Seminars in Fetal & Neonatal Medicine 21 (2016) 2–9

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

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

Keywords:
Anemia
Neonate
Treatment
Transfusion

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).

http://dx.doi.org/10.1016/j.siny.2015.12.001
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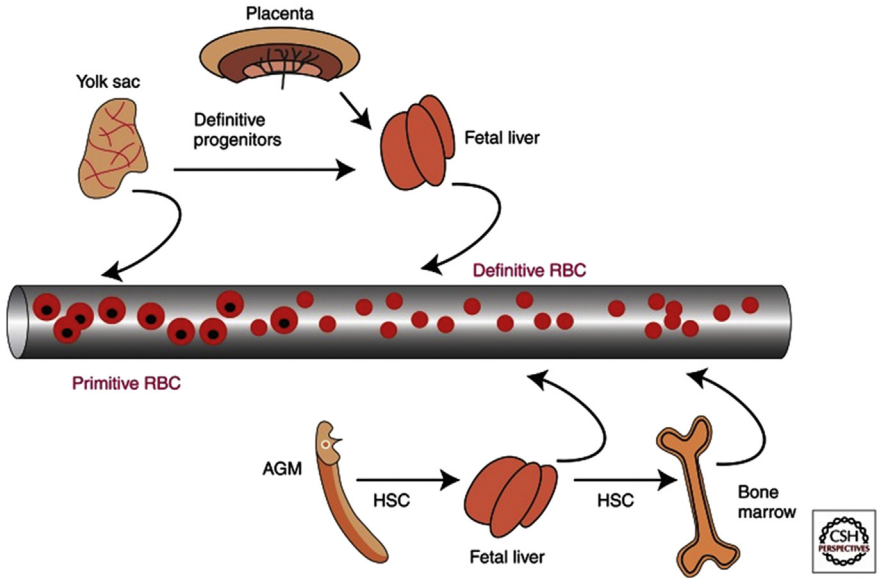

Fig. 1. Ontogeny of erythroid lineage cells in the circulation. Embryonic erythrocytes [primitive red blood cells (RBCs)] are made by the yolk sac at E7.5 and are found in the circulation until ~E11/12. At E9, the yolk sac and placenta generate definitive progenitors that migrate to the fetal liver, 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

Table 1
Reference hematologic values in term newborns (adapted from Italian National Guidelines) [23].

Age	Hb (g/dL)		Hct (%)		RBC (10^{12}/L)		MCV (fL)		MCH (pg)	
	Mean	−2 SD	Mean	−2 SD	Mean	−2 SD	Mean	−2 SD	Mean	−2 SD
Cord blood	16.5	13.5	51	42	4.7	3.9	108	98	34	31
1–3 days	18.5	14.5	56	45	5.3	4.0	108	95	34	31
7 days	17.5	13.5	54	42	5.1	3.9	107	88	34	28
14 days	16.5	12.5	51	39	4.9	3.6	105	86	34	28
4 weeks	14.0	10.0	43	31	4.2	3.0	104	85	34	28
8 weeks	11.5	9.0	35	28	3.8	2.7	96	77	30	26
12 weeks	11.5	9.0	35	29	3.8	3.1	91	74	30	25

Hb, hemoglobin; Hct, hematocrit; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin.

blood oxygen content and tissue oxygen delivery downregulate EPO production so that erythropoiesis is suppressed. The Hb concentration continues to decrease until tissue oxygen needs are greater than oxygen delivery. Normally, this point is reached between 6 and 12 weeks of age, when the Hb concentration is between 9.5 and 11 g/dL. As hypoxia is detected by renal or hepatic oxygen sensors, EPO production increases and erythropoiesis resumes. In the term newborn the supply of iron is sufficient for Hb synthesis, even in the absence of dietary intake, until ~20 weeks of age. Physiologic anemia in healthy term infants is essentially benign, they remain asymptomatic, and no treatment is necessary [3,8]. The nadir Hct in term infants occurs between 10 and 12 weeks of age, and rarely falls to <30% with Hb concentrations of 10–12 g/dL. After 10–12 weeks, the Hct and Hb increase slowly to reach adult values by 2 years of age.

3.2. Anemia of prematurity

Anemia of prematurity (AOP) is an exaggeration of the normal physiologic anemia and is defined as: anemia in a preterm infant <32 weeks of gestation; inappropriately low reticulocyte count for severity of anemia; and inappropriately low circulating EPO concentration for the degree of anemia. Premature babies (1200–2500 g) reach the nadir earlier (5–10 vs 6–12 weeks) and at lower Hb (8–10 vs 9.5–11 g/dL) or Hct (28 vs >30%) levels compared to term newborns; small premature babies (<1200 g) display even more rapid and more severe anemia (nadir at 4–8 weeks, Hb 6.5–9 g/dL, Hct 21%).

