Neonatal red cell transfusions

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This review discusses RBC transfusion in the neonatal age group and explores how one institution arrived at current common practice. Special considerations such as CMV infectious risk and GVHD are discussed. Immunohematology 2008;24:10–14.

The neonatal intensive care unit (NICU) patient population is one of the patient groups in the hospital most heavily transfused with RBCs. All infants experience a normal decline in hemoglobin concentration during the first weeks of life; however, this is problematic in premature infants because of a diminished output of erythropoietin in response to anemia. In addition, these patients, who often have low birth weights, need close monitoring of blood gases, electrolytes, and other laboratory variables, which contributes substantially to the transfusion requirement as a result of the small circulating RBC volume. Although these tests are often impossible to do without, there is some help that can be provided to the phlebotomists to relieve the blood loss volume from being even greater. The infant younger than 4 months of age is immunologically immature, which makes RBC alloimmunization exceedingly rare, so some of the serologic testing performed in the blood bank for other age groups can be abbreviated. This 4-month period is often defined in the blood bank as the neonatal period because of this distinction. In other medical subspecialties the term neonate may describe different age ranges. For this patient population the reverse grouping and the crossmatch that are seen in routine blood bank practice can be waived. This saves the repeated drawing of a crossmatch specimen every 3 days. Initial testing must determine ABO group and D type and include a screen of the serum (infant’s or mother’s) for unexpected antibodies. If there are antibodies present in the serum, blood that tests negative for the corresponding antigen can be provided without crossmatch.1

In the start of the 1990s the sick infant who underwent multiple transfusions was typically exposed to 9 or 10 different donors.2 These transfusions were dispensed in small amounts or “aliquots” of the original unit because of the small size of the patient, but even so the number of donors increased the risk of certain transfusion-related complications, such as infectious risks, which are proportional to donor exposure. Neonatal transfusion practices have changed since then, not in reducing the total volume of blood transfused, but in decreasing the number of donor exposures. At the outset of the decade the rise in potassium that was seen in RBC units stored for any length of time was feared by neonatologists because of the risk that a posttransfusion rise in serum potassium to abnormal levels would cause fatal arrhythmias. Studies of small-volume transfusions in neonates that compared units of RBCs stored until their expiration date with fresher units showed that posttransfusion potassium concentrations did not rise to abnormal levels and were not a clinical issue.3–5 It is important to note that the transfusions being discussed were small-volume (15 mL/kg), slow transfusions. Large-volume, rapid transfusions performed in this age group can occur in surgery, exchange transfusion, and extracorporeal membrane oxygenation. When the potassium load cannot distribute itself throughout the total blood volume quickly enough, it may result in arrhythmia. This was described in 1993 in a neonate who received older RBCs as a rapid transfusion in cardiac surgery, and died of cardiac arrest.6 The RBCs were stored in CPDA-1; today more commonly used additive solutions have a better potassium profile. However, it is still prudent in a rapid or large-volume transfusion setting to use the freshest RBCs possible as opposed to units that are close to their expiration date, although in a small-volume, slow transfusion setting, minimizing donor exposures is more important than age of the RBCs.

Another change in practice occurring at the same time, as alluded to previously, was the use of additive solutions, which were new to transfusion services. These solutions increased RBC storage to 42 days because they were better for RBC metabolism and decreased hemolysis. The first additive solution in widespread use was AS-1 (Adsol), which contained additional dextrose...
and mannitol. Mannitol may cause an osmotic diuresis, which again was worrisome to neonatologists because of the potential consequences. This was a theoretical risk, and in 1991 before controlled studies appeared Luban et al.7 addressed this eloquently by calculating the amount of supernatant fluid present in a small-volume transfusion and the volume of these additives actually transfused to the infant. In fact the concentration of mannitol actually transfused per kilogram was substantially less than would be needed to cause an osmotic diuresis.7 Indeed, this was borne out when controlled studies began to appear. A study comparing AS-1 units with CPDA-1 units showed that the patients receiving AS-1 actually had an improved glucose homeostasis in that the amount of hypoglycemia seen after neonatal transfusions was reduced. (Hypoglycemia seen with neonatal transfusions is usually a function of high-glucose fluids being discontinued during a transfusion to use the current intravenous access owing to the difficulty of obtaining multiple access sites in this patient group.) Also, urine output, pH, and serum electrolytes were not significantly different.8

