Red Blood Cells (Infants <4 months of age)

How Supplied:

All Red Blood Cell (RBC) products supplied by Versiti undergo pre-storage leukocyte-reduction.

Empty, unlabeled pediatric aliquot bags (example 3 or 6 pedi-bags) may be attached to an adult RBC unit for filling and labeling at the hospital. Pediatric aliquots may also be supplied by Versiti as pre-filled aliquots (if 3 bags filled, each contain approximately 80-100 mL or if 6 bags filled, each contain 40-50 mL). Outdate for the filled aliquots is the original expiration date of the main donor unit. Check with your Hospital Relations Representative for availability and number of pediatric aliquot bags that may be supplied in your region.

General Comments:

- The neonatal period is defined as the first 4 weeks after birth (<28 days old) and includes both full-term (>39 weeks of gestation) as well as premature infants (neonate born prior to 37 weeks of gestation).[1] Very low birth weight (VLBW) is defined as <1500 mg and extremely low birth weight (ELBW) as <1000 mg.
- When evaluating neonates with anemia, thrombocytopenia, bleeding, or coagulopathy, the following should be taken into consideration:[1]
    - Gestational and postnatal age,
    - Any congenital disorders,
    - Maternal factors,
    - Transplacental antibody transfer

Key Practice Points:

- For most neonates, a restrictive strategy or lower hemoglobin threshold for transfusion appears to be safe, and is recommended over a liberal transfusion strategy or higher hemoglobin threshold.[2,3]
- Guidelines on the hemoglobin (Hgb) threshold for transfusion vary according to gestational age at birth, postnatal age, respiratory support, extracorporeal membrane oxygenation (ECMO) requirement, or the presence of congenital heart disease.[4] Within professional guidelines in the literature there may be subtle differences for the published Hgb thresholds and criteria to guide transfusions in the neonate. Hgb thresholds cited in these guidelines are based on thoughtful review of the recent clinical trials and expert opinon of the Versiti Transfusion Medicine physicians.
- The decision to transfuse in the neonate should be based on clinical status, rather than solely on a hemoglobin (Hgb) or hematocrit (Hct) value. Several factors influence transfusion requirements in the premature neonate including postnatal age, severity of anemia, need for respiratory support or oxygen dependence, and tissue oxygen demand. Other clinical factors that may affect decision to transfuse include severity of illness, rate of fall of Hgb concentration,

anticipated blood loss, and nutritional status. Accordingly, careful clinical assessment is paramount when deciding to transfuse the neonate.[3,4]

- Important measures to limit the need for transfusion in the preterm neonate may include delayed cord clamping, minimizing phlebotomy losses, good nutritional and iron supplementation, and possible use of erythropoiesis-stimulating agents.[3,5]
- Longer storage age of blood is not associated with increased morbidity in neonates.[6] The potential risk of transfusion-associated hyperkalemia in neonates could be a concern when older blood is used in specific clinical situations (e.g. large-volume transfusion, exchange transfusion, cardiac surgery) and may warrant the use of RBCs with shorter storage times.[4,5] See **Additional Information**.
- Only one filtration step is necessary for infant transfusions. This can occur either in the hospital transfusion service between the blood component and syringe (if aliquots prepared on site) or at the bedside between the component/syringe and the infant.

Utilization Review Guidelines:

Red cell transfusions are primarily indicated to improve oxygen carrying capacity. Documentation of the indication(s) for transfusion and special circumstances for transfusion that take place outside these guidelines is recommended.

Transfusion May be Considered for:

1. Massive blood loss or acute blood loss due to trauma, surgery or other cause associated with hypovolemic shock.
2. Suggeted Hgb thresholds based on infant's postnatal age, severity of illiness and supplemental respiratory needs include:[7-10]

Postnatal Age of Infant	**Suggested Transfusion Hgb Threshold:**	
	Critically ill and/or significant respiratory support^*	*No or minimal respiratory support*
≤7 days old	<11 g/dL	<10 g/dL
8-21 days old	<10 g/dL	<8.5 g/dL
>21 days old	<9 g/dL	<7 g/dL

Note: Above recommendations are based on results of 2 large randomized controlled trials in VLBW infants, and should be applicable to older premature and term babies.