Several endogenous and exogenous factors contribute to the AOP [7,8,34]. Among the first are the low plasma EPO levels in response to anemia due to decreased EPO production and accelerated EPO catabolism. The mechanisms responsible for the diminished EPO output by preterm neonates are only partially defined. As the fetus transitions from the hypoxic intrauterine environment to the oxygen-rich postnatal environment, EPO production is downregulated. Moreover, after birth, EPO production passes from the liver to the kidney. This transition occurs during the first 3–4 months past term birth. Therefore, the primary site of EPO production in preterm infants is still in the liver, rather than the kidney. The timing of the switch from liver to kidney is set at conception and is not accelerated by preterm birth. This is an important contributor to the AOP because the liver is less sensitive to tissue hypoxia as a stimulus for EPO production than the kidney. This postnatal decrease in EPO production translates into a 20% decrease in erythroid progenitor cells in the marrow. EPO clearance and volume of distribution is also high in neonates relative to adults, and this likely contributes to low circulating concentrations. Increased growth rate compared to that of term infants is also an endogenous factor causing AOP.

Exogenous factors contributing to the AOP include: iatrogenic blood loss for frequent laboratory testing, iron deficiency, or other nutritional deficiencies, inflammation, infections, and chronic illness [34].

Table 2
Reference hemoglobin (Hb) values in preterm newborns (adapted from Italian National Guidelines) [23].

Age (weeks)	Hb according to birth weight	
	1000–1500 g	1501–2000 g
2	16.3 (11.7–18.4)	16.8 (11.8–19.6)
4	10.9 (8.7–15.2)	11.5 (8.2–15)
8	8.8 (7.1–11.5)	9.4 (8.0–11.4)
12	9.8 (8.9–11.2)	10.2 (9.3–11.8)
16	11.3 (9.1–13.1)	11.3 (9.1–13.1)

3.3. Causes of anemia

The causes of anemia in the newborn period are listed in Box 2 [2,6,32], according to the three main categories: blood loss, decreased production, increased destruction (hemolysis). Only those hereditary RBC disorders causing neonatal symptoms are considered.

4. Diagnostic approach to the newborn with anemia

In view of the great number of entities that may be responsible for anemia in the newborn period, a disciplined approach to diagnosis is necessary.

The diagnostic approach in a suspected case of anemia should include the following:

4.1. Family and maternal history

Family history is important to investigate for genetic diseases causing anemia (i.e. spherocytosis, congenital dyserythropoietic anemias, glucose-6-phosphate dehydrogenase), and should include questions on jaundice, gallstones, splenomegaly, history of transfusions or iron supplementation in the family. Maternal history should highlight medical conditions predating pregnancy (i.e. autoimmune disorders) or antepartum period (nutritional status of the mother and hematologic values).

4.2. Obstetric history

This includes fetal growth, congenital viral infections, method of delivery, evidence of fetal distress, pathology of the placenta or the umbilical cord.

4.3. Physical examination

Physical examination can provide significant insight into the cause of anemia and should consider signs of chronic anemia

Box 2
Causes of anemia in the newborn period.

Blood loss

Occult blood loss prior to birth
- Fetomaternal (placental malformation or tumors, spontaneous, etc.)
- Twin-to-twin

Obstetric causes
- Abruptio placentae
- Placenta previa
- Rupture of a normal umbilical cord
- Rupture of anomalous vessels
- Cesarean section
- Intrauterine manipulation
- Incision of placenta at cesarean section

Internal hemorrhage and bleeding in the newborn period
- Intracranial due to various causes (rapid delivery, prematurity, second twin, hypoxia, etc.)
- Retroperitoneal
- Ruptured spleen or liver
- Giant cephalohematoma
- Gastrointestinal bleeding

Increased destruction (hemolysis)

Hereditary red blood cell disorders
- Disorders of the RBC membrane (spherocytosis, elliptocytosis, etc.)
- RBC enzyme defects (G6PD deficiency, pyruvate kinase deficiency, etc.)
- Hemoglobinopathies (α and γ thalassemias and chain structural abnormalities)

Immune
- ABO incompatibility
- Rh incompatibility
- Minor blood group incompatibility
- Maternal autoimmune diseases (lupus, hemolytic anemia, etc.)
- Drug-induced hemolytic anemia

Acquired
- Infections
- Disseminated intravascular coagulation
- Micro- or macroangiopathic anemia (renal artery stenosis, cavernous hemangioma)
- Nutritional anemias (vitamin E deficiency)

Decreased production
- Physiologic anemia of infancy
- Anemia of prematurity
- Diamond–Blackfan anemia
- Congenital anemia or tumor
- Down syndrome
- Pearson syndrome
- Osteopetrosis
- Drug-induced infections (rubella, parvovirus B19, cytomegalovirus, adenovirus)

RBC, red blood cell; G6PD, glucose-6-phosphate dehydrogenase.