With time many centers accepted the use of AS-1 units with no negative consequences; however, blood centers began to purchase bag sets from manufacturers who used AS-3 (Nutricel). This product differed from AS-1 in the presence of phosphate rather than mannitol. Again, a study confirmed that in clinical use the additive solution did not cause harm to the neonates transfused.9

Use of all group O, D– or only group O, D– and group O D+ for neonates stemmed from the practice of using only fresh RBCs for transfusion. This way the unit could be used for many neonates before it reached its 5- or 7-day expiration date. The problem with this method is that it depletes group O units from the blood supply, when they are already used excessively (i.e., trauma patients). When the practice changed to using dedicated units many centers switched to ABO-specific RBCs. The changeover was not complete, unfortunately, and this exacerbates group O shortages in many regions. Some blood bank workers advocate not switching to ABO-specific units in a patient of any age until a second sample is drawn for confirmation as a safety measure. Whether this will become the practice in neonates, in whom blood draws should be kept at a minimum, is unknown, but obligating this entire group of patients to receive only group O RBC units will certainly have an impact on the supply in the community at large.

A consideration in the choice of blood in the NICU is that the multiply transfused preterm infant of a CMV-seronegative mother is at an increased risk of transfusion-transmitted CMV infection. CMV infection has a highly variable clinical picture and can be asymptomatic, severe, or fatal. There is often sepsis associated with hepatosplenomegaly, abnormal blood counts, and pneumonitis.

Blood products can be tested for CMV antibodies, and seronegative products can then be provided for use. Because CMV is an organism that is associated with WBCs, providing WBC-reduced cellular blood components is an appropriate way to reduce the risk.10–13 With the increasing use of leukoreduction this method has become well accepted as a CMV safe alternative, but there are some physicians who will still insist on CMV-seronegative blood. Because most communities have high rates of seropositivity in the donor population, it is unacceptable to waste seronegative blood on seropositive patients in a situation in which only CMV-tested blood products are requested. Many hospitals find it easier to provide leukoreduced blood to all than to test all mothers and provide selective blood products.

Transfusion-associated graft-versus-host disease (TA-GVHD) occurs when an immunocompromised patient is transfused with blood from an immunologically competent donor. The donor T lymphocytes can then proliferate unimpeded and engraft. Fever follows at about 4 weeks (versus 10 days in an adult) and rash at about 30 days (versus 12 days in an adult);14 liver and gastrointestinal involvement and severe cytopenia ensue. The pancytopenia differs from the GVHD seen after bone marrow transplant because in TA-GVHD the bone marrow is part of the host, thus it is affected also. This accounts for the very high fatality rate seen in the latter, attributable to hemorrhage and infection. There is also a longer course of infection from transfusion to death in neonates than adults. Several theories as to the mechanism of these differences are discussed in the thorough literature review from Japan of Ohto and Anderson.14

Irradiation of blood components is the only method to render the T lymphocyte nonmitogenic and prevent the reaction. Although leukoreduction reduces the number of WBC greatly, there is no known threshold below which TA-GVHD will not occur; therefore, it is not an adequate method for prevention.

The infants who are at risk for TA-GVHD have specific risks other than being an infant. These include immunodeficiency disorder, intrauterine transfusion followed by postnatal exchange transfusion, severe prematurity and low birth weight, and family members
providing directed donations.\textsuperscript{15} Therefore a blanket policy of irradiating blood for all infants or NICU patients is not required. Some hospitals, however, may opt to do this. A number of factors should go into this consideration. A hospital with a high-level NICU, with very premature or sick infants, and a blood bank that has its own irradiator and can easily irradiate before transfusion for infants who are at sufficient risk is most likely to find a policy to irradiate RBCs for all neonates useful. This is more efficient than expecting clinical staff to provide birth weight and clinical history so that each patient’s risk can be determined and will avoid missing the one patient who falls through the cracks. Hospitals without this high-risk population or an irradiator of their own will have to wait for irradiated components to be sent specially from the blood center. If they are not used as originally planned then the issue of storage lesion comes into play. (Irradiated RBCs have a shorter shelf life, 28 days, because of increased storage lesion.) Considering the wait time and the decreased shelf life of units, it would be more efficient to determine the actual risk of each patient than to set a broad policy.

