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Review

Anemia and transfusion in the neonate

Raffaella Colombatti [a, *], Laura Sainati [a], Daniele Trevisanuto [b]

[a] Clinic of Pediatric Hematology Oncology, Department of Child and Maternal Health, Azienda Ospedaliera – University of Padova, Padova, Italy
[b] Neonatology Intensive Care Unit, Department of Child and Maternal Health, Azienda Ospedaliera – University of Padova, Padova, Italy

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SUMMARY

Neonatal anemia is a frequent occurrence in neonatal intensive care units. Red blood cell transfusion criteria in case of blood loss are clearly defined but optimal hemoglobin or hematocrit thresholds of transfusion for anemia due to decreased production or increased destruction are less evident. This review focuses on the causes of anemia in the newborn period and the most recent evidence-based treatment options, including transfusion and erythropoiesis-stimulating agents.

1. Introduction

Neonatal anemia, defined as a hemoglobin (Hb) or hematocrit (Hct) concentration of >2 standard deviations below the mean for postnatal age, is a major problem encountered in neonatal intensive care units (NICUs). Newborns are one of the most transfused categories, with 90% of extremely low birth weight infants receiving at least one red blood cell (RBC) transfusion during their stay in the NICU [1–3]. A low Hb level at birth has emerged recently as an independent risk factor for mortality and probability of receiving a blood transfusion in preterm infants born at <32 weeks of gestation, irrespective of mode of delivery and time of umbilical cord clamping [4]. Moreover, long-term anemia has the potential to affect both brain growth and other components of chronic disease of both the premature and the term infant [5,6].

The interpretation of hematologic abnormalities in the neonate is confounded by the interactions of genetics, acquired disease, and maternal factors with the peculiarities of the fetal erythrocyte. Therefore, the approach to the newborn with anemia has to consider the specifics of newborn erythropoiesis, the gestational age, the different causes of anemia in the term and preterm infant, their clinical conditions, and the risk and benefits of each available treatment option [7,8]. Whereas the approach to the term infant with anemia has remained substantially the same in the last decade, recent years have seen the development of various clinical trials to inform evidence-based practice for the diagnosis and treatment of anemia in the preterm newborn [9], including RBC transfusion [10–13], erythropoiesis-stimulating agents [14,15], and standardized practice [16]. Several national guidelines [17–23] and many locally agreed guidelines have been implemented and are currently available to guide clinicians' transfusion practice, but many uncertainties remain, including those regarding short- and long-term outcomes [7,24,25].

2. Erythropoiesis in the fetus and newborn

Hematopoiesis in the fetus and neonate is in a constant state of flux and evolution as the newborn adapts to a new milieu. Fetal erythropoiesis occurs sequentially during embryonic development in three different sites: yolk sac, liver, and bone marrow. Yolk-sac formation of RBCs is maximal between 2 and 10 weeks of gestation. Bone marrow production of RBCs begins at around week 18, and, by the 30th week of fetal life, bone marrow is the major erythropoietic organ [7,26]. At birth, in term newborns, almost all RBCs are produced in the bone marrow, although a low level of hepatic erythropoiesis persists through the first few days of life (Fig. 1).

Fetal erythropoiesis is independent from the mother. An increasing role for erythropoietin (EPO) is observed during the hepatic and bone marrow phase of erythropoiesis, the liver being the most likely candidate for EPO production during fetal life. The development of hematopoiesis both in utero and at birth is controlled by the effect of several growth factors on cell proliferation and the activation of cell-specific genes. Increasing evidence shows that an abnormality in one of these genes (i.e. GLUT1, GLUT4, KLF) can cause anemia in the neonate [27–30].

Fetal RBCs contain mainly fetal Hb which has higher oxygen affinity compared to adult Hb that is produced after birth. Hb, Hct,

* Corresponding author. Address: Clinic of Pediatric Hematology Oncology, Department of Child and Maternal Health, Azienda Ospedaliera – University of Padova, Via Giustiniani 3, 35129, Padova, Italy. Tel.: +39 049 8218006.
E-mail address: rcolombatti@gmail.com (R. Colombatti).