(pallor, poor weight gain, etc.) and signs of acute anemia (tachycardia, cardiac failure, respiratory distress, etc.), signs of congenital disease in which anemia can be a part of the clinical picture (i.e. malformations for Fanconi anemia) or signs of hemolysis (jaundice, splenomegaly, cephalohematoma, anasarca, etc.).

4.4. Laboratory investigations

These should include, first of all, a complete blood count to establish a diagnosis of anemia. The newborn's Hb or Hct should be evaluated according to reference values appropriate for gestational age, and site of sampling (see Box 1 and Tables 1 and 2). Successively, reticulocytes, red cell indices, peripheral blood smear, indices of hemolysis (total and indirect bilirubin, lactate dehydrogenase, direct and indirect Coombs test) can be performed in a stepwise manner. A practical interpretation of hematologic parameters that can aid in the diagnosis of anemia in newborns is listed in Fig. 2.

5. Treatment of anemia

5.1. RBC transfusion

The treatment of anemia has the objective to maintain adequate oxygen delivery to tissue. Transfusion has a clear indication in case of blood loss or shock for the restoration of blood volume. In the remaining situations, both in term and preterm newborns, the transfusion guidelines published so far [17–23] are based, predominantly, on expert opinion. In the absence of good evidence of definitive criteria for transfusion, including when to transfuse, it is widely suggested that the decision to transfuse takes into consideration a combination of clinical signs and laboratory parameters, considering the infant's health condition and physiologic needs [1,10,16,24,25]. Many institutions have adopted single-center protocols in order to standardize transfusion practices and aid clinicians in the decision to transfuse preterm and term newborns, using a combination of clinical signs and laboratory parameters. Examples of transfusion guidelines for term and preterm newborns are given in Boxes 3 and 4 and in Table 3.

Transfusion products [32,35] for neonatal transfusions should be leukocyte-depleted, irradiated for infants weighing <1200 g (even though some centers use irradiated RBCs for all neonatal transfusion) and from selected donors to limit donor exposure. National guidelines describe the characteristics transfused RBCs should have [17–23].

5.1.1. Open issues in transfusion of preterm newborns

Several open issues remain regarding the optimal threshold for transfusion (high vs low), the side-effects and the short- and long-term consequences of transfusion.

Four trials investigated low Hb or Hct vs high Hb or Hct threshold (average difference 2 g/dL for Hb) for transfusion for preventing mortality and morbidity in very low birth weight (VLBW) infants and were included in a recent Cochrane Review [11–13,36]. No differences in survival, short-term complications such as necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), or neurological outcome at 18–22 months were observed, showing that there is no clear benefit or risk attributable to the use of low versus high haemoglobin transfusion thresholds in VLBW infants. Observations from post-hoc analyses in the Premature Infants in Need of Transfusion (PINT) study suggest poorer outcomes in neurodevelopment [37] and at hospital discharge [11] in the low threshold groups, and make it difficult to reject a conclusion that the use of a high threshold may be beneficial. The Cochrane Review

