neonatal

hematopoiesis is directly proportional to fetal erythropoietin (EPO) levels, the production of which also transitions from the fetal liver prenatally to the neonatal renal system after birth.<sup>27,28</sup> This physiological transition leads to a temporary decline in EPO levels after birth, especially in preterm infants, leading to a hypo-regenerative state.<sup>29</sup> Additionally, there is a transition from a relatively hypoxic state *in utero* to a relatively hyperoxic state *ex-utero* that further suppresses hematopoiesis.<sup>30</sup> As the infant establishes a normal respiratory pattern, there is a rapid increase in oxygen in the blood that inhibits EPO production. However, this does not translate to increased oxygen delivery at the tissue level due to greater affinity of fetal hemoglobin (HbF) for oxygen.<sup>27</sup> Oxygen delivery via HbF is highly dependent on the blood pH, where in an acidic environment, HbF has 20% higher potential of releasing oxygen to peripheral tissues as seen *in-utero*. The fetus, therefore, thrives well in a relatively hypoxic state and lower pH, where HbF becomes an excellent vector for picking up oxygen at the placental level where the pH is high and delivering it to the fetal tissues. Lastly, the rapid expansion of blood volume after birth contributes to hemodilution and rapid degradation of red blood cells occurs due to the shorter life span of neonatal RBCs, both contributing to physiologic anemia of infancy.<sup>27</sup> The nadir of this physiologic anemia occurs at 10–12 weeks of life with hemoglobin rarely falling below 10 gm/dL in a healthy term infant<sup>29,31</sup> and well-tolerated with no need for a therapeutic intervention.<sup>32</sup> Physiologic





**Figs 1A to F:** Hematoxylin-eosin stained peripheral blood smears. Images obtained at 400x magnification. (A) Normal erythrocytes show a biconcave shape with central hypochromia. The level of staining in various cells is fairly uniform across the smear; (B) Hypochromic anemia. The most common cause iron deficiency. The RBCs show hypochromia, microcytosis, marked anisocytosis and mild poikilocytosis. Poikilocytosis is defined as altered shape in >10% of all RBCs (flat, elongated, teardrop-shaped, crescent-shaped, sickle-shaped, or having pointy or thorn-like projections); (C) Hereditary spherocytosis. Marked spherocytosis, some anisocytosis. Spherocytes show round contour. Larger cells have a faint blue tinge, indicating that the reticulocyte count is increased; (D) Megaloblastic anemia: shows macrocytes, oval macrocytes and a hypersegmented neutrophil. There are also hypochromic cells. Could be due to folic acid and/or vitamin B12 deficiency. Many patients also have concurrent iron deficiency; (E) Hereditary elliptocytosis. Many RBCs are elliptical, and others are oval; (F) Abnormal RBC staining. A Pappenheimer body (thin arrow; abnormal basophilic granules of iron) and a Howell-Jolly body (thick arrow; nuclear remnants) n arrow) are seen. These abnormalities can be seen occasionally in infants. This smear was obtained from a older child with autoimmune thrombocytopenic purpura who had undergone splenectomy; we included it in this review to highlight these abnormalities

anemia of infancy can be exaggerated by maternal factors like malnutrition, iron deficiency, infection, and hereditary hemolytic anemia.<sup>21,30</sup> For preterm infants, due to an immature hematopoietic system, the nadir may occur earlier at 6–8 weeks of life and can be more pronounced with hemoglobin reaching 8 gm/dL or even lower.<sup>29</sup> This is referred to as anemia of prematurity (AOP), often exaggerated due to secondary phlebotomy losses, and infants are commonly symptomatic.<sup>27,33</sup> With pRBC transfusion, there can be a reduction in the HbF from almost 92–43% in infants born EP.<sup>34</sup> HbA has reduced affinity to oxygen compared to HbF, which makes it challenging to use a strict Hb threshold for determining the need for pRBC transfusion in infants with variable Hb subtype concentrations and properties.

