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Treatment and Prevention of Neonatal Anemia

John A. Widness, MD*
* Department of Pediatrics, Carver College of Medicine, The University of Iowa, Iowa City, Ia

Abstract

Because red blood cell (RBC) transfusion therapy remains the primary treatment of anemia encountered in early life, the basis for RBC transfusion in the treatment of symptomatic anemia is discussed in this review along with several important aspects of neonatal blood banking practices. Nontransfusion approaches to the prevention and treatment of neonatal anemia also are described. Finally, this review covers the controversy surrounding whether neonatal RBC transfusion therapy should be restrictive or liberal. The evaluation and treatment of uncommon and rare acquired and genetic causes of anemia in newborn infants are beyond the scope of this review.

Introduction

> "The premature newborn who appears well and is growing as expected probably knows whether he is anemic even though his geriatric care givers may think otherwise at times." James A. Stockman, III (1977) (1)

Despite advances in identifying the causes of anemia and in developing new treatments for anemia in preterm infants, allogeneic red blood cell (RBC) transfusion continues to be the primary therapy. In the United States, an estimated 260,000 RBC transfusions are administered annually to preterm very low-birthweight (VLBW) infants weighing less than 1,500 g at birth. Considerable controversy surrounds the hemoglobin (Hb) value and clinical circumstances under which RBC transfusions should be administered to preterm infants. Moreover, although infectious and noninfectious risks are known to be associated with RBC transfusion, little is known about the long-term consequences of neonatal anemia or its treatment. Two recent randomized clinical trials, in which results of restrictive and liberal RBC transfusion practices were reported, have not resolved the controversy of when RBC transfusions are indicated. (2)(3) Resolution of this important issue and others related to therapy of neonatal anemia awaits results of additional scientifically sound, evidence-based studies.

RBC Transfusions Received by VLBW Infants

Preterm critically ill newborns are among the most heavily transfused patient groups. Nonetheless, without regional or national surveillance of neonatal RBC transfusions, it is not possible to know with certainty the annual number of neonatal RBC transfusions administered or if changes occur over time. National livebirth statistics combined with our University of Iowa Children's Hospital neonatal intensive care unit (NICU) data lead to the conclusion that the total and relative number of RBC transfusions administered to VLBW infants has declined

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Objectives After completing this article, readers should be able to:
1 Understand the basis and effective methods for the prevention and treatment of anemia of prematurity, with emphasis on the use of red blood cell transfusion therapy.
2 Describe effective nontransfusion methods for the treatment and prevention of neonatal anemia.

in recent decades (Table 1). National statistics show that both the total number and percentage of liveborn VLBW infants increased by 30% from the 1980s to 2000. According to Iowa NICU data during this same period, the relative percentage of VLBW infants receiving one or more transfusions decreased by 25% (from 88% to 65%), and of those VLBW infants transfused, the mean number of RBC transfusions decreased by 30% (from 7.0 to 4.9). (5) Taken together, these data suggest a 32% decline in the number of RBC transfusions received by VLBW infants from 1980 to 2000. Based on our unpublished data comparing Iowa with other academic center NICUs, we speculate that the total number of RBC transfusions administered annually in the United States is as much as 30% higher than indicated in Table 1 or approximately 260,000 RBC transfusions. Using these transfusion estimates, anemia among VLBW infants is likely to continue as a significant clinical problem requiring RBC transfusions for the foreseeable future.

As noted in the companion article in this issue on the pathophysiology of neonatal anemia, strong evidence supports nonphysiologic factors as primary contributors to the development of anemia and to the large numbers of RBC transfusions received by critically ill VLBW infants. Foremost among these is the need for laboratory testing during the early weeks after birth, when blood sampling for patient monitoring is at its zenith.