Note (*): Critically ill might include: hypotension or shock requiring vasopressor support; acute sepsis or necrotizing enterocolitis; significant apnea or bradycardia; significant tachycardia or tachypnea; deteriorating respiratory status; severe traumatic brain injury; or postoperative from major surgery.

Note (^): Significant respiratory support may include: mechanical ventilation, continuous airway support (CPAP) or other non-invasive positive pressure ventilation; O_2 requirement >35%.

3. Hgb <7g/dL (Hct <24%) in stable neonates older than 21 days regardless of gestational age at birth who have clinical manifestations of anemia (tachycardia, tachypnea, poor feeding, poor weight gain, apnea).
4. Neonates with cyanotic congenital heart disease and Hgb <7 to 9 g/dL depending on the degree of cardiopulmonary reserve.[11] See **Additional Information**.
5. Neonates on ECMO. No prospective studies have been completed to evaluate optimal RBC transfusion threshold; recommendations are to maintain Hgb between 10-12 g/dL.[4]

Dosing Recommendations:

- Volume of RBC is ordered per body weight, generally 10-15 mL/kg in a non-bleeding neonate. Small volume (SV) transfusion is considered <20 mL/kg; whereas large volume (LV) transfusion is ≥20 mL/kg.
- Transfusion rate is dependent on the clinical condition and age of the infant; rate of transfusion should be prescribed by the ordering provider.

Outcome Indicators:

- 10-15 mL/kg of body weight should raise the Hgb by about 2-3 g/dL or Hct by 6%. Monitor for desired outcome.[4,5]
- Increase in Hgb may vary based on Hct of RBC unit which depends on preservative used (e.g. CPD vs. AS-1), whether a method to concentrate the red cells (i.e. washing, supernate removal) is performed, and clinical status of the neonate.
    - Typical Hct for the RBCs manufactured by Versiti are as follows:
      AS-1 RBC 55-60%; AS-3 RBC 55-60%; CPD RBC 70-75%.

Additional Information:

Transfusion Thresholds:

- Hemoglobin threshold in neonates with cyanotic congenital heart disease should be based on the degree of cardiopulmonary reserve of the neonate. Recommendations are to maintain Hgb between 7-9 g/dL since there is no evidence that transfusing to Hgb over 9 g/dL is beneficial.[11]
- Two recent independent large trials [ETTNO (Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants)[7] and TOP (Transfusion of Prematures)[8]] randomized over 2800 ELBW infants to compare the long term outcome of RBC transfusions based on either a liberal (higher Hgb) or restrictive (lower Hgb) transfusion threshold strategy. The transfusion threshold (Hct or Hgb depending on trial) for both cohorts was determined according to postnatal age and whether or not the infant was critically-ill and required respiratory support (higher threshold when critically ill or respiratory support was warranted). While there was differences in the number of infants receiving transfusion in the two trials, the primary outcome in both trials – death or neurodevelopmental impairment (cognitive delay, cerebral palsy, or hearing or vision loss) at 24 months of corrected age – were

similar between restrictive and liberal transfusion groups. Coupled with prior studies which demonstrated no significant differences in short-term outcomes for restrictive versus liberal transfusion thresholds in neonates, the current evidence supports the use of a restrictive transfusion threshold.[1,4,13-15,]

Potential Risks of RBC Transfusion:

- The pathophysiology of necrotizing enterocolitis (NEC) is not clearly understood. Past data differed on the effect of enteral feeding during RBC transfusion and development of NEC. However, recent studies have shown that the degree of anemia at the time of the transfusion appears to play a more critical role than the transfusion itself.[3,16,17]
- All neonates are at risk for transfusion-transmitted CMV infection, regardless of their serostatus since any antibodies will be passive maternal antibodies. Leukocyte-reduced RBCs are now the standard of care and reduce the risk for transfusion-transmitted CMV to a level similar to that of CMV-seronegative RBCs.[1,4] See *Versiti Blood Utilization Guidelines - Modifications of Blood Components* and *TxMD ™ News – In the Era of Leukoreduction, are CMV-Seronegative Tested Blood Products Beneficial?*
- Neonates, especially those who are extremely preterm, are believed to be at risk for transfusion-associated graft-versus-host disease (TA-GVHD). However, the extent of risk and whether to mandate transfusion of irradiated blood components for all infants is controversial. To avoid overlooking a neonate who may be truly at risk for TA-GVHD (i.e. infant with immunodeficiency disorder) and the high mortality rate of TA-GVHD, many centers have implemented blanket protocols for infants admitted to a particular patient care unit (i.e. neonatal intensive care unit) or up to a specified age (i.e. at least until 4-6 months or even up to 1 year of age) to receive irradiated blood components. RBC units or prefilled pediatric aliquots supplied by Versiti designated for neonate transfusion may be irradiated prior to distribution.[5] See *Versiti Blood Utilization Guidelines - Modifications of Blood Components* .
- Hypocalcemia is common in critically ill, premature neonates and is often asymptomatic. With multiple or *large volume* RBC transfusions, neonates could be at risk of citrate toxicity and resultant worsening hypocalcemia. Ionized calcium levels should be closely monitored when large volume transfusions are given.[1,18]

RBC Product Selection:

- Transfusion of RBC units containing additive solution (e.g. AS-1, AS-3, AS-5 RBCs) in neonates is an acceptable practice for SV transfusion (up to 20 mL/kg), and commonly used at pediatric academic centers. While RBCs with additive solution could be considered for LV RBC transfusions (e.g. >20mL/kg per transfusion event), their use is an institutional choice and likely depends on several factors including indication and urgency for the transfusion, ability to remove the additive solution by washing or centrifugation, and availability to obtain RBCs without additive solution. See *TxMD ™ News – RBC Transfusions for Neonates: Are RBCs Stored in Additive Solutions Safe?*

- While trials in LVBW infants have reported no difference on mortality or morbidity with transfusion of fresh (≤7 days) versus standard-issue RBCs[6], specific clinical conditions may warrant the use of "fresher" RBCs. Use of older RBC units with high extracellular potassium (K+) concentrations may be a concern for neonates with preexisting hyperkalemia or renal failure, need for rapid infusion of blood through a central line, or for LV transfusions as with exchange transfusion, ECMO or during cardiac surgery. Washing of the RBC units, removal of the supernatant, or use of fresh blood (i.e. less than 7 to 10 days old) are options to decrease the risk of transfusion-associated hyperkalemia in these clinical situations.[4,5,19,20]
- Although the risk of transfusion-transmitted infectious disease is low today, some centers utilize a dedicated RBC unit protocol (e.g. one adult RBC unit reserved for 1 or 2 neonates receiving frequent transfusions). This approach can minimize donor exposures as well as be cost-effective. The use of empty pedi-packs connected to a fresh adult unit by the blood supplier and later filled when needed or on-demand preparation of aliquots (or syringes) at the hospital are options for providing multiple transfusions from a dedicated adult unit.[5]
- For hospitals that order pre-filled, irradiated aliquot units for neonates from the blood supplier, K+ will accumulate in these aliquots over time. For routine SV transfusions given slowly, this is generally not of clinical concern. However, as the unit ages, the increasing K+ load may place the neonate at risk for hypekalemia if an older unit is used for multiple transfusions over a short duration or for *large volume* transfusion (more than 25 mL/kg) given rapidly.
- Neonatal blood contains maternal ABO antibodies, thus any RBC units selected for transfusion must be compatible with the infant's blood group as well as the maternal antibodies present in the neonatal circulation. For simplicity, many transfusion services provide group O, Rh compatible RBCs to all neonates. To conserve group O RBCs, especially O Negative RBCs, some transfusion services have policies for release of ABO-group-specific RBCs if the neonate's serum lacks maternal anti-A and/or Anti-B which may be directed against the neonatal ABO antigens and the ABO group of the unit selected for transfusion. Because the antibodies in the neonate's plasma are of maternal origin, maternal blood may be used as the source for antibody detection/identification testing. In addition, since the neonate's immune system rarely produces antibodies in response to RBC transfusions, if the antibody screen is negative, it does not need to be repeated during the patient's hospitalization until the infant is 4 months old.