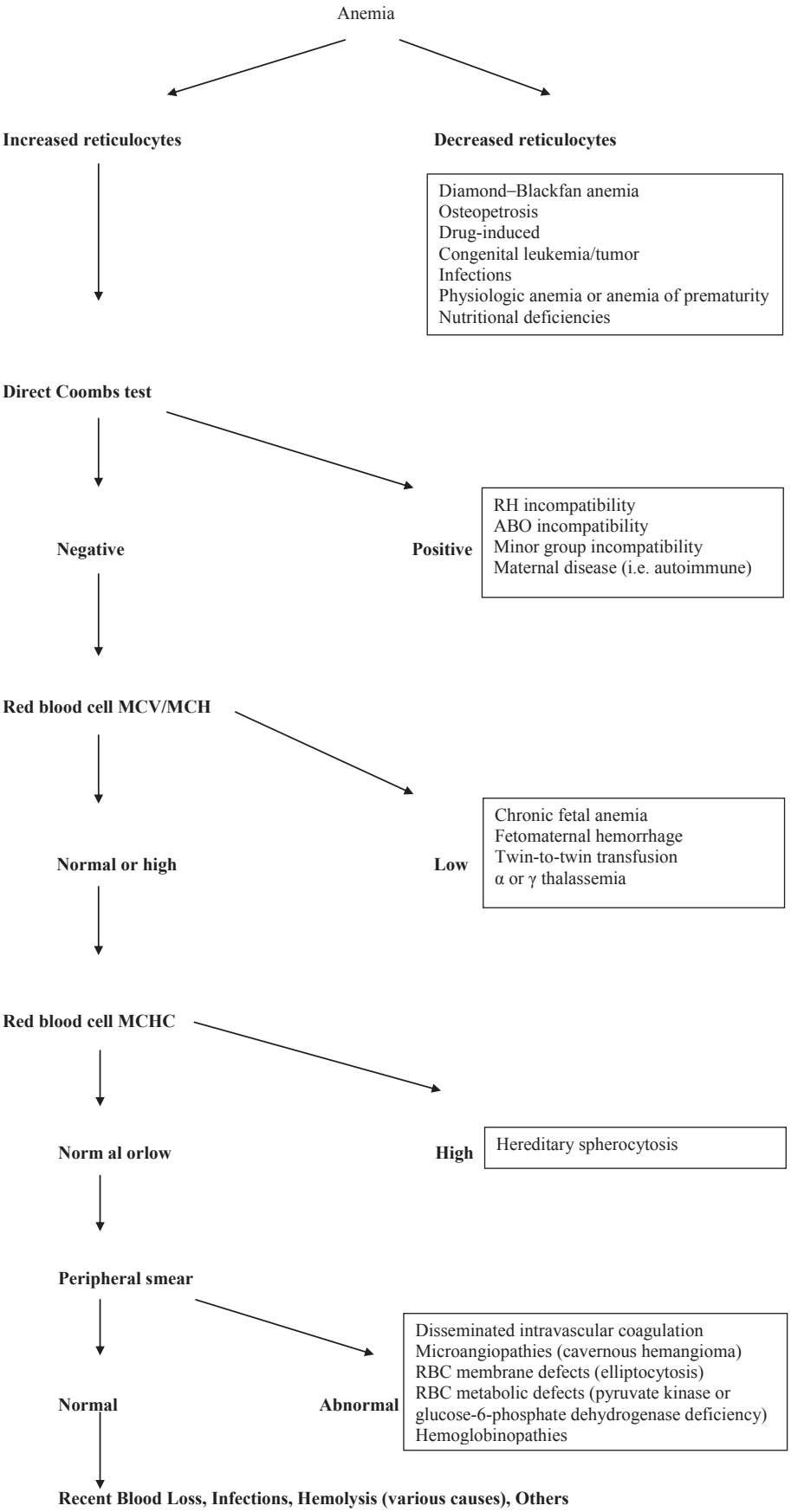

Fig. 2. Diagnostic approach to the newborn with anemia based on hematologic indices. MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin.

Box 3
Examples of transfusion guidelines for newborns [17–21].

Recommendations for RBC transfusion (Canadian 2002; also in Irish 2007) [17–21].

RBC transfusions should be considered in newborn infants in the following specific clinical situations:

- Hypovolemic shock associated with acute blood loss
- Hct between 30% and 35% or Hb concentration between 100 and 120 g/L in extreme illness conditions for which RBC transfusion may improve oxygen delivery to vital organs
- Hct between 20% and 30% or Hb concentration between 60 and 100 g/L, and the infant is severely ill and/or on mechanical ventilation with compromised oxygen delivery
- Hct falling (≤20%) or Hb concentration (≤60 g/L) with reticulocyte count of ≤100,000–150,000/mm^3 (suggesting low plasma concentration of erythropoietin), and if the following clinical signs are present: failure to thrive or no weight gain, tachycardia >180 breaths/min, respiratory signs including tachypnea and supplemental oxygen needs, and lethargy [12,51]

Guidelines for RBC transfusion in patients aged <4 months (USA 2000; also in Irish 2007) [18,21]

1. Hct <20% with low reticulocyte count and symptoms of anemia (tachycardia, tachypnoea, poor feeding)
2. Hct <30% with an infant:
   - On <35% hood O_2
   - On O_2 by nasal cannula
   - On continuous positive airway pressure and/or intermittent mandatory ventilation with mechanical ventilation with mean airway pressure <6 cmH_2O
   - With significant apnea or bradycardia[a]
   - With significant tachycardia or tachypnea[b]
   - With low weight gain[c]
3. Hct <35% with an infant:
   - On >35% hood O_2
   - On continuous positive airway pressure/intermittent mandatory ventilation with mean airway pressure ≥6 –8 cmH_2O
4. Hct <45% with an infant:
   - On extracorporeal membrane oxygenation
   - With congenital cyanotic heart disease