### Anemia in Preterm Infants

In the last two decades, there has been a practice shift from a liberal RBC transfusion strategy to a more restrictive strategy and tolerating lower levels of hemoglobin. The premature infants in need of transfusion (PINT) Trial recruited ELBW infants who were then assigned to either a high or low threshold hemoglobin transfusion threshold and studied for death or survival with comorbidity (retinopathy, bronchopulmonary dysplasia, or brain injury on cranial ultrasound).<sup>35</sup> The ETTNO trial conducted by Franz et al. that recruited preterm infants from 2011 to 2014 in

Europe analyzed death and disability after randomizing 1013 subjects in liberal vs restrictive red blood cell transfusion strategy. Infants were followed up till 24 months corrected age. Recently the TOP trial recruited 1824 preterm infants from 2012 to 2017, randomized to two transfusion strategy groups, and reported death or neurodevelopment impairment in each group till 26 months corrected age. All three trials favored a restrictive approach to transfusions. The consensus seems to suggest a transfusion approach based on hematocrit triggers and the clinical status of the infant.<sup>36,37</sup> Even though these studies have promising results, the restrictive approach allows infants to be exposed to lower levels of hemoglobin with no well-defined guidelines with a safe threshold without increasing the comorbidities and mortality.<sup>37</sup>

The clinical decision-making for RBC transfusions should be weighed against the potential for known associations with neonatal diseases. Severe anemia has been shown to be an independent risk factor for NEC,<sup>14,38</sup> possibly through activation of the pro-inflammatory cytokines, such as IFN gamma and TNF alpha, by intestinal macrophages leading to damage to the gut epithelium.<sup>39,40</sup> This superimposed with hypoxia, and the presence of a relatively fragile vascular bed further disrupts the mucosal barrier.<sup>41,42</sup> Likewise, severe anemia results in tissue hypoxia, oxidative injury, and disturbance in cerebral perfusion leading to cerebral injury with potentially impact short and long-term

**Table 3:** Tiered approach for investigation of neonatal anemia

| Investigations                                                                                                                                                                                                                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Tier 1 ( <i>guided by clinical setting</i> ): CBC with RBC indices and peripheral smear, reticulocyte count, LFTs (if infant has hyperbilirubinemia or concerns for congenital infections), and Coombs' test                               |
| Tier 2 ( <i>focused on etiology</i> ): TORCH antibodies, urine/buccal CMV, hemoglobin electrophoresis, blood culture for sepsis, haptoglobin, lactate dehydrogenase (LDH) level, Kleihauer Betke test, follow-up newborn screening results |
| Tier 3 ( <i>more invasive and focused on etiology</i> ): Bone marrow biopsy/aspirate (for neonatal leukemias, bone marrow infiltrative disorders, neonatal hemochromatosis)                                                                |

neurodevelopmental outcomes.<sup>43–45</sup> Multiple studies have reported a decrease in regional oxygen saturation in the brain and an increase in fractional tissue oxygen extraction with increasing anemia severity.<sup>46–48</sup> Despite this, the exact clinical significance in terms of brain development and cognitive outcomes is not well defined. Whyte et al. analyzed a subgroup of infants in the PINT trial and reported lower cognition at 18–21 months' age in infants that were managed under a restrictive transfusion group.<sup>20,49</sup> While the TOP and ETTNO studies noted that there was no difference in neurodevelopmental outcome at two years corrected age when infants were randomized to liberal vs restrictive transfusion groups.

Neonatal anemia has also been linked with acute kidney injury (AKI), especially in the surgical population.<sup>50</sup> Nada et al. evaluated newborns from the Assessment of Worldwide AKI Epidemiology in Neonates (AWAKEN) database and were the first to show an association between anemia in the first week of life with late AKI in 2020.<sup>51</sup> But the findings were not significant after controlling for fluid balance. On the other hand, Nashimoto et al. recently highlighted AKI as an independent predictor for anemia due to less EPO production after interstitial damage.<sup>51,52</sup> Further studies are needed to describe anemia and its relationship with AKI.

