Use of Blood Components in the Newborn

Summary of recommendations

- **Transfusion in the newborn requires selection of appropriate donor, measures to minimize donor exposure and prevent graft versus host disease and transmission of Cytomegalovirus.**
- **Component therapy rather than whole blood transfusion, is appropriate in most situations.**
- **A clear cut policy of cut-offs for transfusions in different situations helps reduce unnecessary exposure to blood products.**
- **Transfusion triggers should be based on underlying disease, age and general condition of the neonate.**

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Introduction

Blood forms an important part of the therapeutic armamentarium of the neonatologist. Very small premature neonates are amongst the most common of all patient groups to receive extensive transfusions. The risks of blood transfusion in today's age of rigid blood banking laws, while infrequent, are not trivial. Therefore, as with any therapy used in the newborn, it is essential that one considers the risk- benefit ratio and strive to develop treatment strategies that will result in the best patient outcomes. In addition, the relatively immature immune status of the neonate predisposes them to Graft versus Host Disease (GVHD), in addition to other complications including transmission of infections, oxidant damage, allo-immunization and so on. Since neonatal physiology varies with the maturity, age, weight and the presence of morbidities, it is difficult to formulate one parameter to guide all transfusion decisions. This guideline addresses the following issues:

- What specific pretransfusion processing is performed before transfusing blood products to neonates?
- What are the indications for the use of various blood products?

Foe some of the indications, there is robust evidence but many are based on biological principles, expert recommendations and consensus statements.

Pre-transfusion Issues: *Recommendations*

1. Donor selection
    a. Avoid blood donation from first and second degree relatives.
    b. In addition to routine screening tests, the donor should be seronegative for Cytomegalovirus (CMV).
2. Pre-transfusion testing of donor blood
    a. Blood typing errors can result from
        i. Weak expression of red blood cell(RBC) antigens in neonates
        ii. Presence of maternal antibodies that can mask the corresponding antigens.
        iii. Umbilical cord samples contaminated by maternal blood/ Wharton's jelly.
    b. When indicated following tests should be performed before selecting the right donor blood
        i. Mother's blood: ABO/Rh blood group and irregular antibodies against RBCs using the indirect antiglobulin test (IAT).
        ii. Neonate's blood: ABO/Rh blood groups, (when possible, confirmed on a second sample). Direct antiglobulin test (DAT) and, if positive, elution of any antibody and its identification.
3. Leucodepletion: Whole blood, Packed RBC and platelet concentrates should be leucodepleted ($<5 \times 10^6$ leucocytes per pack). This may be done in the blood bank (pre issue) or using online filters at the bedside (post issue).
4. Hematocrit: Reconstituted blood should have a hematocrit 0.5 ± 0.05
5. Gamma irradiation: It renders donor lymphocytes effete and unable to mount a graft versus host reaction on the immunologically incompetent neonate. The dosage required is 25-50 gray (2500-5000 rads). Irradiation of packed RBC should be done within 14 days of collection of the cells;

once irradiated packed RBC should be transfused within 48 hours. Irradiation does not change the shelf-life of platelet concentrates. Irradiation is indicated for

i. Intrauterine transfusion of packed RBC and platelets
ii. Transfusion of packed RBC and platelets (also in blood exchange transfusion) after intrauterine transfusion
iii. Transfusion of RBC and platelets in neonates with birth weight < 1500grams and/or gestation at birth < 30weeks
iv. Donations from first or second degree relatives
v. Neonates with congenital or acquired immunodeficiency.

6. Prevention of Cytomegalovirus infection: This can be achieved by using CMV seronegative donors and leucodepletion. CMV negative blood is indicated for
   i. Intrauterine transfusion of packed RBC and platelets
   ii. Neonates with birth weight <1500 grams and/or gestation < 30weeks
   iii. Neonates with congenital or acquired immune deficiency;
7. Use of satellite (piggyback) bags: This reduces wastage and exposure to multiple donors. Blood banks should be encouraged to use these for all blood components.
8. T activation: T antigens (and the closely related Th, Tk and Tx antigens) are present on the neonate's RBC surface and get activated in certain clinical situations (e.g. Necrotizing enterocolitis and Septicemia) when RBC get exposed to bacterial or viral enzymes (neuraminidase). This leads to polyagglutination of the RBCs (unexpected agglutination on testing with sera from ABO compatible donors) and thereby hemolysis. In high risk situations avoid all plasma or plasma products as most adults have anti T antibodies due to prior exposure to bacteria and vaccines. If unavoidable use plasma with low titres of anti T antibody to prevent hemolysis.
9. Reconstitution of packed cells for exchange transfusion: At present, in India no regulatory guidelines exist for reconstitution of blood. In the West, the FDA clearly states that although reconstitution of blood can be done either at the blood bank or at the ward, whoever reconstitutes the blood must be registered with the FDA.[1]
10. Single vs multiple donors: Preterm infants frequently require multiple blood transfusions. A unit of blood with additional satellite packs ordered for each infant and used up to its expiry date, allows up to eight transfusions from a single donation, reducing the number donor exposures .[2]