Suggested transfusion thresholds for infants aged <4 months (UK, 2004) [19,20]

- Anemia in the first 24 h: Hb 12 g/dL (Hct ~0.36)
- Cumulative blood loss in 1 week, neonate requiring intensive care: 10% blood volume
- Neonate receiving intensive care: Hb 12 g/dL
- Acute blood loss: 10%
- Chronic oxygen dependency: Hb 11 g/dL
- Late anemia, stable patient: Hb 7 g/dL

RBC, red blood cell; Hct, hematocrit; Hb, hemoglobin.

[a] More than six episodes in 12 h or two episodes in 24 h requiring bag and mask ventilation while receiving therapeutic doses of methylxanthines.

[b] Heart rate >180 beats/min for 24 h; respiratory rate >80 breaths/min for 24 h.

[c] Gain of <10 g/day observed over 4 days while receiving ≥100 kcal/kg/day.

authors' overall recommendation is, therefore, not to exceed the higher levels of Hb used in these trials, and thus diminish the risks of overtransfusion, but not to allow the level of Hb to fall below the lower limits tested in these studies until further studies are completed.

Bronchopulmonary dysplasia, ROP, and NEC all likely involve oxidative damage to immature tissues. It has been postulated that transfusions of adult erythrocytes contribute to the risk of developing these morbidities, as a consequence of adult Hb releasing non-physiological quantities of oxygen to developing tissues. Published data support two new potential risks of transfusions among VLBW neonates. The first is an association between “early” RBC transfusions and the subsequent occurrence of a grade 3 or 4 intraventricular hemorrhage [38,39]. Although the underlying pathophysiological mechanism of this association remains to be demonstrated, efforts aimed to reduce early RBC transfusions during the first postnatal days in VLBW infants should be done.

The second reported risk is an association between “late” RBC transfusions and the subsequent occurrence of NEC. In recent years, the association between receipt of a blood transfusion and development of NEC within the following 48 h has being increasingly recognized [40].

The potential pathogenic mechanism(s) resulting in transfusion-associated NEC include the variables for which the transfusion was ordered (i.e. the Hct value of the patient at transfusion), immunologic mechanisms, and impaired biomechanical properties of the banked erythrocytes [38].

In a review in 2005, Agwu and Narchi found only low quality evidence that blood transfusion was associated with the development of NEC in preterm infants [41]. Since then further studies, including a systematic review and meta-analysis, have provided additional supportive evidence [40]. However, significant controversy remains [42].

An important clinical issue is whether withholding feeding during transfusion may reduce the risk of NEC in preterm infants. The level of evidence of the reviewed studies is low and several studies are available only in abstract form. Retrospective observational studies are vulnerable to methodological problems,

Box 4
Allogeneic red blood cell transfusion guidelines (indications and threholds) for the anaemia of prematurity [19,34].

Transfuse to maintain the blood hematocrit per each clinical situation:

>40% (35–45%[a]) for severe cardiopulmonary disease
>30% for moderate cardiopulmonary disease
>30% for major surgery
>25% (20–25%[a]) for symptomatic anemia
>20% for asymptomatic anemia

[a] Reflects practices that vary among neonatologists. Thus, any value within range is acceptable for local practices.

Table 3
Suggested hemoglobin levels (g/L) and hematocrit thresholds (%) for transfusing infants with anemia of prematurity [22,23].

Postnatal age	Respiratory support[a]	No respiratory support
Week 1	115 (35)	100 (30)
Week 2	100 (30)	85 (25)
Week 3 and older	85 (25)	75 (23)

[a] Defined as an inspired oxygen requirement >25% or the need for mechanical increase in airway pressure.

including confirmation bias, unblinded assessment, publication bias, and confounding factors. Some authors suggest that, since the risk of the intervention is low, and the potential benefit substantial, it would be reasonable to withhold feeds during transfusion pending further evidence [43]. However, there is no agreement on this practice.

Uncertainties therefore remain on the optimal transfusion regimen for preterm infants and, hopefully, two ongoing trials will aid in this. The Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-Weight Infants (ETTNO) Study will provide definitive data about the efficacy and safety of restrictive versus liberal RBC transfusion on long-term neurodevelopment outcome [44]. The 'Transfusion of Premature Trial (TOP): Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to a Restrictive Strategy?' will evaluate transfusion thresholds and neurologic sequelae [45].