### Laboratory Diagnosis

Hemoglobin measurements are now the primary index for the diagnosis of anemia. These results show the amount of the Hb protein found in RBCs and are expressed as grams per deciliter (gm/dL) or grams per liter (gm/L) of blood. Several high-quality laboratory techniques are available for these measurements. Several other indices are also frequently assessed and can be useful:

- *Hematocrit* is a calculated value on most instruments and reflects the number and size of the RBCs. The hematocrit can drop with the loss of RBCs during hemorrhage or when there is a loss of MCV, as in microcytic anemia. Thus, the influence of MCV makes it less useful as a measure of anemia than Hb.
- *Red blood cell count (RCC)* is not a good indicator of the severity of anemia as it can remain unchanged even when changes in other indices such as the MCV or MCHC can lower the total amount of Hb.
- *Mean corpuscular volume (MCV)* can be a useful measurement. Low MCVs are referred to as microcytosis (microcytic RBCs) and high figures as macrocytosis. Red blood cell count volume is an important parameter in distinguishing the cause of anemia since some anemias cause red blood cell volume to drop while others cause it to rise. For example, microcytic anemias are usually due to defective HB synthesis while macrocytic anemias are often the consequences of problematic cell development.
- *Mean corpuscular hemoglobin concentration (MCHC)* is also reported. Low MCHCs indicate hypochromia. It is a frequently seen feature in anemia due to low Hb synthesis. A low hematocrit but a high MCHC may be seen in a hemolyzed sample in which the Hb from the RBCs is present in the plasma, but the RBCs

contributing to the hematocrit will be reduced, however. A similar situation occurs on some instruments with cold agglutinins that show the RBC counts and calculated hematocrit as falsely low while the Hb is accurate for the infant. The instruments can usually flag elevated MCHCs, even suggesting a cause such as a possibility of lipemia.

- *Mean cell hemoglobin (MCH)* is the actual weight (amount; picograms) of hemoglobin in the average RBC. It is dependent on the RBC size; small cells cannot contain as much Hb. The MCH usually correlates with the RBC volume, the MCV. It is expected that if the MCH is low then the MCV is also low, but hypochromia cannot be determined using the MCH. Thus, the MCH is usually not as useful as the MCHC, which correlates better with hypochromia.
- *RBC distribution width (RDW)* can be important. High RDWs indicate anisocytosis. The RDW is a statistical estimation of the variability in RBC size and is indicated as a standard deviation (RDW-SD) or the coefficient of variation (RDW-CV; SD divided by the MCV). Both indices show increased ranges of RBC size. Most anemic infants with increased hematopoiesis or following transfusions show increased RDWs.
- *RBC morphology* is still a useful evaluation (Fig. 1). The confirmation of microcytosis or macrocytosis suspected from MCV figures can help. High MCHCs can be evaluated for the presence of spherocytes, and if not found, then a cause of spurious elevation should be investigated. Hypochromia on the blood film should be correlated to a reduced MCHC. Infants with elevated RDWs but the normal volume and hemoglobin content may show anisocytosis with spherocytes and other sickle cells, hereditary ovalocytes/elliptocytes, stomatocytes, echinocytes, acanthocytes, and most teardrops/dacryocytes. High RDW but slightly lower MCV can be seen in schistocytes and keratocytes (helmet cells). Megaloblastic anemia with macro-ovalocytes may correlate with elevated MCV, but the shape change is not evident in most other numerical parameters. Target cells (codocytes) in thalassemia are hypochromic and can reduce the MCHC and perhaps the MCH.

