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Nonpharmacological, Blood Conservation Techniques for Preventing Neonatal Anemia—Effective and Promising Strategies for Reducing Transfusion

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Abstract

The development of anemia after birth in very premature, critically ill newborn infants is a universal well-described phenomenon. Although preventing anemia in this population, along with efforts to establish optimal red blood cell (RBC) transfusion and pharmacologic therapy continue to be actively investigated, the present review focuses exclusively on nonpharmacological approaches to the prevention and treatment of neonatal anemia. We begin with an overview of topics relevant to nonpharmacological techniques. These topics include neonatal and fetoplacental hemoglobin levels and blood volumes, clinical and laboratory practices applied in critically ill neonates, and current RBC transfusion practice guidelines. This is followed by a discussion of the most effective and promising nonpharmacological blood conservation strategies and techniques. Fortunately, many of these techniques are feasible in most neonatal intensive care units. When applied together, these techniques are more effective than existing pharmacotherapies in significantly decreasing neonatal RBC transfusions. They include increasing hemoglobin endowment and circulating blood volume at birth; removing less blood for laboratory testing; and optimizing nutrition.

Keywords

erythrocyte transfusions; phlebotomy; neonatal anemia; delayed cord clamping; umbilical cord blood; anemia of prematurity

The development of anemia after birth in very premature and critically ill newborn infants is a universal well-described phenomenon. Since the 1950s, research has increased knowledge and understanding of the causes and therapies for neonatal anemia. Since the late 1980s, when the human erythropoietin gene was cloned and recombinant human erythropoietin and other erythropoiesis-stimulating agents became available, research has focused on the pharmacotherapy of these agents, usually in combination with oral and, occasionally, parenteral iron. Recently, several non-pharmacological approaches—the focus of this review—have begun to attract the attention of clinicians and researchers. Although some of these approaches may be perceived as simple or self-evident, they too must undergo scrutiny for

safety and efficacy. Although the jury remains out for some of these, they appear to include among the safest, most effective techniques available to most neonatal caregivers.

To understand the basis for nonpharmacological blood conservation strategies in decreasing red blood cell (RBC) transfusions, one needs to understand the factors associated with neonatal transfusions. These factors include fetoplacental blood volume, the normal postnatal decline in hemoglobin (Hb), phlebotomy blood loss in the neonatal intensive care units (NICU), and trends in transfusion practices.

Fetoplacental Blood Volume

The volume of circulating blood in the placenta has not been extensively studied in humans. Westgren et al¹ evaluated unborn fetuses at 17–31 weeks' gestation with Rh-isoimmunization to determine fetoplacental blood volume after intra-uterine intracardiac fetal transfusion, using a method in which the dilution of HbF after transfusion with donor HbA is determined. The mean ($\pm$ standard deviation [SD]) fetoplacental blood volume measured in this study was 115 ± 40 mL/kg. Although useful, this study included only one select group with a specific disease process that may not represent the fetoplacental blood volume of normal fetuses or those affected by other conditions. Morris et al² using a protein-bound tracer method to determine fetoplacental volume in previable, but otherwise normal, fetuses reported a considerably greater mean ($\pm$ SD) total conceptus blood volume of 162 ± 21 mL/kg.

The volume of circulating blood in the placenta at birth has been more extensively studied. These studies too are wrought with challenges of when and how to evaluate this blood volume accurately because of residual blood. In the study by Eichler et al³ aimed at using cord blood for autologous transfusion using gravity collection, 34 mL/kg was collected. Although sample size was small, there was a trend toward higher volumes per kilogram collected in the smallest infants. In a similar study by Jansen et al⁴ of all infants born at 24–36 weeks' gestation also with the purpose of collecting blood for autologous transfusion, 22 mL/kg was collected using gravity combined with syringe aspiration. Khodabux et al⁵ reported decreasing placental blood volumes when collected by gravity in premature infants at <32 weeks' gestation with decreasing weights, that is, 20, 18, and 15 mL/kg for birth weights >1250 g, 1000–1250 g, and <1000 g, respectively.

Neonatal Blood Volume

In 1965, Usher and Lind⁶ reported the blood volume of premature infants whose mean birth weight and gestational age were 2024 g and 33.2 weeks, respectively. Delayed cord clamping was the routine practice in this hospital at the time. The mean blood volume measured with ¹²⁵I-labeled albumin was 89 mL/kg within the first 12 hours of life. This method tends to overestimate blood volume because of extravascular leakage of ¹²⁵I label.

Additional studies using various techniques have reported mean blood volumes at birth ranging from 66 to 95 mL/kg.^{7–13} These values are assumed to be without delayed cord clamping, although this is not clearly specified in all studies. The gestational age of infants within these studies ranged from 23 weeks to term. A relatively new method of measuring for blood volume using biotin labeling of RBCs and hematocrit is promising in that it can be performed safely and accurately using as less as 20 μ L of blood.¹⁴ Furthermore, this method may to be more accurate than the previously performed methods.