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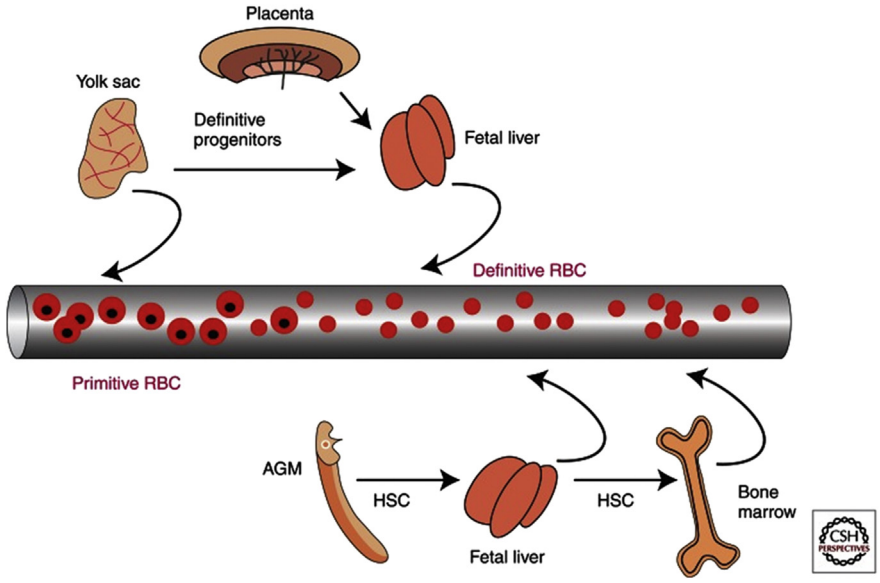

Fig. 1. Ontogeny of erythroid lineage cells in the circulation. Embryonic erythrocytes [primitive red blood cells (RBCs)] are made by the yolk sac at E7.5 and are found in the circulation until ~E11/12. At E9, the yolk sac and placenta generate definitive progenitors that migrate to the fetal liver, where they differentiate to definitive RBCs (expressing fetal/adult globin) and enter the circulation. At E10.5, the aorta–gonad–mesonephros (AGM) generates the first hematopoietic stem cells (HSCs) that migrate to the fetal liver and differentiate to the erythroid lineage (among other lineages), and these definitive RBCs enter the circulation. Fetal liver HSCs migrate and colonize the bone marrow at birth, where they supply lifelong production of definitive RBCs for the circulation. The spleen also is a site of differentiation for erythroid cells (not shown). Reproduced with permission from Dzierzak et al., Cold Spring Harb Perspect Med 2013;3:a011601 [26]; © Cold Spring Harbor Laboratory Press.

and RBC count increase throughout fetal life with a rate of RBC production during the latter part of fetal life that is fivefold that of a normal adult. Extremely large RBCs with an increased content of Hb are produced early in fetal life. The size and Hb content of these cells decrease throughout gestation, but the mean corpuscular hemoglobin concentration (MCHC) does not change significantly.

Therefore, RBC indices and morphology at birth are different from the adult ones and gradually modify to reach childhood values several months after birth. The distinct features of newborn erythrocytes and their metabolism (Box 1) both in term and preterm infants must be taken into consideration when evaluating a neonate with anemia.

Box 1
Characteristics of the neonatal erythrocyte [6,31].

- Life span of the red blood cell (RBC) at birth is lower than that in adult: 60–70 days (preterm 35–50 days) compared to 90–120 in the adult, probably due to increased RBC rigidity.
- The RBCs at birth are more resistant to osmotic lysis, have larger mean corpuscular volume and lower mean corpuscular hemoglobin concentration, and are more susceptible to oxidant-induced injury mainly due to a deficiency in phosphofructokinase activity.
- Peripheral blood smear: high frequency of dysmorphology of RBC in term neonates (only 43% have disc appearance compared to 78% in adults and 14% are spherocytes and poikilocytes compared to 3% in adults) and even more in preterm neonates.
- Hemoglobin switching from HbF to HbA occurs in the first weeks after birth.
- Rate of haemoglobin synthesis and RBC production decreases sharply during the first few days after delivery due to decrease in EPO in the plasma.
- Iron homeostasis is different in newborns with lower hepcidin levels.

Reference hematologic values for term and preterm newborn have been published; examples are shown in Tables 1 and 2 [23]. Due to population variation in RBC indices and variability of the norms in different automated machines, many centers determine normative values for their population [3,32,33] and display reference values in their websites. Values displayed by newborns in developing countries can be different from those of developed countries [6].

Several variables influence what can be considered reference values for newborns and during the first few weeks of life. These variables include the gestational age of the newborn (term vs preterm), the conduct of labor, and the treatment of the umbilical vessels (delayed vs early cord clamping), the site of sampling (capillary vs venous), and the time of sampling.

3. Etiopathology of anemia in the newborn

At birth a considerable number of changes occur in erythropoiesis which are physiologic and which lead, in the term infant, to a transitory anemia named physiologic anemia of childhood. The premature infant might present an exaggerated physiologic anemia due to several adjunctive endogenous and exogenous factors. The etiology of neonatal anemia may be subdivided into the three major categories: blood loss, decreased production, and increased destruction of erythrocytes.

3.1. Physiological anemia of infancy

When infants take their first breath, considerably more oxygen is available for binding to Hb, and Hb oxygen saturation increases from ~50% to ≥95%. The normal developmental switch from fetal to adult Hb synthesis replaces high-oxygen-affinity fetal Hb with low-oxygen-affinity adult Hb, which can deliver a greater fraction of Hb-bound oxygen to the tissues. Therefore, after birth the increase in