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Transfusing the Neonate: Unique Issues and Guidelines

This *Blood Bulletin* reviews published guidelines and unique issues around neonatal transfusion. Controversies are addressed, but the reader is referred to the references for full discussion.

Infectious risks

Cytomegalovirus (CMV): Premature infants are at particular risk for overwhelming CMV infection. The requirement for use of CMV "safe" blood in the CMV seronegative pregnant woman/fetus and to premature infants (<1200g) of CMV seronegative mothers is non-controversial.

The need for CMV "safe" products for full term or premature infants of CMV seropositive mothers is less well established. Second strain CMV infections following transfusion of CMV seropositive mothers during pregnancy have been documented.¹ Many US newborn intensive care units (NICU) use pre-storage leukoreduced cellular components in lieu of blood seronegative for CMV.

Non-Infectious Risks

Neonatal Transfusion Reactions:

Acute hemolytic. These reactions are limited to situations in which passive antibody from the mother is acquired transplacentally (IgG), or from transfusion of products containing plasma. Thus, if an infant is to receive non-group O red blood cells (RBCs), it is important to screen the infant's serum for clinically significant concentrations of anti-A and/or anti-B (AABB *Standard* (24th ed.) 5.16.2). Furthermore, due to relatively large volumes transfused, neonates are at particular risk for hemolytic reactions from incompatible plasma-containing components.

Delayed hemolytic. Antibody (Ab) screening or crossmatching are not required for the first four months because neonates rarely make alloantibodies to transfused red cells.

Hemolysis. Exposure to excessive heat may occur if blood tubing is too close to warming lights.

Metabolic Complications are disproportionately more common in neonatal transfusions.

Hyperkalemia. Potassium (K⁺) leaks out of aging cells. Irradiation doubles the rate of leak. Extracellular K⁺ rises with extended storage (in CPDA-1: 78mmol/L on day 35, and in Adsol 45-50 on day 42). However, multiple studies have shown that small volume transfusions (10-20ml/kg) given over 2-3 hours cause no change in K⁺ levels.² Conversely, hyperkalemia is frequently reported when large volume transfusions are administered rapidly in premature and full term neonates. It is routine to provide either blood <7-14 days old, or regular blood products that are washed or dialyzed for cardiac bypass or ECMO and, at some institutions, neonatal exchange transfusion.

Hypocalcemia. Citrate, especially in rapidly infused plasma containing products, may result in hypocalcemia. Metabolic alkalosis may follow metabolism of large amounts of citrate.

Hypothermia is prevented by the routine use of blood warmers.

Hyper- and Hypoglycemia. The glucose concentration of fresh red cells often exceeds 300mg/dL and may cause misleading glucose measurements during an RBC transfusion. Of greater physiological consequence is the paradoxical hypoglycemia that often follows transfusion because of endogenous insulin release.

Table 1. Neonatal Transfusion Issues

<u>Problem/Unique characteristic</u>	<u>Solution</u>
Relatively large volumes are transfused	Attention to metabolic complications including Ca ⁺⁺ , K ⁺ , glucose, hypothermia
Passive transfer of maternal IgG antibody	Test before giving type specific RBC units
Lack of iso-hemagglutinins	Lack of back-type, no need to cross-match
Long life expectancy	Limit donors, transfuse with special components
Immature immune system – CMV, TA-GVHD risk	Provide CMV "safe" components, Irradiate for very low weight preemies, exchange TX

Dilutional Hemostatic Dysfunction occurs following massive RBC transfusion, and is exacerbated because neonatal levels of vitamin K-dependent factors normally are lower.

Transfusion-Associated Graft-Versus Host Disease (TA-GVHD). Donor lymphocytes in the transfused blood may attack host antigens when the host is immunocompromised; overwhelmed (preemie); or immune-competent, when the donor is homozygous for an HLA haplotype for which the recipient is heterozygous. Thus, the most common setting for TA-GVHD is the related donor.

The practice of transfusing premature infants with irradiated blood to prevent TA-GVHD is controversial. Premature infants are one of the most frequently affected groups (>100 cases of TA-GVHD reported to date). However, >95% of the TA-GVHD has occurred in neonates with immunodeficiency or exposed to fresh blood from a close relative. In practice, most NICUs irradiate all cellular products for premature infants below some institutionally-defined age or weight cut-off to avoid TA-GVHD.

Transfusion-Related Acute Lung Injury (TRALI). Although rarely reported in pediatric transfusion recipients, TRALI is a reason to avoid unnecessary transfusions in neonates because they often have life-threatening pulmonary conditions. Plasma transfusions for unproven indications such as "abnormal" clotting time in the absence of bleeding should be avoided.

T activation of RBCs has been associated with necrotizing enterocolitis (NEC) and sepsis. Many bacteria release sialidases that cleave sialic acid and expose hidden red blood cell T antigen leading to polyagglutination and, rarely, hemolysis. Although T activation is common (~13% of NICU infants), hemolysis is not, and there is controversy about the need for providing washed red cells to all neonates with T activation and NEC or only to those with hemolysis.³

Neonatal Anemia and Transfusion. During the first weeks of life, hemoglobin declines in all infants, termed the "Physiologic Anemia of Infancy" and associated with loss of fetal hemoglobin (which has a different O₂ dissociation curve) and decreased production of erythropoietin (EPO) in response to anemia.