Effect of Delayed Cord Clamping on Fetoplacental Blood Volume

Decades ago, Yao et al reported term fetal and placental blood volumes at various times after cord clamping and at various heights relative to the maternal introitus.^{15,16} Sisson et al¹⁷ extended this work by studying the effect of delayed cord clamping in term infants delivered by cesarean section held at various heights with respect to the maternal abdominal wall (Table 1). Independent of the timing of cord clamping, these investigators estimated the total fetoplacental blood volume as ~105 mL/kg.

Among infants at 24–32 weeks' gestation with early cord clamping, Aladangady et al¹⁸ measured neonatal blood volume at 4 hours of life as 63 mL/kg. This blood volume was <74 mL/kg, which was measured after a delay in cord clamping of 30–90 seconds for this group. The authors further reported that this difference was more pronounced with vaginal (61 vs 80 mL/kg) compared with cesarean delivery (64 vs 70 mL/kg).¹⁸

Normal Decline in Hb Levels After Birth

There is wide variability in “normal” initial Hb values immediately after birth, with lower Hb levels in less mature infants (Fig. 1).²⁰ After birth, the PaO₂, which is generally ~27 mm Hg before delivery, increases dramatically once the newborn infant has taken his/her first breaths. With increased oxygenation, there is a resultant rapid decrease in endogenous erythropoietin production, which is followed in 5–7 days by a decrease in reticulocyte count. These factors contribute to physiological anemia that universally occurs after birth (Fig. 2). In term infants, the physiological nadir of Hb levels occurs at about 2 months of life, reaching 11.0 g/dL. The physiological Hb nadir is more pronounced and occurs slightly earlier in premature infants, with Hb levels reaching 9.5 mL/dL for infants weighing 1500–2000 g and 9.0 g/dL for infants weighing <1500 g at birth.²¹

In a European observational study, Hb levels encountered among 150 very low-birth-weight (VLBW) infants during the first 6 weeks of life, the median Hb nadir was 10.6 g/dL.²² In this study, the authors indicate that this nadir is not completely representative of normal because some infants were transfused. Additionally, because this study was stopped earlier than previously reported physiological nadirs (Fig. 2) and because of heavy laboratory phlebotomy losses (Table 2), the authors' findings should not be viewed as indicative of the true physiological nadir Hb levels for VLBW infants.

Impact of Laboratory Phlebotomy Loss on Neonatal Anemia and RBC Transfusion

Iatrogenic phlebotomy loss resulting from the intensive clinical monitoring required for critically ill newborns in the weeks immediately after birth remains a key contributor to neonatal anemia and the need for RBC transfusion. Evidence supporting this includes the following:

1. Estimates of NICU laboratory blood draws primarily in the first weeks of life among premature VLBW infants when clinical illness is at its zenith (Fig. 3).²⁹ During the first 6 weeks of life, laboratory blood losses have been reported to range from 11 to 22 mL/kg per week, which is equivalent to 15%–30% of the circulating blood volume (Table 2).²⁹ To further place this in perspective, 6–7 mL of blood drawn from an infant weighing 1 kg is equivalent to a 450 mL blood loss in an adult.
2. The temporal association in the intensity of laboratory phlebotomy loss and the administration of RBC transfusions. Approximately 70% of all RBC transfusions to

VLBW infants are given in the first month of life with 44% given in the first 2 weeks (Fig. 4).³¹

3. The direct relationship between the volume of blood removed for laboratory testing and the volume of blood transfused from VLBW infants (Fig. 5).³² In several studies, highly significant direct associations have been observed between volume of blood removed and that transfused (ie, correlation coefficients of 0.75–0.90).^{24,28,32,33}

When considering neonatal laboratory blood loss, it is important to be aware of the specific blood tests most frequently performed on VLBW and other critically ill neonates. This information can guide strategies for reducing laboratory blood loss, as technologic advances impact the future design and capabilities of blood analyzers and monitors. One study in the 1990s reported the frequency of specific laboratory analytes drawn in the routine management of 50 consecutive, critically ill, ventilated VLBW infants managed while an umbilical arterial catheter was available for blood sampling.³⁴ The frequency of laboratory analytes drawn in order of decreasing frequency in this study was pH, PCO₂, PO₂, electrolytes, glucose, Hb, calcium, lactate, bilirubin, creatinine, blood urea nitrogen, and others (eg, blood culture, type and screen/cross-match, newborn metabolic screen) (Fig. 5).