RBCs are supplied to replace oxygen carrying capacity, but the improvement in oxygen offloading at the tissue level and its effects on patient outcome cannot be measured. Therefore we do not actually know whether we are improving the patient’s condition. It is important for clinicians to believe there is a benefit before transfusing and not just have a knee-jerk reaction to a number on a lab report, which is all too common. However, conflicting evidence provides reason for debate among clinicians.

Iatrogenic losses were discussed earlier; however, to quantify, these losses should be replaced when 10 percent of the blood volume has been phlebotomized. Anemia is harder to define in this age group because of the changing normal values. At this institution, the hemoglobin range on the first day of life is 16.5 to 21.5 g/dL. This declines throughout the next few months, and at 3 months of age a hemoglobin of 10.4 g/dL is the lower limit of normal. This is called the physiologic anemia of infancy. As this change takes place HbF is replaced by HbA, which has a lower affinity for oxygen, and thus releases it for tissue consumption more efficiently. In preterm infants the hemoglobin levels are lower at any given point and the decline is more pronounced, and the switch over to HbA is affected by the degree of prematurity. There is even controversy over defining the signs of anemia in this age group, with tachycardia, tachypnea, bradycardia, recurrent apnea, and poor weight gain being used.\textsuperscript{15,16}

Table 1 summarizes guidelines by the AABB Pediatric Hemotherapy Committee. It is interesting to note that these are from the mid-1990s; more recent, more restrictive guidelines are available from Britain and are summarized in Table 2.\textsuperscript{17}

Two recent studies provide a glimpse of the conflicting opinions. A study from 2005 that randomized 100 preterm infants to a restrictive or liberal transfusion group showed there may be harm to patients in the restrictive group.\textsuperscript{18} The liberal group received transfusions for hematocrits less than 46%, and the restrictive group used 34% as the cutoff for transfusion. However, these thresholds were adjusted lower as patients progressed through three stages of clinical condition. Infants in the restrictive group had more intraparenchymal brain hemorrhage, periventricular leukomalacia, and apnea. In 2006, a larger study was published.\textsuperscript{19} It was called the PINT study for premature infants in need of transfusion. It also used a low and high threshold for hemoglobin, which changed for clinical condition, starting with 10 to 11.5 g/dL versus 12 to 13.5 g/dL. Differences in each group depended on whether or not there was respiratory support. There were 451 infants enrolled in this study, and there was no significant evidence of benefit to the high transfusion threshold.

An exception to using hemoglobin values as an aid to determining transfusion threshold is seen when a newborn suffers from HDN. In HDN the mother has formed IgG antibodies to an antigen on the fetal RBCs. It can be the D of the Rh system or another RBC antigen. There is immune-mediated hemolysis resulting in anemia, but a further problem exists related to the bilirubin levels. This is because at birth the newborn’s liver is not mature enough to conjugate the large