### Clinical Management

It is very important to differentiate an infant that is asymptomatic at low hematocrit vs a clinically sick infant who will benefit from treatment. Severe anemia in a symptomatic infant may present with pallor, tachypnea, tachycardia, hepatomegaly, high cardiac output shock/hypovolemic shock, systolic ejection murmur, need for respiratory support and oxygenation, and signs of sepsis.<sup>29</sup> Table 3 presents the Tiered approach or investigation of neonatal anemia and guide management strategies.

There are no numerical cut-offs/thresholds for initiation of iron supplements, erythropoietin administration, or red blood transfusion as management is individualized to each infant with careful consideration to clinical status and etiology of anemia.<sup>10</sup> Social factors

**Table 4:** Indications for red blood cell transfusions*Indications for blood transfusion in acute blood loss*

Acute blood loss >20 percent of blood volume.

Acute blood loss >10 percent of blood volume with symptoms of decreased oxygen delivery (such as persistent acidosis) after volume resuscitation.

*Indications for blood transfusion in chronic blood loss*

Transfusions should be considered based upon the respiratory support needed by the infant.

They are dependent upon an HCT or hemoglobin value that is preferably measured from either a central venous or arterial sample.

- For infants requiring moderate or significant mechanical ventilation, defined as a fraction of inspired oxygen (FiO<sub>2</sub>) ≥0.4, and mean airway pressure (MAP) >8 cm H<sub>2</sub>O on a conventional ventilator or MAP >14 on a high-frequency ventilator, the HCT trigger is <30 percent (hemoglobin ≤10 gm/dL).
- For infants requiring minimal mechanical ventilation, defined as a fraction of inspired oxygen (FiO<sub>2</sub>) <0.4, and MAP ≤8 cm H<sub>2</sub>O on a conventional ventilator or MAP ≤14 on a high-frequency ventilator, the HCT trigger is <25 percent (hemoglobin ≤8 gm/dL).
- The HCT trigger is <25 percent (hemoglobin ≤8 gm/dL) for infants requiring supplemental low- or high-flow oxygen but not mechanical ventilation, and one or more of the following: tachycardia (heart rate ≥180 beats per minute) for ≥24 hours, tachypnea (respiratory rate ≥60 breaths per minute) for ≥24 hours, doubling of oxygen requirement from the previous 48 hours, metabolic acidosis as indicated by a pH 7.2 or serum lactate ≥2.5 mEq/L, weight gain <10 gm/kg per day over the previous four days while receiving ≥120 kcal/kg per day, or if the infant undergoes major surgery within 72 hours. For infants requiring oxygen without any signs, a transfusion is not considered until signs occur.
- In asymptomatic infants, the HCT trigger is 21 percent (hemoglobin ≤7 gm/dL) with an absolute reticulocyte <100,000/μL (<2 percent). Infants without signs or oxygen requirements who are actively producing new red cells and have an elevated reticulocyte count likely do not require a red cell transfusion. Other centers and societies have transfusion guidelines with higher HCT (hemoglobin) triggers, which are based upon similar requirements for respiratory support.

<sup>†</sup>Adapted from Ohls R, Garcia-Prats JA, Kim MS. Red blood cell transfusions in the newborn. UpToDate 2021. <http://www.uptodate.com/contents/red-blood-cell-transfusions-in-the-newborn> [Accessed April 12, 2022]

(e.g., access to the medical system, treatment of co-morbidities in pregnant females, and improvement in nutritional status) also need to be identified and exclusive breastfeeding mothers need to be supported in nutrition and correction of iron deficiency.<sup>53,54</sup>

### Iron Supplementation

A term healthy asymptomatic infant with physiologic anemia of infancy usually does not need treatment.<sup>31</sup> Iron is an essential micronutrient required for hemoglobin synthesis and oxygen transfer. A late preterm infant that is clinically asymptomatic and exclusively breastfed benefits with iron supplementation ranging from 2 to 6 mg/kg/day (higher doses for infants with more robust reticulocyte response or lower gestational age to support the hematopoiesis). Preterm infants fed with iron-fortified formula need less supplementation. Side effects of iron medication range from feeding intolerance, diarrhea, constipation, and black tarry stools.