Variability in and Factors Influencing Laboratory Phlebotomy Loss in Neonates

As described earlier, phlebotomy loss is a significant contributor to anemia in extremely low-birth-weight (ELBW) and VLBW infants. Despite widespread acceptance of this practice, sometimes referred to as “hemorrhaging into the laboratory,” marked variation in blood loss because of laboratory testing has been noted. For example, in comparing laboratory blood loss during the first 2 weeks of life in infants with birth weights <1500 g, Ringer et al²⁵ reported that one NICU drew 17.5 mL/kg of blood, whereas another drew nearly twice as much (34.1 mL/kg). After statistical adjustment for birth weight, gestational age, and severity of illness, the difference in laboratory blood loss was 10.7 mL/kg per patient between the 2 NICUs. Obladen et al²⁴ in the late 1980s reported blood loss of 24, 60, and 67 mL/kg for increasingly sick infants in their cohort. In addition to reporting significant variation in phlebotomy loss (7–51 mL/kg), Nexø et al³⁵ reported that among 20 VLBW infants, 25% of the phlebotomy losses were in excess of the need for analytical procedures. Although variation in phlebotomy loss may in part be explained by differences in gestational age, birth weight, severity of illness, and other factors, the wide variation observed indicates considerable opportunity in limiting phlebotomy loss. By critically examining each laboratory blood draw for its need and timeliness in terms of interventions in care, individual and groups of neonatal caregivers may be able to limit unnecessary blood sampling.

Current State of and Factors Influencing RBC Transfusion Practice

In parallel with laboratory phlebotomy loss, the likelihood of infants receiving RBC transfusions decreases with both increasing gestational age and birth weight. Jansen et al⁴ reported that infants born at 24–28, 28–30, and 30–32 weeks' gestation experienced RBC transfusion rates of 94%, 62%, and 35%, respectively. A similar pattern was observed for infants with birth weights of <1000, 1000–1499, and 1500–1999 g having transfusion rates of 90%, 58%, and 28%, respectively, of their groups receiving one or more RBC transfusions. Using multivariate regression modeling, Ringer et al²⁵ demonstrated that each week gestational age an infant is delivered prematurely, the infant's transfusion requirements are increased by 3.8 mL/kg in the first 14 days of life and by 5 mL/kg from day 15 to discharge, when holding other factors constant.

In the mid-1990s, Widness et al reported the decreasing trend in RBC transfusions (Fig. 6). The mean ($\pm$ SD) number of transfusions decreased from 7.0 ($\pm$ 7.4) in 1982 to 5.0 ($\pm$ 5.3) in

1989 and further to 2.3 ($\pm$ 2.7) by 1993. The number of donor exposures decreased from 4.8 in 1982 to 2.2 in 1993.³¹ This trend was also reported by Maier et al²⁷ who also reported a temporal decreased RBC transfusions among VLBW infants, that is, from 70% in 1990 to 65% in 1994.

In 2000, Maier et al³⁶ demonstrated that changing transfusion practice guidelines resulted in decreased transfusions among ELBW infants. The number of transfusions in their cohort decreased from 7 to 2 transfusions per infant between 1989 and 1997. Donor exposure decreased from 5 to 1 donors per patient, whereas the volume of blood transfused decreased from 131 to 37 mL/kg of packed RBCs.

In 2009, Rabe et al³⁷ evaluated the effect of a multipronged approach to decreasing RBC transfusions in VLBW infants. The components of this approach included delaying cord clamping for 30 seconds, increasing early protein intake, beginning early oral iron supplementation, and instituting restrictive transfusion guidelines. When this approach was employed, median transfusions decreased from 4 to 1.5 per infant.

Despite a trend toward fewer RBC transfusions in recent years, significant variation remains in transfusion practices between NICUs. Two NICUs in the United States reported transfusion data for infants weighing <1500 g. The rate of transfusion in 1 NICU was almost 87%, whereas the other NICU reported a rate of 65%. After correcting for gestational age, birth weight, and severity of illness, a significant difference remained in the volume of donor blood transfused. One NICU transfused 20.9 mL of blood per patient more than the other in the first 14 days of life and an additional 36.8 mL per patient more than the other NICU after day 15.²⁵ In a similar study by Bednarek et al³⁸ comparing transfusion practices of 6 NICUs, there was significant variation in transfusion practices after correcting for birth weight and severity of illness, with 1 NICU transfusing an additional 24.1 mL in the first 14 days of life and an additional 47.3 mL from day 15 onward compared with the NICU with the lowest rate of transfusion.