Reducing Iatrogenic Blood Loss and the Need for RBC Transfusion

Based on multiple compelling lines of evidence supporting iatrogenic laboratory blood loss as a key contributor to the need for the large number of RBC transfusions preterm infants receive, an obvious prevention strategy is to reduce laboratory blood loss. One strategy for accomplishing this is to improve the technology of bench-top laboratory "analyzers," so that smaller analytic blood volumes are required. This evolving, technology-based approach has led to the development of point-of-care testing devices capable of performing laboratory measurements accurately and reliably on ever smaller blood volumes, with rapid turnaround time and acceptable preanalytic error. Recently, in vivo and ex vivo point-of-care "monitors" (instruments that return the blood analyzed to the patient) attached to intravascular catheters have been shown to operate with blood loss that is one order of magnitude less than that required by bench-top analyzers and approximately half the volume needed by near-patient point-of-care analyzers. In a two-center randomized trial in the NICU setting, we demonstrated that an inline, point-of-care monitor using an umbilical artery catheter significantly reduced iatrogenic blood loss and RBC transfusions during the first postnatal week, when cardiorespiratory illness is most intense. (5)

A second strategy for reducing iatrogenic blood loss is to limit laboratory blood testing to only those tests deemed absolutely necessary. Although this approach has been applied in some European centers where fewer RBC transfusions are being administered to VLBW infants, this approach has not been validated as safe and effective in prospective, randomized clinical trials.

Indications for Neonatal RBC Transfusion

> "Blood transfusion is like marriage; it should not be entered on lightly, unadvisedly or wantonly, or more often than is absolutely necessary." R.W. Beal (1976) (6)

Critically ill preterm infants are among the most frequently transfused groups of patients. Despite this, no clearcut, evidence-based guidelines exist for when RBC transfusion is indicated; rather, a variety of nonspecific clinical and laboratory "triggers" are used for this purpose. Clinical factors that have been suggested as helpful in making decisions about whether to transfuse include poor weight gain, respiratory irregularities (including apnea), and hemodynamic perturbations (particularly tachycardia). A comprehensive review of the literature on this topic concluded that: 1) the value of RBC transfusions in boosting weight

gain in otherwise stable preterm infants is tenuous, 2) the effect of RBC transfusions on respiratory irregularities is equally unfounded, and 3) the clinical significance of hemodynamic adaptive responses to anemia is questionable. (7) With respect to hemodynamic responses, the lack of left ventricular hypertrophy and the absence of change in the mean velocity of circumferential fiber shortening suggest that most neonates' circulatory compensation to anemia is adequate.

The use of laboratory parameters to determine the need for RBC transfusion has been equally unreliable. Suggested parameters include blood lactate, plasma erythropoietin (EPO), total body RBC mass, gut pH and PCO_2 by tonometry, and central and peripheral mixed venous oxygen saturation. The failure of previous efforts to demonstrate conclusively the merit of these parameters (eg, blood lactate and plasma EPO) as clinically useful RBC transfusion indicators may be explained, in part, by the fact that infants who were studied exhibited only modest anemia with adequate tissue oxygen delivery. Recently, several promising, safe, noninvasive, but as yet unproven approaches to establish more objective RBC transfusion criteria have been suggested. These include near-infrared spectroscopy and orthogonal polarization spectral imaging.

Despite having no clearcut guidelines for determining when RBC transfusions are indicated in newborns, increasingly restrictive transfusion criteria were adopted over the previous 2 decades. In the late 1980s, this movement was driven initially by concerns about the infectious risks of transfusion, particularly for human immunodeficiency virus (HIV). With the change to more restrictive RBC transfusion practices came reports in the early 1990s of substantial reductions in the number of neonatal RBC transfusions administered. Within the past decade, studies in critically ill adults demonstrated that increasingly restrictive Hb values (ie, 7.0 to 9.0 g/dL [70 to 90 g/L]) were well tolerated and safer. The latter has resulted in support for restrictive RBC transfusion practices in infants, but without evidence for the safety and efficacy of this practice in this group.

During the past several years, two randomized clinical trials have addressed the controversy of whether restricted or liberal RBC transfusion criteria should be applied in infants. (2)(3) Both reported that neonates transfused on the basis of restrictive transfusion criteria required slightly fewer RBC transfusions when transfusion guidelines were followed. From the standpoint of safety, one study observed significantly more apnea, intraparenchymal brain hemorrhage, and periventricular leukomalacia in the restrictive transfusion group. (2) This clinical trial also was based on a greater Hb difference between the restrictive and liberal transfusion groups (2.7 versus 1.1 g/dL [27 versus 110 g/L]) and a higher Hb value in the liberally transfused group. (3) Thus, it is possible that the higher Hb values may have conferred protection against apnea and brain injury and that the Hb difference between the restrictive and liberal groups in the study finding no differences may have been too narrow to demonstrate differences. Unfortunately, neither study group has yet addressed the critically important question of long-term neurodevelopmental outcome.