Intrauterine and Exchange Transfusion

While less common today than in prior years, selection and preparation of blood for intrauterine or exchange transfusions may be requested at the hospital transfusion service. Intrauterine transfusion is often a scheduled procedure which allows time for coordination with the blood supplier and/or immunohematology reference lab to obtain a fresh, antigen-negative (if applicable) RBC unit that is collected in the preferred anticoagulant (CPD). On the other hand, an exchange transfusion for a newborn shortly after birth is typically a STAT request and availability of certain RBCs may be limited.

Exchange transfusion is an effective and immediate method for rapidly removing bilirubin in newborns who are at risk for developing bilirubin-induced neurologic disorders, and when present removal of antibody-coated neonatal RBCs and unbound maternal antibody.

Typical indications may include:

- Intrauterine transfusions:[21]
  - Fetal anemia due to Hemolytic Disease of the Fetus and Newborn (HDFN)
  - Severe fetal anemia due to other causes, e.g. hemoglobinopathy, infection (e.g. parvovirus B19), or maternal injury
- Exchange transfusions in the newborn:[22]
  - Signs of acute bilirubin encephalopathy (ABE)
  - Severe hyperbilirubinaemia secondary to HDFN (see Note)
  - Severe hyperbilirubinaemia or rapidly rising total bilirubin despite intense phototherapy due to any cause and infant at risk of ABE (see Note)
  - Severe anemia (where there is normal or increased circulating blood volume)
  - Severe metabolic disturbances and/or circulating toxic subatances

  Note: The total bilirubin threshold for exchange transfusion is based on gestational age as well as other risks factors for neurotoxicity, including hemolytic conditions, clinical instability in the previous 24 hours, sepsis, and hypoalbuminemia.[22,23]

For exchange transfusion, the volume typically needed is based on 160 mL/kg (double exchange transfusion). This replaces approximately 85 percent of the infant's circulating red blood cells.

Infants may require more than 1 exchange transfusion to achieve an acceptable bilirubin level.

Attributes for the selection of blood for intrauterine and exchange transfusions are described in the **Table**.[5]

Selection of Red Cell Units for Intrauterine or Exchange Transfusion		
	Intrauterine Transfusions	**Exchange Transfusions**
ABO/Rh	Group O, Rh-negative RBC	Group O, Rh-negative or compatible RBC (Rh compatible based on mother's and baby's blood type)
Compatibility	Antigen negative for underlying maternal RBC alloantibodies (if applicable).	Antigen negative for underlying maternal RBC alloantibodies (if applicable).
Type of Component	CPD additive solution preferrerd. If unavailable, RBCs in AS-1 or AS-3 that are volume reduced or washed. Target HCT 70-85%.	RBCs in CPD, AS-1 or AS-3 based on availability. If AS-1 or AS-3, RBCs should be modified by volume reduction or washing depending on hospital resources. RBCs are reconstituted to desired HCT (40-60%) with AB plasma or compatible FFP.
Modifications	Leukocyte-reduced (CMV-reduced risk) or CMV seronegative RBCs	Leukocyte-reduced (CMV reduced risk)
	Negative for Hgb S	Negative for Hgb S
	Irradiated but no longer than 24 hours before scheduled transfusion.	Irradiated
Age of RBC	Freshest available but no older than 5 days after collection.	Freshest available but no older than 7-10 days after collection.
Volume for Transfusion	Based on gestation age of fetus. Typically issue either one-half or entire RBC unit and volume infused is determined during the procedure.	Typically double volume exchange (160mL of modified WB per kg body weight).

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Additional Resources:

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