5.2. EAs: erythropoietin, dapopoietin

EPO has been the most-used EA tested in newborns with anemia, the rationale for its use being the transitory reduction in EPO production in the first few months after birth. It was hoped that, by administering EPO, erythropoiesis would resume more rapidly and the need for RBC transfusion would be reduced. Dapopoietin is a long-lasting EA with the advantage of a less frequent administration schedule compared to EPO [15].

In the term infant with hemolytic anemias, it is current practice in some centers to administer EPO to children with spherocytosis in the first year of life in order to reduce the number of transfusions. The evidence-based proof for this treatment is lacking although several studies have shown a clear benefit of EPO use [46–48].

5.2.1. Open issues for EA use in preterm newborns

There is no evidence that EAs are indicated for the treatment of anemia in the preterm infant. Many studies have investigated their role in the prevention of anemia in order to reduce the number of transfusions, as early (before 8 days of life) or as late (after 8 days) administration. Early administration of EPO reduces the use of one or more RBC transfusions, the volume of RBC transfused, and the number of donor and transfusions the infant is exposed to, but these reductions are of limited clinical importance and are accompanied by significant increase in ROP [49]. EPO does not significantly reduce or increase any important adverse outcomes including mortality, intraventricular hemorrhage and NEC [49]. Therefore, the authors of the Cochrane Review conclude that EPO should not be routinely used. Nevertheless, use of EPO or darbopoietin-alfa show improved long-term neurocognitive outcomes [50].

Late administration of EPO reduces the use of one or more RBC transfusions, the number of RBC transfusions per infant (<1 transfusion per infant), but not the total volume (mL/kg) of RBCs transfused per infant. Any donor exposure is likely not avoided as most studies included infants who had received RBC transfusions prior to trial entry. Late EPO does not significantly reduce or increase any clinically important adverse outcomes except for a trend in increased risk for ROP. The authors conclude that this should no longer be a field of investigation [51].

6. Prevention of anemia

6.1. Preterm newborn

Maintaining a higher Hct/Hb has the objective of avoiding transfusions and therefore the possible risks of transfusion while allowing a good tissue oxygenation and organ development. Strategies to reduce transfusions, tested during the past 15 years, include:

- Delivery room practices. Low-cost practices that can be implemented in the delivery room to decrease the need for transfusions during the first days after birth: delayed cord clumping, milking or striping of the umbilical cord, and drawing all NICU baseline laboratory blood tests from fetal blood in the placenta.
- Measures to reduce blood loss: limiting phlebotomy losses for blood testing; returning the dead space volume after sampling an arterial catheter; microtechnique laboratory procedures; and the development of non-invasive monitoring methods allow for the reduction of repeated analysis for blood gases and other laboratory tests.
- Adopting transfusion guidelines and locally adapted transfusion criteria.
- Iron-fortified formulas. More iron than fortified formula do not seem to be necessary [9].
- EAs: EPO or dapopoietin. Early administration might be considered in selected circumstances, but should not be routinely recommended [50].

Practice points

- There is not a single clinical or laboratory indicator that defines the necessity for blood transfusion, but a combination of factors.
- Adopting standardized guidelines and criteria ameliorates transfusion strategies.
- Uncertainty remains about the precise timing and basis for transfusion.

Research directions

- Assessing the interplay between anemia, chronically hypoxemic/hypoperfused intestines, and early iron therapy or other pharmacologic approaches for prevention/treatment of anemia and RBC transfusions.
- Identify a suitable or suitable biomarkers for RBC transfusion.
- Early EPO benefits versus risks still need to be investigated.
- Transfusion thresholds and long-term effects.

Conflict of interest statement

None declared.

Funding sources

None.