In the absence of evidence-based criteria indicating when RBC transfusions are needed, neonatal transfusion practices will continue to vary. The neonatal RBC transfusion guidelines used today continue to be those reached by consensus or broad agreement, although differences of opinion exist among experts and professional groups such as the American College of Pathologists. The guideline in use in our NICU, recommended by Strauss (Table 2), (8) includes obtaining weekly Hb measurements and reticulocyte counts in infants who have anemia of prematurity (AOP), are not experiencing frequent laboratory blood loss, and whose Hb values are approaching their nadir (ie, <9.0 g/dL [90 g/L]). A reticulocyte count of at least 75.0 to 100.0×10^3/mcL (75.0 to 100.0×10^9/L) is a reliable predictor that an increase in Hb is imminent

and, therefore, that a RBC transfusion is unnecessary, provided pathologic clinical signs are absent and laboratory blood loss is not high.

In the end, clinical decisions regarding RBC transfusion in VLBW infants must be based on the relative risks and benefits of the various transfusion guidelines and the clinical status of individual infants. As infectious risks associated with RBC transfusion continue to decline to a vanishingly small incidence, it seems prudent to curtail the drive to adopt more restrictive RBC transfusion guidelines. Until more information becomes available, the benefits conferred by restrictive transfusion practices seem small compared with the potential benefit of better neuroprotection associated with more liberal transfusion, which was suggested in one clinical trial. Clearly, additional sound, experimentally based criteria to guide decisions for administering RBC transfusions to anemic preterm infants remains an essential, unmet need. Neonatal research studies in which informed consent is obtained and in which the results of neurodevelopmental outcome are included to establish the safety of restrictive versus liberal RBC transfusion practices are needed.

Blood Banking Practices in RBC Neonatal Transfusion Therapy (9)(10)

> "Confidence in the nation's blood supply became an early casualty of the AIDS epidemic and disproportionate fear of transfusion a feature of its unfortunate legacy … The therapeutic index of blood still exceeds that of many common medications and medical procedures." H.G. Klein (2000) (11)

In deciding whether to administer a neonatal RBC transfusion, the clinician must consider several important efficacy and safety issues. RBC transfusion carries infectious and noninfectious risks. (12) Fortunately, scientific advances have rendered donor blood extremely safe by employing a variety of strategies, including donor deferral criteria, pathogen inactivation, and infectious disease testing (including HIV, hepatitis B, hepatitis C, human T-lymphotrophic virus, syphilis, and West Nile virus). These advances have reduced dramatically the likelihood of developing transfusion-transmitted disease. For example, the risk of acquiring transfusion-associated HIV or hepatitis C infection is now 1 in approximately 2 million blood-donor units.

In addition to these recent advances, other important advances have occurred in blood banking practices, some having particular relevance for neonatal RBC transfusions. These include: 1) transfusion of stored rather than fresh RBCs to reduce donor exposure, 2) selection of white blood cell (WBC)-reduced RBCs for transfusion to eliminate complications mediated by WBCs, and 3) prescribing of gamma-radiated RBCs to prevent graft versus host disease (GVHD).

Transfusion Using Stored RBCs in a Single-donor Program

Providing statistical proof that the risk to infants from the blood supply is reduced with single-donor programs is not currently possible in the United States because there is no regional or national oversight program targeting neonates, such studies would be expensive to conduct, and the development of posttransfusion infectious events is rare. Nonetheless, there is agreement that limiting donor exposure, when it can be accomplished safely and inexpensively, is prudent for infants who are likely to receive multiple transfusions. Studies in the past decade consistently have reported that a dedicated single-donor system, in which RBCs maintained in AS-1 or AS-3 storage media up to the 42-day limit allowed by the United States Food and Drug Administration, can supply nearly all of the small-volume RBC transfusions required by most preterm infants without adverse effects such as hyperkalemia and acidosis. Because many more infants require RBC transfusions than platelets or fresh frozen plasma transfusions and because preterm and other critically ill infants require multiple RBC transfusions, a single RBC

donor system is effective in diminishing overall blood donor exposure during the neonatal period. Long-term infectious and immune modulation risks of transfusion remain to be proven, but it is likely that the risk of infectious disease transmission is reduced when RBC donor exposure is limited.