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Parameter} & \textbf{Hb} \\
\hline
Acute loss of 10% blood volume & 8 g/dL \\
\hline
Severe pulmonary or cyanotic heart disease, heart failure & 13 g/dL \\
\hline
Phlebotomy or other cause & 12 g/dL \\
\hline
Stable neonate with clinical manifestations of anemia & 11 g/dL \\
\hline
\end{tabular}
\caption{RBC indications for infants younger than 4 months of age\textsuperscript{15,16}}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Parameter} & \textbf{Hb} \\
\hline
Anemia in the first 24 hours & 12 g/dL \\
\hline
Cumulative blood loss in 1 week NICU & 10% blood volume \\
\hline
Neonate receiving intensive care & 12 g/dL \\
\hline
Acute blood loss & 10% blood volume \\
\hline
Chronic oxygen dependency & 11 g/dL \\
\hline
Late anemia, stable patient & 7 g/dL \\
\hline
\end{tabular}
\caption{RBC transfusion thresholds for infants younger than 4 months of age\textsuperscript{17}}
\end{table}
amounts of bilirubin produced by the hemolysis. Unconjugated bilirubin presents a great danger to the developing central nervous system. Exchange transfusions are performed with reconstituted whole blood created by removing the additive solution from RBCs and combining with thawed FFP. The infant’s blood is removed in aliquots followed by transfusion of aliquots of reconstituted whole blood. It is best to use a reconstituted product with a hematocrit of 45 ± 5%. The plasma portion of this product is necessary to replace the infant’s plasma, which has high levels of unconjugated bilirubin and maternal antibody. In addition the process removes IgG-coated RBCs before they have been hemolyzed, and the RBCs treat the anemia. The RBCs chosen must be compatible with the mother’s serum, which means they lack the antigen corresponding to the maternal antibody. Typically group AB FFP is used to reconstitute. The need for irradiation should be evaluated as discussed in a previous section.

The levels of bilirubin that lead to this procedure will vary from hospital to hospital based on differing normal ranges, usually more than 25 mg/dL, but the rate of rise of bilirubin is used along with the level to decide when an exchange transfusion is appropriate. When HDN is not severe enough to necessitate exchange transfusion, treatment consists of phototherapy, which exposes the skin to a specific wavelength of light that converts the bilirubin into a more soluble form that can be excreted without conjugation.

The transfusing physician should always be aware that the well-defined risks that are documented in the textbooks are not the only risks to transfusion. There may be consequences to transfusion that are hard to show because of the complexities of the illness of the sick, transfused population. There also may be donor characteristics specific to one region that are not widely seen. One example is lead in the environment. A donor exposed to lead may be a source of lead exposure to a transfusion recipient. This was shown in a study from 1991 to 1992. Posttransfusion increases of lead were seen in 19 premature infants in relation to the amount of blood they received in Oakland, California. Whether this would be seen in other locations or in the present decade is unknown.

Another interesting and more recent study looked at the association of RBC transfusions and necrotizing enterocolitis (NEC). This is a serious acquired gastrointestinal disorder seen in low birthweight neonates. A small group of stable, growing premature neonates developed NEC within 48 hours of transfusion. Whether there are host-specific or RBC storage characteristics that influence this risk is unknown.

HCV look-back is a good example of future consequences to what seems like a life-saving intervention today. The first tests for HCV appeared in 1990, and a second-generation test came out in 1992. In 1998 the FDA recommended HCV look-back to all blood establishments. This meant that donors who tested positive for HCV had previously negative or untested donations traced so that recipients could be found and tested in case the virus had been transmitted by the earlier transfusion. Among patients whose donors were later found to be HCV-positive, children represented 10 to 20 percent of those who acquired posttransfusion hepatitis C. A recent study from Alaska looked at all patients who were transfused while in the NICU as opposed to the FDA-recommended look-back described here, which only tested recipients whose donors later were tested positive. In this study of 216 screened patients, 7 (3%) were hepatitis C antibody-positive; 6 of which were also hepatitis C virus-RNA positive.

Some of their lives may very well have been saved by the transfusions, but it is certainly something the transfusing physician should be thinking about when considering whether or not to transfuse. The risk of serious consequences that may manifest themselves many years in the future is only worth taking if there is a real benefit from the transfusion.

Those in the transfusion medicine community can help patients even though they are not the professionals writing orders at the bedside. From the technologists in the blood bank to the medical directors, every chance to educate the clinicians should be seized. Much of what we know about risks of transfusion has been described in the last 15 to 20 years. This is not covered in the medical school curriculum.

This can be said for all patients, but it is especially true in the infant who has the most years of life ahead of all transfused patients. Although the current healthcare team of transfusing physicians and blood bank workers will probably not be involved in the patient’s care after 15 years, the patient may be dealing with a transfusion-transmitted illness we cannot even imagine today.

References

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