### Packed Red Cell Transfusions

Preterm infants, especially EP infants get at least one transfusion during NICU stay.<sup>55</sup> The decision needs to be individualized with keeping in mind the complications of transfusions.<sup>55</sup> Acute blood loss requires immediate replacement with whole blood in case of emergency or packed red blood cells (RBC). The amount of external blood lost could potentially be determined by weighing the bandages, gauzes, and blankets. Internal blood loss is difficult to assess, and sometimes clinical setting can hint toward the volume (in subgaleal bleeding, 1 cm increase in head circumference equals to 38 cc blood loss).<sup>56</sup>

In contrast to acute blood loss, chronic *in utero* loss may be managed by partial exchange transfusion when newborns already

have increased circulatory volumes, and the main problem is peripheral oxygen delivery at the tissue level. Simple transfusion can add to further volume overload leading to cardiac failure. Examples of such scenarios are twin–twin transfusion or chronic fetomaternal hemorrhage and severe hemolytic anemias.<sup>57</sup> The volume of transfusion in mL is equal to the following calculation:

Wt. (kg) × blood volume per kg × (Desired HCT-Observed HCT)/HCT of PRBCs. Table 4 presents guidance for red cell transfusions in varied scenarios.<sup>54</sup>

Recently, there has been the focus on tolerating lower hematocrits in extremely premature infants who are off respiratory support.<sup>10,35</sup> Many clinical trials have suggested similar or worse clinical outcomes with liberal transfusion, especially in neurodevelopment outcomes such as cognitive ability, cerebral palsy, severe visual/hearing loss at 24 months' age, and even mortality.<sup>36,37,49</sup>

*Complications associated with red cell transfusions:* Transfusions have been associated with potential damage by ischemia-reperfusion damage or oxidative injury. They also inhibit hematopoiesis, have a risk of infection, graft vs host disease, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion-associated gut injury (TRAGI), an extension of IVH, ROP, and hyperkalemia.<sup>15,40,42,58,59</sup>

Transfusion-related acute lung injury (TRALI) is a complication coined by National Heart, Lung and Brain Institute (NHLBI) two decades ago and defined as a new acute lung injury/acute respiratory distress syndrome occurring during or within 6 hours after blood transfusion. A two-hit mechanism theory is described for pathogenesis: Firstly, neutrophils sequestration and priming in pulmonary vessels due to primary damage/insult to endothelium

by disease, followed by secondly, blood products in transfusion causing neutrophil activation and release of cytokines, reactive oxygen species, and proteases that cause further damage.<sup>59</sup> TRAGI is amongst the most controversial transfusion-associated complications and approximately one-fourth of the NEC cases reported are temporally associated within 48 hours of transfusions. One of the pathogenesis suggested includes chronically hypoxic mucosal layer due to anemia undergoes a reperfusion injury after transfusion aggravating the oxidative damage and eventually leading to NEC.<sup>14,38</sup>

Feeding during a blood transfusion is also an area of ambiguity with great variation in clinical practices. Krimmel et al. suggested that feeding stimulates superior mesenteric artery circulation which has been suggested to be protective against NEC and absent in preterm infants that were made NPO during transfusion.<sup>60</sup> Red blood cell transfusion has also been associated with an increase in mesenteric and pulmonary vasoreactivity in lamb models and concern for NEC with worse pulmonary outcomes.<sup>61,62</sup> Others have reported the opposite and reduction in NEC when practicing strict feeds withholding during transfusion.<sup>63</sup> Results are still pending for the pilot WHEAT (WithHolding Enteral feeds Around packed red cell Transfusion) trial that recruited preterm infants around London and Birmingham area from 2018 to 2019 and randomized to two groups, one withholding milk feeds and the second continuing feeding during transfusion.<sup>64</sup>

Lust et al. suggested that early transfusion (<10 days of life) is associated with ROP.<sup>65</sup> This is due to the shift of the Hb dissociation curve of HbF to HbA (contained in the transfusion unit) which leads to greater oxygen delivery at the cellular level.<sup>65</sup> Fresh RBCs transfusions that are leuko-reduced and irradiated are recommended in preterm infants to maximize benefits and reduce organ dysfunction.