To date, there are no universally accepted RBC transfusion thresholds for premature infants. Unlike adults and older children, the relative percentages of HbA and HbF, circulating Hb concentrations, oxyhemoglobin dissociation curves, and oxygen requirements are dynamic, which are highly variable factors influencing tissue oxygen delivery. These and other factors make determining optimal transfusion thresholds elusive. Despite these challenges, both the Canadian Pediatric Society³⁹ and American Association of Blood Banking⁴⁰ have published recommendations for transfusion. Both sets of criteria are based on combination of Hb levels and various clinical indicators and the severity of illness. Several recent randomized clinical trials have been undertaken to determine whether a liberal or restrictive transfusion strategy results in more favorable short- and long-term outcomes. Although it is not our purpose to justify or debate RBC transfusion criteria being currently applied, we acknowledge this as an important area of ongoing study.⁴¹

Nonpharmacologic Blood Conservation Strategies

Neonatal anemia as described previously in association with factors related to avoidance of excessive perinatal blood loss is a well-described phenomenon. Because of the lack of consensus in what constitutes an optimal transfusion threshold trigger, this important clinical topic continues to be debated and studied. Of note with respect to the focus of the present review are 2 recent retrospective research studies by Baer et al^{42,43} demonstrating a highly significant association between RBC transfusions and intraventricular hemorrhage (IVH). Based on the association that these investigators observed between IVH and RBC transfusions and meta-analysis of delayed cord clamping being associated with a decrease in IVH,⁴⁴ one could hypothesize that a decrease in the heavy phlebotomy losses experienced

by VLBW infants in the early days of life when IVH and RBC transfusion are the most common could result in a decrease in the incidence of IVH.⁴⁵ Also noteworthy in considering the association of RBC transfusions with other highly important neonatal conditions are studies demonstrating associations of RBC transfusions with retinopathy of prematurity⁴⁶ and necrotizing enterocolitis.⁴⁷ In this case also, if laboratory phlebotomy loss could be significantly reduced, one could speculate that these morbidities might also be reduced.

In considering effective, yet practical, techniques for avoiding excessive perinatal blood loss, there are several non-pharmacological strategies for prevention and treatment of neonatal anemia that should be considered. These include increasing initial blood volume; removing less blood; and increasing blood production.

Increasing Initial Blood Volume

Recently, 2 strategies have been described to increase initial blood volume: delayed cord clamping and cord milking. Delayed cord clamping is a technique that was described nearly half a century ago.⁴⁴ More recently, cord stripping or cord “milking”—a technique that may be better suited than delayed cord clamping for preterm infants—has been described.⁴⁸ Both techniques share the same goal of transfusing the newborn with his/her own residual placental blood. This can have significant effect on the blood volume of the infant, increasing it by as much as 10–20 mL/kg (Table 1).

Delayed Cord Clamping

Perhaps, the most widely discussed intervention for decreasing transfusion in recent years has been delayed cord clamping.^{44,49–52}

A 2008 systematic review of randomized controlled trials showed that delayed cord clamping of at least 30 seconds among infants at <37 weeks' gestation (most included infants were at <34 weeks' gestational age) resulted in a higher hematocrit (49.3% vs 46.3%) within the first hour of life, 51% decreased risk of transfusion for anemia (25% vs 52% transfused), fewer transfusions per patient, and 47% decreased risk of IVH. There were fewer deaths in the delayed cord clamping group, although this was not statistically significant.⁴⁴

Since the systematic review by Rabe et al in 2008,⁴⁴ a number of additional studies have reported various outcomes with delayed cord clamping. Strauss et al⁵³ reported an increased RBC volume/mass after delayed cord clamping. Developmental follow-up at 7 months suggested that delayed cord clamping in male infants may have a protective effect against motor disability.⁵⁴ Infants who underwent delayed cord clamping had higher superior vena cava flow, and the frequency of low superior vena cava flow after delayed cord clamping was significantly lower than after immediate cord clamping.⁵⁵

Cord Stripping

Manual stripping or milking of the umbilical cord immediately after birth has been suggested as an alternative to delayed cord clamping. Rather than allowing normal pulsations and/or gravity-mediated transfer of placental blood to the newborn infant, actively milking the umbilical cord from placenta toward the infant provides increased blood volume before cord clamping. Although this practice was reported over half a century ago, it did not gain acceptance as the standard of care.^{56,57} Recently, Hosono et al reported their outcome results of milking the umbilical cord 2–3 times after delivery at 24–28 weeks' gestation. Doing so resulted in fewer infants requiring one or more RBC transfusions (35% vs 70% in controls), higher Hb (by 2.4 g/dL), fewer transfusions, fewer days of mechanical

ventilation, and decreased duration of oxygen requirement.⁴⁸ By measuring the residual placental blood volume after birth, Erickson-Owens et al⁵⁸ demonstrated that cord milking transferred blood to the infant at term. In addition, hematocrit (mean $\pm$ SD) in these infants was shown to be higher in the cord milking group compared with no cord milking at 36–48 hours (57.5 ± 6.6 vs 50.0 ± 6.4). Rabe et al⁵⁹ in a 2011 study of infants at <33 weeks' gestation compared delayed cord clamping with cord milking. In this trial, infants were randomized to either 30-second delayed clamping or cord milking 4 times before umbilical cord clamping. Both strategies were effective and yielded similar Hb levels at 1 hour of life, similar numbers of neonates treated with RBC transfusion, and similar numbers of transfusions in the first 6 weeks of life.