Transfusion Using WBC-reduced RBCs to Reduce Infectious Risks

In the past, a common neonatal blood banking practice was to administer blood from only cytomegalovirus (CMV)-seronegative donors. More recently, a sound scientific basis has been established for using WBC-reduced components to prevent transfusion-transmitted CMV infections. This is accomplished by filtering donor blood shortly after collection but before storage, using a closed collection bag system involving built-in inline filters. Strong evidence suggests that WBC-reduced and CMV-seronegative blood components are equivalent in providing a substantial reduction in CMV donor infection (by 92% to 93%), (13) and either may be used as the standard of practice for all neonatal RBC transfusions. Whether a combination of the two is more effective than either alone in reducing CMV infection remains to be proven. Finally, although it is logical to speculate that WBC reduction will prevent the other posttransfusion problems caused by WBCs, data to warrant such a conclusion are insufficient.

Transfusion Using Gamma Radiation of RBCs to Prevent GVHD

Transfusion-associated GVHD is seen rarely in infants. It occurs almost exclusively among infants in recognized high-risk groups, eg, those who have severe primary immunodeficiency, those receiving intrauterine or exchange transfusions, and those receiving transfusions from blood relatives. Debate surrounds which preterm infants, particularly the least mature, are at increased risk of developing GVHD, which has raised questions about the need for gamma radiation of RBCs used for infants. Although a blanket policy employing gamma-irradiated RBC units for all infants cannot be justified purely on a scientific basis, legal and logistical factors have strongly favored such practice. Thus, current practice suggests that it is reasonable to gamma-irradiate cellular blood components for all infants during their first postnatal year, depending on the spectrum of infants being managed at individual hospitals.

Effective Nontransfusion Approaches to the Prevention and Treatment of AOP

Delayed Umbilical Cord Clamping at Delivery

Interest in delayed clamping of the umbilical cord at birth as a means of facilitating placenta transfusion to reduce subsequent RBC transfusion has increased in recent years. Studies from the 1960s and 1970s documented that approximately one third of the fetal blood volume resides in the placenta and that much of this is transfused to the newborn if cord clamping is delayed for 2 to 3 minutes. Until the past decade, these findings have been largely ignored for two reasons. First, preterm infants often require immediate resuscitation, making this procedure unfeasible. Second, there has been unfounded concern that neonatal polycythemia will result from delayed cord clamping. Interest in delaying cord clamping for 30 to 120 seconds in preterm infants has been renewed based on clinical trials showing that such a delay can contribute to a decrease in RBC transfusions. (14) Delaying cord clamping in preterm infants also has been shown to be associated with a decrease in the incidence of intraventricular hemorrhage and improved iron status in late infancy, when iron deficiency most often becomes manifest. (14) Whether similar or better results can be achieved if clamping is delayed slightly (<30 seconds) also appears possible. Recently, the problem that delayed cord clamping with cesarean section delivery is more difficult to perform (because of technical difficulties in being able to benefit from gravity when the placenta is ~20 to 30 cm above the infant) appears to be

overcome by simple, brief (~10 sec) “milking” of umbilical cord blood from the placenta to the just delivered infant. (15) This procedure, which is also applicable to vaginal deliveries, awaits larger, multicenter trials before the technique can be recommended for preterm or other infants at high risk for developing neonatal anemia.