### Erythropoiesis-stimulating Agents

Another modality in the management of neonatal anemia, particularly in infants born EP, is the administration of the erythropoiesis-stimulating agents like erythropoietin (EPO) and Darbopoetin. Studies in 2017 and 2019 noted an association between early EPO and lower total transfusion volume, rates of IVH, PVL, NEC, and donor exposure.<sup>66</sup> But due to a lack of consistency in literature, EPO is not commonly used in many centers. In 2020 Cochrane reported a decreased number of red blood cell transfusions following late EPO administration after 1 week of life.<sup>67</sup> It showed no benefit on avoiding donor exposure as most ELBW/critically sick infants were transfused prior to EPO administration.<sup>67</sup> Hence it might be more suitable for larger or stable/late preterm infants. Another Cochrane Review in 2020 concluded no added benefit of early vs late EPO administration on the frequency of transfusions but raised concern for an increased incidence of ROP. At this time, there is a need for further data for creating standardized guidelines for the use of EPO and Darbopoetin in neonates.

### FUTURE DIRECTIONS

With significant advances in neonatal care there has been a notable improvement in outcomes for newborns, and opportunities are being identified for prevention, identification, and management of neonatal anemia and related morbidities.

Delayed clamping at birth has been adopted by American Academy of Pediatrics and is defined as allowing blood flow from

the placenta to the newborn for at least 60 seconds or till the cord stops pulsating.<sup>32</sup> This has led to a significant reduction in anemia in term and preterm infants as well as improved neonatal hemodynamics with the increase in blood volume, improvement of cerebral perfusion, provision of a greater number of stem cells from the placenta, increase in iron stores, and reduction in the need for transfusions in early neonatal phase.<sup>32,68,69</sup>

Decreasing phlebotomy losses is probably the first major step in the reduction of anemia in preterm infants. In 2012, Hospital Italiano De Buenos Aires practiced a micro-collection technique for blood samples that significantly reduced blood transfusion requirements.<sup>70</sup> Collection of cord blood samples, clustering blood tests together, and performing tests closer to discharge for greater accuracy can potentially help with these efforts.

There have been considerable advances in the evaluation of iron deficiency in adults, and similar evaluations are needed in infants vis-à-vis the gestational and postnatal maturation, ethnicity, and geographic regions. The levels of total body iron are computable from plasma levels of serum ferritin and transferrin saturation. There might also be organ-specific differences in the levels of iron, ferritin, and transferrin saturation in the context of inflammatory disorders. Markers such as the soluble transferrin receptor/ferritin index and hepcidin levels may also be useful in the translational context. New iron preparations and new treatment modalities are available; high-dose intravenous iron compounds may show high degrees of efficacy, although long-term side effects remain to be evaluated.

Utilizing physiological markers to assess needs for red blood cell transfusion is vital. Near-infrared spectroscopy (NIRS) is a novel tool used to monitor cerebral and splanchnic saturations and is being explored to identify hotspots of low regional oxygenation saturation where red cell transfusions might be helpful.<sup>71-74</sup> Research is being done with a focus on having a sensitive marker for oxygen delivery (cerebral oxygen saturation, peripheral fractional oxygen extraction, and consumption),<sup>71-74</sup> cardiac changes identification on echocardiogram,<sup>75,76</sup> and biochemical markers like lactate and VEGF.<sup>77,78</sup>

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