Several authors have described collection of placental blood followed by processing and subsequent autologous transfusion.^{3–5,60} Although this has been successfully performed, the benefits of autologous transfusion may also be achieved by delayed cord clamping or umbilical cord stripping. Collection and storage of cord blood for autologous transfusion requires careful processing just as any blood-banking product requires. Potential concerns with autologous transfusion are the economic consequences of collecting and storing cord blood that goes unused. Brune et al⁶⁰ successfully provided autologous transfusions for surgical patients with necrotizing enterocolitis, gastroschisis, myelomeningocele, and congenital heart disease. As the benefits and risks of delaying cord clamping and stripping become clearer, further research will be required to determine whether specific patient populations, such as those listed previously, or others will benefit from autologous transfusion compared with that of delayed cord clamping or milking.

Removing Less Blood

Obtain Admission Laboratory Tests From the Placenta

The placenta is responsible for delivering/transferring oxygen and nutrients from the mother to the fetus. In this complex organ, the maternal and fetal circulations are separated by the trophoblastic membrane so that blood obtained from the umbilical cord vessels is fetal (ie, not maternal). The otherwise discarded, easy to obtain, placental blood (“cord blood”) can thus be used to obtain initial laboratory studies, thereby avoiding the need to remove significant volumes of blood from the neonate for admission laboratory testing (Fig. 7). In the event of multiple gestation, extreme care must be given to identifying each placenta correctly. Clamping the umbilical cord attached to the placenta of baby “A” with 1 cord clamp, baby “B” with 2 cord clamps, and so forth, is effective in avoiding misidentification. Fortunately, neither delayed cord clamping nor cord stripping precludes obtaining neonatal laboratory tests from the placenta (Carroll, unpublished data, December 2011). Admission blood for laboratory testing that may be obtained from the placenta or umbilical cord is discussed later.

Complete Blood Count and Differential

A recent study evaluated complete blood count and differential in paired samples from the umbilical cord immediately after delivery and from the premature infant in the first hours of life.⁶¹ This study demonstrated minimal difference in Hb level between cord and neonatal blood and no difference in platelet count between cord and neonatal blood. The white blood cell count was lower in cord blood compared with neonatal blood, although significant variation was seen in mean white blood cell count obtained from various neonatal sources (ie, capillary, umbilical venous catheter, etc.)⁶² (Table 3). This study, along with the studies by Hansen et al⁶³ and Christensen et al,⁴⁵ suggests that there would be no change in medical decision making in the great majority of infants using cord blood results.

Blood Culture

Concern most frequently raised regarding the use of cord blood or placental blood for cultures is that of contamination. Because the placenta is delivered through the same vaginal canal or abdominal incision as the infant, proper sterile technique is critical for blood culture collection.

Several studies have compared blood cultures obtained from the placenta or cord with the initial, subsequent neonatal samples (Table 4). In 1981, Polin et al⁶⁴ demonstrated that this could be done with a similar contamination rate as direct infant sampling. Herson et al used a much higher blood culture volume from the placenta. In this study, several of the infants who were clinically ill had negative infant blood cultures and positive placental cultures. This suggests that the increased placenta blood volume cultured may be a better, more accurate source than small volumes taken from the infant.⁶⁵ Most recently, Hansen et al⁶³ and Christensen et al⁴⁵ demonstrated the ability to obtain cord/placental cultures without contaminated samples.

Type and Screen

Although umbilical cord blood for newborn blood type and screen has been recommended in obstetrical literature and by the American Academy of Pediatrics,^{66,67} few studies have evaluated the utility of testing cord blood type and screen for transfusion purposes. Particular care must be given to correct specimen labeling in the case of multiple gestation as described previously.