Recommendations on use of blood products in neonates

a. Characteristics: Blood for transfusion should be less than 5 days old, irradiated, CMV negative, warmed and have a hematocrit of 0.5 to 0.6.
b. Reconstituted blood: Reconstituted whole blood is obtained by combining packed RBC with fresh-frozen plasma (FFP). Ideally FFP should be from the same donor bag from which the packed RBC was produced. Otherwise AB group FFP from a different donor may be used. The final product should be used within 24h of reconstitution and has the same characteristics as whole blood except for reduced platelets.

c. Indications of whole blood:

- Exchange transfusion
- Replacement of blood loss in massive hemorrhage
- Cardiac surgery

Exchange transfusion: The choice of donor blood group is dependent on the mother and infant's blood and Rh grouping.

a. Rh incompatibility:

   Blood arranged prior to birth: O negative cross matched against mother

   Blood arranged after birth: Rh negative of baby's ABO group cross matched against infant and mother

b. ABO incompatibility: Rh matched O group cross matched with mother
c. Other indications (non-hemolytic): Blood group of infant cross matched against infant and mother

To avoid the risk of hyperkalemia, use fresh whole blood (<5 days of age) and reconstitute blood using washed packed red cells. Saline wash if available can reduce the risk of hyperkalemia and also reduce the antigen load on the RBC.

Packed red blood cell (PRBC) transfusions

Oxygen delivery to the tissues is dependant upon multiple factors such as stroke volume, level and type of hemoglobin (Hb), arterial oxygen tension, oxygen extraction fraction, and tissue consumption of oxygen. Thus for a given hemoglobin level, isovolaemic anemia (e.g. anemia of prematurity), is better tolerated than hypovolemic anemia (acute hemorrhage). While various markers for tissue oxygenation (fractional extraction of oxygen, serum lactate levels, echocardiographic parameters), other than hemoglobin (or Hematocrit-PCV) have been studied to guide transfusion thresholds, none are as easily/quickly evaluated in clinical practice. The current recommendations on RBC transfusions in neonates have, therefore, remained related to values of Hb (or PCV), in relation to the clinical state of the neonate and any bone marrow erythropoietic compensation.

Evidence: Many centers have introduced restrictive transfusion policies for preterm infants in recent years. The benefits and adverse consequences of allowing lower hematocrit levels have not been systematically evaluated. The limited evidence regarding the use of restrictive hematocrit levels to guide RBC transfusion are as follows[3-5]:

- The results of trials studying clinically relevant outcomes of restrictive transfusion practices are conflicting. While some authors[4] caution against the use of restrictive guidelines due to higher incidence of major adverse neurologic events (parenchymal brain hemorrhage, periventricular leukomalacia, or both) and significantly more frequent apnea (and potentially adverse long term neurodevelopmental outcome), others[5] found no difference in the frequency of complications. As

such, there is an urgent need to study the short and long term repercussions of using restrictive threshold for the use of red cell transfusions.

- Hb limited oxygen unloading capacity to the tissues is rare even in the intensive care setting The practice of following local guidelines results in fewer transfusions.
- Neurodevelopmental follow up of infants with severe hemolytic disease of the newborn for a period of 62 months were performed using Gesell Developmental schedule and McCarthy's Scales of Children's abilities. There were no delay in mean developmental quotient or mean cognitive index among patients with lowest fetal hematocrit of 0.20 ± 0.078, peak fetal bilirubin 7.1 ± 2.1 mg/dL or with hydrops fetalis (45%) and mean gestational age at delivery being 35.6 ± 2.2 weeks[6.]
- The PINT trial showed a significantly higher cognitive delay in the group of ELBW assigned to receive restricted transfusions.[7]

Recommendations:

Considering the limited evidence, the RBC guidelines are based on the available expert recommendations[8-11] and the need to restrict donor exposure in neonates. Despite hematocrit being an imperfect surrogate marker for oxygen delivery, various guidelines propose cut off values to trigger transfusion. It is worthwhile to bear in mind that the overall clinical picture rather than a particular figure should be considered in the decision to transfuse a neonate. Transfusion triggers vary with etiology, age and general condition of the neonate.