References

[1] Banerjee J, Aladangady N. Biomarkers to decide red blood cell transfusion in newborn infants. Transfusion 2014;54:2574–82.
[2] Aher S, Malwatkar K, Kadam S. Neonatal anemia. Semin Fetal Neonatal Med 2008;13:239–47.
[3] Lokeshwar MR, Singhal T, Shah N. Anemia in the newborn. Indian J Pediatr 2003;70:893–902.
[4] Banerjee J, Asamoah FK, Singhvi D, Kwan AW, Morris JK, Aladangady N. Haemoglobin level at birth is associated with short term outcomes and mortality in preterm infants. BMC Med 2015;13:16.
[5] Andersen CC, Collins CL. Poor circulation, early brain injury, and the potential role of red cell transfusion in premature newborns. Pediatrics 2006;117:1464–6.
[6] Brugnara C, Platt OS. The erythrocyte and its disorders. In: Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher DE, Lux SE, editors. Nathan and Oski's hematology of infancy and childhood. 7th ed., vol. 1. Philadelphia: Elsevier; 2009. p. 36–66.
[7] Juul S. Erythropoiesis and the approach to anemia in premature infants. J Matern Fetal Neonatal Med 2012;25(Suppl. 5):97–9.
[8] Luban NL. Management of anemia in the newborn. Early Hum Dev 2008;84:493–8.
[9] Taylor TA, Kennedy KA. Randomized trial of iron supplementation versus routine iron intake in VLBW infants. Pediatrics 2013;131:e433–8.
[10] Venkatesh V, Khan R, Curley A, Hopewell S, Doree C, Stanworth S. The safety and efficacy of red cell transfusions in neonates: a systematic review of randomized controlled trials. Br J Haematol 2012;158:370–85.
[11] Bell EF, Strauss RG, Widness JA, Mahoney LT, Mock DM, Seward VJ, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. Pediatrics 2005;115:1685–91.
[12] Kirpalani H, Whyte RK, Andersen C, Asztalos EV, Heddle N, Blajchman MA, 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.
[13] Chen HL, Tseng HI, Lu CC, Yang SN, Fan HC, Yang RC. 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.
[14] Ohls RK, Roohi M, Peceny HM, Schrader R, Bierer R. A randomized, masked study of weekly erythropoietin dosing in preterm infants. J Pediatr 2012;160:790–795.e1.
[15] Ohls RK, Christensen RD, Kamath-Rayne BD, Rosenberg A, Wiedmeier SE, Roohi M, et al. A randomized, masked, placebo-controlled study of darbepoetin alfa in preterm infants. Pediatrics 2013;132:e119–27.
[16] Christensen RD, Carroll PD, Josephson CD. Evidence-based advances in transfusion practice in neonatal intensive care units. Neonatology 2014;106:245–53.
[17] Canadian Pediatric Society. Red blood cell transfusions in newborn infants: revised guidelines. Paediatr Child Health 2002;7:553–66.
[18] Roseff SD, Luban NL, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion. Transfusion 2002;42:1398–412.
[19] Gibson BE, Todd A, Roberts I, Pamphilon D, Rodeck C, Bolton-Maggs P, et al., British Commitee for Standards in Haematology Transfusion Task Force: Writing Group. Transfusion guidelines for neonates and older children. Br J Haematol 2004;124:433–53.
[20] Transfusion Task Force. Amendments and corrections to the 'Transfusion Guidelines for neonates and older children' (BCSH, 2004a); and to the 'Guidelines for the use of fresh frozen plasma, cryoprecipitate and cryosupernatant' (BCSH, 2004b). Br J Haematol 2007;136:514–6.
[21] O'Riordan JM, Fitzgerald J, Smith OP, Bonnar J, Gorman WA, National Blood Users Group. Transfusion of blood components to infants under four months: review and guidelines. Ir Med J 2007;100((6) Suppl.):1–24.
[22] Whyte RK, Jefferies AL, Canadian Paediatric Society, Fetus and Newborn Committee. Red blood cell transfusion in newborn infants. Paediatr Child Health 2014;19:213–22.
[23] Antoncecchi S, Casadei AM, Del Vecchio A, Girelli G, Isernia P, Motta M, et al. Recomendation for transfusion therapy in Neonatology. On behalf of the Italian Society of Neonatology and the Italian Society of Transfusional Medicine and Immunohematology. 2014. http://www.simti.it/linee/Volume_Neonatologia_filigrana.pdf [last accessed 19.07.15].
[24] Venkatesh V, Khan R, Curley A, New H, Stanworth S. How we decide when a neonate needs a transfusion. Br J Haematol 2013;160:421–33.
[25] Christensen RD, Ilstrup S. Recent advances toward defining the benefits and risks of erythrocyte transfusions in neonates. Archs Dis Child Fetal Neonatal Ed 2013;98:F365–72.
[26] Dzierzak E, Philipsen S. Erythropoiesis: development and differentiation. Cold Spring Harbor Perspect Med 2013;3:a011601.