(continued on next page)

In a workup for anemia, there is no need to perform DATs on all infants of either Rh negative or group O mothers because the test often is positive (passive from RhoGam or anti-A,B) and has a very low predictive value for hemolytic disease of the newborn.

Many premature newborns require transfusion because of frequent blood sampling. Mean levels of sampling reach 0.8-3.1 ml/kg/day corresponding to 30 - 300% of blood volume over the course of a NICU stay.

Treatment of Anemia of Prematurity. Healthy infants tolerate significant anemia (see Table II). The PINT study (Premature Infants in Need of Transfusion) is a randomized controlled trial comparing higher and lower hemoglobin triggers, analogous to the Hebert TRICC study.⁶ The PINT study was designed as a superiority trial, on the hypothesis that a restrictive transfusion protocol would prove superior. However, the combined rates of death/severe morbidity were *not* different in the two groups. Fewer infants required transfusion in the low threshold group (89% vs. 95%, $P=.037$). The study found no negative outcomes of the restrictive policy in a group usually transfused to higher levels.⁷ However, a restrictive transfusion strategy remains controversial.⁸

Anticoagulants for the neonate. There is controversy about the appropriate age of RBCs and the type of anticoagulant used for storage. Several studies document the safety of blood stored up to 42 days using AS-1 (Adsol anticoagulant, which contains both Adenine and Mannitol as preservatives.² Of note, Strauss *et al.* used inverted spins drawing off RBC aliquots with high hematocrit and relatively depleted of preservative solution. One argument for providing fresh blood to neonates has been that 2,3 DPG levels are depleted during RBC storage. However, 2,3 DPG is rapidly regenerated following transfusion, and post-transfusion levels fresh or stored blood are similar.

Additional Considerations

Limiting Blood Donors. The importance of limiting the neonate's donor exposure has decreased with the relative vanquishing of most transfusion-transmitted infections through advances in donor screening. Approaches to anemia include limiting diagnostic phlebotomy, erythropoietin² and transfusion. Parents and neonatologists often request directed donations – but no study has shown that they are safer. Some studies have suggested that they are *less* safe because of risk of TA-GVHD.

Crossmatching should be performed according to the AABB Standards (24th edition) 5.16.1, 5.16.1.1, and 5.16.1.2.

Intrauterine Transfusion (IUT). By definition, the recipient is premature and the initial ABO, Rh type are unknown. Most institutions transfuse irradiated, CMV “safe” (Ab negative or leukoreduced), group O Rh(D) negative cells (as well as negative for any antigen for which the mother has an antibody) either concentrated or diluted with AB plasma. Extended post-delivery follow-up of hemolytic disease of the newborn (HDN) for patients who received IUT is warranted, as they may have prolonged erythroblastopenia, due to a large circulating load of maternal alloantibodies to RBCs.

Neonatal Bleeding. The normal range for platelet counts in premature infants is similar to the adult range. However, thrombocytopenia may have unique consequences for premature infants, such as intracranial hemorrhage (ICH). Specifically, in one prospective observational study an ICH rate of 78% was observed for thrombocytopenic infants ($<100,000/\mu\text{l}$) vs. 48% among non-thrombocytopenic infants.⁹ However, a prospective randomized trial by the same author showed no benefit of platelet transfusion with a 150K trigger vs. 50K trigger for preemies.¹⁰ There appears to be consensus supporting transfusion for premature neonates with a platelet count $<50\text{K}$ either with clinical bleeding or pre-procedure. Asymptomatic infants are generally transfused to $>20\text{K}$ with a goal of $= > 100\text{K}$. This is achieved by transfusion of 5-10ml/kg of plate-

Table II. When to Transfuse the Neonate

- Hgb $< 13\text{g/dl}$ (Hct $<40\%$) with severe cardiopulmonary disease
- Hgb $< 10\text{g/dl}$ (Hct $<30\%$) with moderate cardiopulmonary disease or surgery
- Hgb $< 8\text{g/dl}$ (Hct $<24\%$) with symptomatic anemia
- Bleeding or phlebotomy exceeding 25% of red cell volume.⁴
- Transfuse to maintain minimum hematocrit. Do not replace iatrogenic loss.
- Transfuse with platelet count $<50\text{K}$ either with clinical bleeding or pre-procedure.
- Transfusion to treat apneic episodes is controversial
- Adherence to a strict protocol reduced blood use by 17%.⁵

let-rich plasma or whole blood. No additional concentration is required unless no unit with compatible plasma is available.¹⁰

Pediatric Plasma Transfusion. Many infants – especially premature infants – have a prolonged INR which, in the absence of clinical bleeding, is *not* an indication for plasma transfusion. Most have low levels of vitamin K-dependent factors. Standard prophylaxis for hemorrhagic disease of the newborn is vitamin K. Cryoprecipitate may be required to treat bleeding if the fibrinogen level is $<100\text{mg/dl}$.

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