Autologous Transfusion Using Blood Harvested from the Placenta at Delivery

An alternative to delayed cord clamping is the practice of harvesting autologous blood from the placenta immediately following delivery for later transfusion to the same patient. (16) As noted previously, the number of RBC transfusions administered to individual VLBW infants has declined; the volume of blood removed for laboratory testing has decreased; and the collection, processing, and storage of autologous placental blood have improved. Such developments have made it feasible to consider using the limited volume of autologous placental blood harvested at delivery as the sole RBC source for satisfying the total transfusion needs of preterm infants. This option is attractive because it reduces an infant’s exposure to life-threatening viral infections associated with iatrogenic blood products while conserving limited blood resources. Challenges associated with this practice are the relatively small volumes collected (~10 to 30 mL/kg), particularly in VLBW infants, where the technical process of collection is more difficult, and problems of bacterial contamination, hemolysis, and clotting (before an adequate volume of blood is harvested).

Protein Supplementation

Substantial evidence indicates that inadequate protein intake is an important contributor to anemia in preterm infants. Good evidence documents that the “normal” postnatal decrease in Hb can be attenuated by 1.0 to 1.5 g/dL (10 to 16 g/L) in preterm VLBW infants provided with daily protein intake 3.5 to 3.6 g/kg compared with those who receive intakes of only 1.8 to 1.9 g/kg. (17) These and other data indicate that the amount of protein intake needed for optimal body growth is related to body size and the level of maturity, with the smallest infants requiring the greatest daily protein intakes per kilogram of body weight.

Enteral Iron

No compelling evidence suggests that enteral iron provided to preterm infants during the neonatal period and in early infancy enhances erythropoiesis to any significant degree. Although some data indicate that parenteral iron has a small effect on enhancing erythropoiesis in preterm infants treated with recombinant human erythropoietin (r-HuEPO), (18) no data are available for untreated infants. During the early months after birth, liver and bone marrow iron stores are replete under normal conditions. However, preterm infants have proportionally smaller iron endowments at birth, and once these stores are exhausted, infants must rely on dietary iron and require daily enteral iron supplementation of 2 to 3 mg/kg elemental iron for the first postnatal year. (19) In some rapidly growing preterm infants, the stores are exhausted as early as 2 to 3 months of age, a time by which some have doubled their birthweights. (20) If current trends in more restrictive RBC transfusion practices of preterm infants continue, the need for iron supplementation may occur earlier. Although only limited supportive data are available, screening for iron deficiency between 6 and 12 months of age by measuring serum ferritin and Hb concentrations is a potential addition to the AOP treatment plan.

Vitamin Supplementation

Because preterm infants have limited body supplies of the water-soluble vitamins and higher protein requirements, adequate intake of vitamin B_{12} and folate may be important in preventing anemia. (21)(22) At discharge, it also may be prudent to supplement breastfed preterm infants with both of these vitamins to avoid pathologic anemia.

Erythropoietin and Other Erythropoiesis-stimulating Agents

During the third trimester of pregnancy, the daily rate of RBC production for the healthy fetus is approximately sixfold greater than that of maximally stimulated erythropoiesis in adults. For many critically ill VLBW infants, this level of replacement still is less than blood loss attributable to iatrogenic laboratory phlebotomy loss that requires RBC transfusion. Because of the low plasma EPO concentrations encountered in infants, r-HuEPO and other erythropoietic-stimulating agents have been suggested for the treatment of neonatal anemia to reduce the large number of RBC transfusions administered to preterm infants. As of 2006, more than 1,300 preterm infants were enrolled in 28 controlled trials in which "late administration" of EPO, ie, after the first postnatal week, was evaluated for its efficacy in reducing RBC transfusions and preventing donor exposure. Because these trials differed in multiple respects and produced markedly variable results that were difficult to reconcile, consensus recommendations regarding the use of r-HuEPO for reducing RBC transfusions in infants were not achieved. A recent Cochrane meta-analysis concluded that late administration of r-HuEPO (after the first post-natal week) reduces the number and the volume of RBCs transfused per infant, but the clinical importance of this treatment was deemed "marginal." (23) In a second Cochrane meta-analysis comparing late with early (first postnatal week) administration of EPO in 262 infants, the authors reached similar conclusions and observed an increase in the risk of retinopathy of prematurity. (24) The authors could not recommend early or late administration of EPO. Instead, they suggested that future studies focus on methods for reducing donor exposure and efforts to reduce the amount of blood withdrawn from sick newborns. If laboratory blood loss can be decreased substantially, the efficacy of EPO administration should be revisited.