Newborn Metabolic Screening

Using otherwise discarded placental/cord blood for metabolic screening offers several advantages in the sickest pre-term and term infants by the following ways:

1. Acquiring neonatal RBCs for testing before the infant's first transfusion is needed, except for rare infants needing in utero transfusions.
2. Offering an opportunity to obtain potentially useful, critical metabolic screening test results sooner than if obtained days later.
3. Speeding the admission and stabilization process by eliminating nursing time and attention required for this blood draw.
4. Minimizing hemodynamic fluid shifts associated with neonatal sampling, particularly when obtained from a catheter.⁶⁸

Current recommendations by the Clinical and Laboratory Standards Institute⁶⁹ are used by most states for their newborn screening guidelines. These recommendations acknowledge that, "it is unrealistic to expect a single specimen, no matter when it is collected, to be adequate for (the premature, low birth weight, or sick infant) population." Therefore, Clinical and Laboratory Standards Institute recommends serial dried blood spot screening with the first screen obtained on admission, the second at 48–72 hours, and the third at 28 days of life. Metabolic screening tests obtained at birth are accurate for sickle cell disease, biotinidase deficiency, galactosemia, and fatty acid oxidation disorders. Dried blood spot testing for cystic fibrosis within the first 12 hours of life may yield false-positive results owing to elevated immunoreactive trypsinogen associated with acute illness and the stress of birth. Congenital hypothyroidism testing in premature infants is often falsely negative for up to 6 weeks because of an immature hypothalamic-pituitary-thyroid axis. False-positive urea cycle, amino acid and organic acid disorder, and homocystinuria results may occur during parenteral nutrition, although too early specimen collection can also yield false-negative results in premature infants.

Laboratory-Based Approaches to Decreasing Laboratory Phlebotomy Loss

As NICU critical care continues to evolve, the need for minimal and noninvasive laboratory testing on smaller and smaller sample volumes is likely to increase. This pressing need was highlighted at a National Institute of Child Health and Human Development (NICHD) Workshop in 2009, focused on safe and effective devices and instruments for use in NICUs.⁷⁰ As indicated earlier, laboratory blood testing in the NICU is highly associated with low gestational age and severity of illness. Technological advances have taken place in recent years in bench-top laboratory analyzers, point-of-care testing devices, and transcutaneous measurement that allow increasing numbers of analytes to be measured on smaller and smaller—or no—volumes of blood. Indeed, the development of these technologies,^{28,71,72} along with restrictive neonatal transfusion criteria,^{28,73,74} has already been shown to reduce neonatal laboratory blood loss and/or RBC transfusions (Figs. 8 and 9). Of note with this regard is a report in which laboratory phlebotomy loss in VLBW neonates was limited to 3.6–5.4 mL/kg in the first week of life (compared with the 33.2 mL/kg shown in Fig. 3) and was not associated with anemia.⁷⁶

In some NICUs, a majority of the blood drawn for laboratory testing is wasted in the interest of having to return to the bedside to repeat testing for inadequate or questionable results (Fig. 4). How often this occurs is uncertain, but it is likely infrequent. Laboratory methods that require individualized handling of small neonatal blood samples, including hand dilution (eg, for hematological measurements),⁷⁷ are not easily adapted for today's highly automated central laboratories. Furthermore, they are costly when viewed from the perspective of the costs of sample analysis.

In the future, microchip, microarray, and nanotechnology devices performing polymerase chain reaction, immunoassay, and other analytical procedures on submicroliter samples, for example, dried blood spots,⁷⁸ are also likely to become available.⁷⁹ This technology will almost certainly open up new areas for diagnosis and treatment of the neonate.

Also worthy of special mention are devices capable of non-invasive measurement of key blood analytes. This has always been the “Holy Grail” for clinicians seeking to significantly reduce, or if possible eliminate, all RBC transfusions neonates receive. Infrared spectrophotometric methods for noninvasive oxyhemoglobin arterial and tissue saturation, tissue Hb, and bilirubin determinations are now available. Others such as glucose, lactate, blood urea nitrogen may not be far off in the foreseeable future.

It is anticipated that future advances in laboratory technology will continue the trend of allowing for the determination of more analytes on smaller and smaller volumes of blood. This in turn is likely to improve treatment of critically ill neonates by reducing RBC transfusion needs—and RBC transfusion-associated morbidities—by preventing the development of clinically significant anemia attributable to laboratory phlebotomy loss.

Removal of Unnecessary Indwelling Catheters

Recent emphasis on decreasing catheter-related bloodstream infections has led to the recommendation to remove intravascular catheters as soon as they are no longer necessary. An advantage in doing so is the associated decrease in laboratory blood loss. Bednarek et al retrospectively compared RBC transfusion practices in 6 NICUs. Using regression modeling to adjust for severity of illness, this group demonstrated that indwelling arterial lines were associated with significantly higher phlebotomy loss.³⁸

Optimizing Nutrition

Adequate protein intake is an important factor in stimulating erythropoiesis and thereby avoids anemia in preterm infants. In 1985, Rönnholm and Siimes provided the first strong evidence documenting that Hb levels are 1.0–1.5 g/dL greater in preterm VLBW infants provided daily protein intakes that are close to that recommend today, that is, 3.5–3.6 g/kg, compared with protein intake of 1.8–1.9 g/kg (Fig. 10).⁸⁰ Consistent with the well-established fact that adequate protein intake is needed for optimal body growth, the protein-supplemented VLBW group also demonstrated greater weight gain: 1490 versus 633 g during the 6-week study period. In successful multipronged treatment-prevention strategy for minimizing neonatal anemia and reducing RBC transfusions by Rabe et al,³⁷ these investigators included enhanced protein intake beginning immediately after birth.