- *Severe anemia of antenatal onset*: Anemia occurring before birth, characterized by Hb < 8/dL at birth, requires prompt transfusion, as specified below
    a. In severe anemia associated with congestive heart failure (due to immunohemolysis, chronic feto-maternal or feto-fetal hemorrhage) the most appropriate treatment is "partial" exchange transfusion (PET) with packed RBC with the aim of correcting the anemia while avoiding volume overload.
    b. In severe anemia with hypovolaemic shock (placenta previa, abruption placentae, rupture of the cord), the intravascular volume must be restored and the anemia corrected.
- *Early neonatal anemia*: For anemia developing after birth or in the first week of life, in which the values of Hb are moderately decreased, transfusion treatment is necessary in the case of severe cardio-pulmonary diseases, in order to maintain the PCV greater than 0.35 to 0.40.
- *Late neonatal anemia*
    a. **Acute blood loss** greater than 10% of blood volume with features of decreased oxygen delivery or greater than 20% of blood volume.
    b. **PCV < 30%:** Moderate or significant mechanical ventilator support [MAP >8 cm , FiO2 >0.40 with conventional ventilation or MAP >14 and FiO2 > 0.40 with High frequency ventilation-HFV]
    c. **PCV < 25%**: Minimal mechanical ventilator support [MAP < 8 cm, FiO2 < 0.40 on conventional ventilation or MAP <14 and/or FiO2 0.40 on HFV]
    d. **PCV < 20%**: Supplemental oxygen not requiring mechanical ventilatory support plus the presence of one or more of the following :
        i. Tachycardia >180/minute or Respiratory rate > 60 for ≥ 24hours
        ii. Doubling of the oxygen requirement in last 48 hours
        iii. Lactate > 2.5 mEq/L or acute metabolic acidosis with pH <7.20

iv. Weight gain less than 10 grams/kg/day over 4 days while receiving 120 kcal/kg/day

v. If the infant will undergo major surgery within 72 hours

e. **PCV< 18%:** Consider transfusion for asymptomatic infants with absolute reticulocyte count of < $100x10^3/\mu L$ ($100x10^9/L$) or < 2 percent.

Platelet transfusions

Evidence: Asymptomatic thrombocytopenia occurs in about 1% of term and 25% of preterm neonates. Characteristics of platelet transfusions used in the NICUs have been studied[12-14]. Platelet transfusions are common in the NICU, being administered to 2% - 9.4% of neonates admitted to NICUs. Majority of platelet transfusions were used prophylactically in non-bleeding neonates with platelet counts in the range of 30 to 50 x 10^9/L. Repeated platelet transfusions were common with more than 50% infants receiving more than one platelet transfusion during their NICU stay. Thrombocytopenic neonates who receive platelets are up to 10 times more likely to die than neonates who do not receive platelet transfusion (usually to causes unrelated to severe hemorrhage). Andrew et al[14] found no benefit in terms of hemorrhage when maintaining a normal platelet count by platelet transfusion in a study of preterm neonates compared with controls with moderate thrombocytopenia (platelets (50 to 150 x 10^9/L).

Recommendations:

Platelets (x10^9/L)	**Bleeding**		**Immune status**	
	Yes	**No**	**AITP***	**NAIT****
<30	Transfuse	Consider platelet transfusion	Transfuse if bleeding/ IVIG not available	Transfuse if bleeding
30 to 49	Transfuse	Transfuse if Weight <1000grams *or* postnatal age <1week *or*Unstable (IVH Gr3-4) *or* associated coagulopathy *or* Surgery required	Transfuse, if unstable, bleeding	Transfuse if bleeding
50 to 99	Transfuse	Do not transfuse	Do not transfuse	Transfuse if bleeding
> 99	Do not transfuse			

**AITP: Autoimmune thrombocytopenia, **NAIT: Neonatal alloimmune thrombocytopenia ,IVH: Intraventricular hemorrhage*

Fresh frozen plasma and Cryoprecipitate

Recommendations for use of Fresh frozen plasma:

- Indications
    a. Severe clotting deficiency (including DIC) with bleeding
    b. Severe clotting deficiency in a neonate undergoing an invasive procedure
    c. Vitamin K deficiency with bleeding
    d. Dilutional coagulopathy with bleeding
    e. Severe anticoagulant protein deficiency
    f. Reconstitution of packed RBC for exchange transfusion
- Incorrect indications for which FFP is often prescribed but should not be used[16]
    a. Prevention of intraventricular hemorrhage in premature neonates
    b. Volume replacement in the management of sepsis
    c. As an adjunct in the management of thrombocytopenia
    d. To "correct" prolonged indices of coagulation

***Recommendations for Factor VIII/ cryoprecipitate*:**

Congenital factor deficiencies are rare in the neonatal period. While treating bleeding neonates, cryoprecipitate is often considered an alternative to FFP because of its small volume. However, cryoprecipitate contains only factors VIII, XIII and fibrinogen and is not effective in treating the more extensive clotting factor deficiencies.