Summary

Presently, RBC transfusion remains the primary treatment for anemia in the neonatal period and early infancy. Because laboratory blood loss remains the primary contributor to neonatal anemia, strategies aimed at reducing the volume of blood required for testing are likely to have a significant impact on reducing the need for RBC transfusions. Experimentally based criteria to guide decisions for administering RBC transfusions to preterm infants experiencing anemia remains an essential, unmet need. Although the use of restrictive RBC transfusion criteria has become more widespread, the merits of this practice have yet to be documented and may be associated with significant long-term neurodevelopmental risks. Thus, before more data become available, more restrictive neonatal RBC transfusion criteria are strongly discouraged outside of the research setting.

Fortunately, the risks of RBC transfusion for the treatment of neonatal anemia are low and continue to decrease, largely as a result of advances in blood bank practices. Single-donor programs for neonates limit donor exposures, cost less, and lead to better preservation of limited blood resources without incurring additional risk. WBC reduction using inline filters is a cost-effective alternative to using seronegative donors. Although gamma irradiation of RBCs for transfusions remains controversial scientifically, such practice continues.

Promising nontransfusion approaches to the treatment and prevention of neonatal anemia continue to be defined and developed. These include delayed umbilical cord clamping at birth; autologous transfusion of harvested blood at delivery; and provision of adequate nutrients, including protein, vitamin B_{12}, folate, and perhaps others. Despite the ability of r-HuEPO to stimulate erythropoiesis, until laboratory blood loss can be substantially reduced, there is not a compelling rationale for prescribing r-HuEPO for the treatment of neonatal anemia.

Abbreviations

AOP	anemia of prematurity
CMV	cytomegalovirus
EPO	erythropoietin
GVHD	graft versus host disease
Hb	hemoglobin
HIV	human immunodeficiency virus
NICU	neonatal intensive care unit
RBC	red blood cell
r-HuEPO	recombinant human erythropoietin
VLBW	very low-birthweight
WBC	white blood cell

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Table 1

Estimated Annual Small-volume RBC Transfusions Administered to VLBW Infants Weighing ≤ 1.5 kg at Birth in the United States in 1980 and 2000

	1980	2000
Total number of liveborn infants	3,600,000	4,025,000
Percentage of VLBW births	1.2%	1.4%
Annual number of VLBW births	43,200	56,350
Percentage of VLBW infants transfused	88%*	65%†
Estimated number of VLBW infants transfused	38,000	36,600
Mean number of RBC transfusions/transfused VLBW infant	7.0*	4.9†
Estimated number of RBC transfusions administered to VLBW infants	265,000	180,000

*Based on 50 consecutive Iowa neonatal intensive care unit admissions in 1982, excluding infants dying before 2 weeks of age, undergoing cardiac surgery, and receiving RBC transfusions before or after transfer (4).

†Based on 819 consecutive Iowa VLBW admissions from 2000 through 2005, excluding RBC transfusions before or after transfer (unpublished).

RBC=red blood cell, VLBW=very low-birthweight

Table 2

Red Blood Cell Transfusions for Anemia of Prematurity[*†]

- Maintain >40% to 45% (0.40 to 0.45) hematocrit for *severe* cardiopulmonary disease
- Maintain >30% to 35% (0.30 to 0.35) hematocrit for *moderate* cardiopulmonary disease
- Maintain >30% to 35% (0.30 to 0.35) hematocrit for *major* surgery
- Maintain >20% to 25% (0.20 to 0.25) hematocrit for infants with *stable* anemia, especially if:
  - –Unexplained breathing disorders
  - –Unexplained tachycardia
  - –Unexplained poor growth

[*] Words in italics must be defined locally. For example, “severe” pulmonary disease may be defined as requiring mechanical ventilation with > 0.35 FiO_2 and “moderate” as less intensive ventilation.

[†] Reprinted with permission from Strauss RG. How I transfuse red blood cells and platelets to infants with the anemia and thrombocytopenia of prematurity. *Transfusion*. 2008;48:209–217 (8).