Summary and Conclusions

The most effective and promising nonpharmacological blood conservation strategies and techniques for newborn infants covered in the present review include (1) increasing the Hb endowment and circulating blood volume at birth; (2) removing less blood for laboratory testing; and (3) maintaining optimal nutrition. Taken together, these strategies are effective in significantly decreasing—and sometimes eliminating—neonatal RBC transfusions. Results of delayed cord clamping studies in ELBW and VLBW infants are promising with some demonstrating decreased IVH, higher Hb, and fewer RBC transfusions. These data suggest that focusing on nonpharmacological approaches for the prevention and treatment of neonatal anemia may also result in improved long-term outcomes for these vulnerable, high-risk infants. For example, based on the association observed of IVH with RBC transfusions, it is possible that by decreasing the large phlebotomy losses in the first days of life when IVH and RBC transfusions are most common, the incidence of IVH can be further reduced. Additional research is needed to assure the safety and efficacy of the nonpharmacological techniques begun just before or shortly after birth. Research directed at ensuring adequate Hb mass and blood volume at birth, minimizing phlebotomy, and providing adequate nutritional support for effective growth and erythropoiesis has potential for further decreasing RBC transfusion needs and in doing so improves the outcomes of neonates at greatest risk for adverse outcomes.

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Figure 1.

Reference ranges (5th percentile, mean, and 95th percentile) are shown for blood Hb concentrations obtained during the first 6 hours after birth, among patients at 22–42 weeks' gestation. Values were excluded if the diagnosis included abruption, placenta previa, or known fetal anemia or if a blood transfusion was given before the first hemoglobin was measured. Reprinted with permission from Christensen et al.¹⁹

Figure 2.

Hemoglobin concentrations and reticulocyte counts in pre-term and term infants during the first 6 postnatal months. Median values and 95% confidence limits are indicated for each of 3 birth weight groups: >3000 g, 1501–2000 g, and 1000–1500 g. Reprinted with permission from Dallman.²¹

Figure 3.

Mean cumulative blood loss for laboratory testing in the first 28 days of life in 14 very low-birth-weight (VLBW) infants. At the end of 28 days, 36% of blood was required for the laboratory instrument for analysis, 54% of blood was discarded as waste, and 9% was lost as hidden waste (ie, on gauze, syringes, bedding materials, Band-Aid). Adapted with permission from Friese et al.³⁰

Figure 4.

Number of red blood cells (RBC) transfusions administered in successive weeks of life to study infants weighing 1500 g or less at birth in the years 1982 (prerecognition of AIDS virus), 1989, and 1993. The mean percentage of RBC transfusions before hospital discharge that were administered was 29% in the first week of life, 44% in the first 2 weeks, 59% in the first 3 weeks, and 70% in the first 4 weeks. Reprinted with permission from Widness et al.³¹

Figure 5.

Volume of packed blood red cells transfused and phlebotomized. The bar graph shows the mean ($\pm$ SEM) values for transfused and phlebotomized blood volumes per kilogram birth weight. The scatter plot compares the volumes and the Goodness of Fit value and regression line. Volume of blood transfused per kilogram of infant weight is 2 times higher than volume of blood phlebotomized (Nonparametric sign test, $P < 0.0001$). Reprinted with permission from Valieva et al.³²

Figure 6.

Mean ($\pm$ SEM) number of laboratory tests per infant in 50 consecutive, ventilated very low-birth-weight (VLBW) infants with umbilical artery catheter in place for 7.0 ± 4.0 days of life (DOL; mean $\pm$ SD). A total of 7039 blood tests were performed, equivalent to 20.1 tests per infant per day. Adapted with permission from Alves-Dunkerson et al.³⁴

Figure 7.
Procedure for obtaining placental blood for admission laboratories. An 18-gauge angiocatheter attached to a 10-mL syringe is used to puncture the umbilical vein.

Figure 8.

Number of RBC transfusions administered per infant in the first 2 weeks of life. A significant marked reduction in RBC transfusions was observed after introduction of the point of care testing device. Adapted with permission from Madan et al.⁷¹

Figure 9.

Difference in blood volumes required for in-line ex vivo monitor versus bench-top blood analyzer capable of measuring blood analytes that are among those most frequently measured in critically ill neonates: pH, PCO₂, PO₂, sodium, potassium, and hematocrit. Adapted with permission from Widness et al.⁷⁵

Figure 10.