[27] Montel-Hagen A, Blanc L, Boyer-Clavel M, Jacquet C, Vidal M, Sitbon M, et al. The Glut1 and Glut4 glucose transporters are differentially expressed during perinatal and postnatal erythropoiesis. Blood 2008;112:4729–38.
[28] Magor GW, Tallack MR, Gillinder KR, Bell CC, McCallum N, Williams B, et al. KLF1-null neonates display hydrops fetalis and a deranged erythroid transcriptome. Blood 2015;125:2405–17.
[29] Doshi BS, Abramowsky C, Briones M, Bunting ST. Concomitant a novel ALAS2 mutation and GATA1 mutation in a newborn: a case report and review of the literature. Am J Blood Res 2014;4:41–5.
[30] Iolascon A, Heimpel H, Wahlin A, Tamary H. Congenital dyserythropoietic anemias: molecular insights and diagnostic approach. Blood 2013;122:2162–6.
[31] Collard KJ. Iron homeostasis in the neonate. Pediatrics 2009;123:1208–16.
[32] Christou HA. Anemia. Manual of Neonatal Care 2012;45:563–71.
[33] Jopling J, Henry E, Wiedmeier SE, Christensen RD. Reference ranges for hematocrit and blood hemoglobin concentration during the neonatal period: data from a multihospital health care system. Pediatrics 2009;123:e333–7.
[34] Strauss RG. Anaemia of prematurity: pathophysiology and treatment. Blood Rev 2010;24:221–5.
[35] Sloan SR. Blood products used in the newborn. Manual of Neonatal Care 2012;42:529–37.
[36] Whyte R, Kirpalani H. Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. Cochrane Database Syst Rev 2011;(11):CD000512.
[37] Whyte RK, Kirpalani H, Asztalos EV, Andersen C, Blajchman M, Heddle N, et al., PINTOS Study Group. Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. Pediatrics 2009;123:207–13.
[38] Christensen RD. Associations between "early" red blood cell transfusion and severe intraventricular hemorrhage, and between "late" red blood cell transfusion and necrotizing enterocolitis. Semin Perinatol 2012;36:283–9.
[39] Christensen RD, Baer VL, Lambert DK, Ilstrup SJ, Eggert LD, Henry E. Association, among very-low-birthweight neonates, between red blood cell transfusions in the week after birth and severe intraventricular hemorrhage. Transfusion 2014;54:104–8.
[40] Mohamed A, Shah PS. Transfusion associated necrotizing enterocolitis: a meta-analysis of observational data. Pediatrics 2012;129:529–40.
[41] Agwu JC, Narchi H. In a preterm infant, does blood transfusion increase the risk of necrotizing enterocolitis? Archs Dis Child 2005;90:102–3.
[42] Wallenstein MB, Arain YH, Birnie KL, Andrews J, Palma JP, Benitz WE, et al. Red blood cell transfusion is not associated with necrotizing enterocolitis: a review of consecutive transfusions in a tertiary neonatal intensive care unit. J Pediatr 2014;165:678–82.
[43] Keir AK, Wilkinson D. Do feeding practices during transfusion influence the risk of developing necrotizing enterocolitis in preterm infants? Archs Dis Child 2013;98:386–8.
[44] ETTNO Investigators. The 'Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-Weight Infants (ETTNO)' study: background, aims, and study protocol. Neonatology 2012;101:301–5.
[45] Kirpalani H. The Transfusion of Premature Trial (TOP): Does a liberal red blood cell transfusion strategy improve neurologically-intact survival of extremely-low-birth-weight infants as compared to a restrictive strategy? www.nichd.nih.gov/about/Documents/TOP_Protocol.pdf [last accessed 01.08.15].
[46] Tchernia G, Delhommeau F, Perrotta S, Cynober T, Bader-Meunier B, Nobili B, et al., ESPHI working group on hemolytic anemias. Recombinant erythropoietin therapy as an alternative to blood transfusions in infants with hereditary spherocytosis. Hematol J 2000;1:146–52.
[47] Morrison JF, Neufeld EJ, Grace RF. The use of erythropoietin-stimulating agents versus supportive care in newborns with hereditary spherocytosis: a single centre's experience. Eur J Haematol 2014;93:161–4.
[48] Christensen RD, Yaish HM, Gallagher PG. A pediatrician's practical guide to diagnosing and treating hereditary spherocytosis in neonates. Pediatrics 2015;135:1107–14.
[49] Ohlsson A, Aher SM. Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2014;(4):CD004863.
[50] Ohls RK, Kamath-Rayne BD, Christensen RD, Wiedmeier SE, Rosenberg A, Fuller J, et al. Cognitive outcomes of preterm infants randomized to darbepoetin, erythropoietin, or placebo. Pediatrics 2014;133:1023–30.
[51] Aher SM, Ohlsson A. Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2014;(4):CD004868.