Influence of human milk protein supplementation on the hemoglobin concentration. *P* values represent the statistical significance between the protein supplemented (3.5–3.6 g/kg-d) (—) and unsupplemented (1.8–1.9 g/kg-d) infant groups (----). **P* < 0.05, ***P* < 0.01. Reprinted with permission from Ronnholm and Siimes.⁸⁰

Effect of Relative Position of Infant During Delayed Cord Clamping and Duration of Delayed Cord Clamping on Fetal and Residual Placental Blood Volumes

Table 1

Mode of Delivery	Infant Position	Time of Delayed Clamping (Seconds)	Blood Volume (mL/kg)			Author
			Fetus	Placenta		
Vaginal	Neutral	5	70	35		Yao et al, 1969 ¹⁵
	Neutral	180	93	12		
	40 cm above introitus	180	n/a	24		Yao and Lind, 1969 ¹⁶
	20 cm above introitus	180	n/a	20.5		
	10 cm below introitus	180	n/a	13.8		
Cesarean section	40 cm below introitus	30	n/a	16.3		
		Immediate clamping	87	n/a		Sisson et al, 1973 ¹⁷
	15 cm above abdominal wall	180	67	n/a		
	15 cm below vagina	180	106	n/a		

n/a, not available.

Table 2
Studies of Neonates Weighing <1500 g Reporting Laboratory Phlebotomy and RBC Transfusion Data

Authors	Year	N	Infant Study Population	Postnatal Age (weeks)	Mean Birth Weight (grams)	Weekly Phlebotomy Loss (mL/kg)	Weekly RBC Transfusion Volume (mL/kg)	Correlation Phlebotomy vs Transfusion (r^*)
Blanchette and Zipursky ²³	1984	57	<1500	Birth to 6 weeks	Not reported	11.1	6.7	0.82
Obladen et al ^{24, †}	1988	60	<1500	Birth to 4 weeks	1161	12.7	10.6	0.91
Ringer et al ²⁵	1998	270	Hospital A: <1500 Hospital B: <1500	Birth to 2 weeks	1073	8.2	15.7	Not reported
Alagappan et al ²⁶	1998	80	<1250	Birth to 2 weeks	978	21.4	16.8	Not reported
Maier et al ^{27, †}	2002	79	500–1000 g	Birth to 2 weeks	948	20.7	21.7	Not reported
Widness et al ²⁸	2004	47	500–1000 g 3 umbilical artery catheter	Birth to 2 weeks	734	36.7	22.2	0.73
						Mean	14.1	0.82
						SD	6.9	0.09

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* Correlation coefficient for phlebotomy volume versus transfusion volume.

[†] Indicates European study.

Table 3

Paired Comparison of White Blood Cell, Hb, Hematocrit, and Platelet Count in Fetal Cord Blood and Neonatal Admission Blood

Laboratory Test	Fetal Cord Blood	Neonatal Admission Blood	Difference (95% CI)*
White blood cell count ($\times 1000$ cells/ μL)			
Capillary (n = 18)	9.5	14.1	4.6 (3.1, 6.0)
Radial artery (n = 25)	8.6	11.4	2.8 (1.5, 4.0)
Umbilical venous catheter (n = 58)	8.3	9.5	1.2 (0.5, 1.9)
Umbilical arterial catheter (n = 38)	7.4	10.3	2.9 (1.7, 4.1)
All sources (n = 139)	8.3	10.7	2.4 (1.9, 2.9)
Hemoglobin (g/dL)			
Arterial and venous specimen (n = 146)	14.5	15.1	0.6 (0.3, 0.9)
All sources (n = 174)	14.5	15.5	1.0 (0.7, 1.2)
Platelet count ($\times 1000$ platelets/ μL)			
All sources (n = 141)	224	230	6 (−4, 15)

Adapted with permission from Carroll et al.⁶²

* Paired *t* test.

Table 4
Comparison of Blood Cultures Obtained from the Umbilical Cord/Placenta and Postnatal Neonatal Sampling

	Culture Volume	Cord/Placental Cultures						Patient Cultures					
		Positive Cultures			Contaminants			Positive Cultures			Contaminants		
		n	n	Rate	n	n	Rate	n	n	Rate	n	n	Rate
Polin et al, 1981 ⁶⁴	2 mL	200	6	3.0%	5	2.5%	29	2	6.9%	1	3.4%		
Herson et al, 1998 ⁶⁵													
High risk		35	10	28.6%	3	8.6%	35	2	5.7%	1			
Medium risk	5 mL × 2–3	26	0	0%	0	0%	26	0	0%	0			
Low risk	20	0	0%	0	0%	20	0	0%	0				
Hansen et al, 2005 ⁶³	1 mL	113	0	0%	0	0%	113	0	0%	0	0%		
Total		394	16	4.1%	8	2.0%	223	4	1.8%	2	0.9%		