Practice points

- Use components wherever feasible/ available.
- Follow guidelines: It is difficult to obtain clear scientific evidence on the criteria to use for the administration of PRBC in premature VLBW neonates, who constitute the category of patients with the highest transfusion needs.[17-18] It however, has been demonstrated that transfusing according to agreed criteria limits both the number of neonates undergoing transfusion and the number of donors to which each neonate is exposed.[19-20] The use of "local" transfusion protocols in the various Neonatal Intensive Care Units is, therefore, recommended (Level of evidence Ib, grade of recommendation A).
- Treat patient/ not lab values: Fallacies arise in the collection and processing of blood samples, and in the reporting and interpretation of laboratory results. The final guide for a particular treatment strategy is finally based upon the clinical condition of the patient.
- Awareness of complications of blood transfusions: Homologous blood transfusion is associated with the risk of transmission of infections such as HIV, hepatitis B and C, cytomegalovirus, syphilis, and malaria. The rates of transfusion associated infection increase when multiple transfusions from multiple donors are given. Other transfusion related complications of a non-infectious nature may also occur in neonates and include fluid overload, graft-versus-host disease, electrolyte and acid base disturbances, iron overload, increased susceptibility to oxidant damage and allo-immunisation.

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Annexure

1.Whole blood/ reconstituted whole blood

- Collection and storage: Total volume of blood collected is 450-500 ml. Anticoagulant used is CPD (Citrate, Phosphate, and Dextrose). Blood can be stored for three weeks in CPD containing 25grams/litre of dextrose. Adenine which retards glycolysis in the RBC is added to CPD and increases storage to 35 days. Other nutrient solutions for extended storage of RBCs upto 42 days include Adsol (AS-1), Nutricel (AS-3) and Opticel (AS-5). The ratio of blood to anticoagulant is maintained at approximately 7:1.
- Biochemical changes that occur in the stored blood are
    - fall in pH due to accumulation of pyruvate and lactate
    - fall in extracellular sodium levels and rise in potassium levels
    - depletion of 2,3 DPG
    - loss of platelet and factor VII function after 48hours.

2.Whole blood for Exchange transfusion

a. In neonates exchange transfusion is used for the severe jaundice mostly due to Rh and ABO isoimunisation, severe anemia leading to cardiac dysfunction and in some special situations such as septicemia, inborn errors of metabolism, and disseminated intravascular coagulation.
b. Double volume exchange transfusion is the standard in management of severe hyperbilirubinemia in neonates (weight x 80ml x 2). This removes nearly 90% of red cells and approximately 50% of circulating bilirubin. There is a risk of hyperkalemia in the neonate after or during the exchange transfusion as the serum potassium levels in blood bag can reach 50mEq/L after storage for 42 days.

3. Packed Red blood cells

Dosage: The dose to be infused depends upon the desired and actual hematocrit of the infant.

$$\text{Packed RBC volume to be infused} = \frac{\text{Blood volume} \times \text{desired PCV} - \text{actual PCV}}{\text{PCV of packed RBC being transfused}}$$

The rate of infusion should not exceed 10ml/kg/hour in the absence of cardiac failure and 2ml/kg/hour in its presence. A dose of intravenous frusemide (1-2mg/kg) may be administered during the infusion to prevent fluid overload.

Preparation and characteristics: A unit of packed red blood cells made allowing cells in a bag of whole blood to separate by centrifuging or by gravity. It has a volume of about 250ml and a hematocrit of 0.7-0.8 and contains all types of cells including platelets and leucocytes.

4.Platelet concentrate

- Preparation and characteristics: Platelets separated by centrifugation are pooled to make random donor platelet packs which have a volume of 50-60 ml and contain about 5 to 7 x 10^{10} platelets. Platelets obtained by aphaeresis from a single individual (single donor platelets) provides about 3 to 4 x 10^{11} platelets. Platelet packs contain leucocytes, plasma and some red cells.
- Storage: platelet packs are stored at 22°C with continuous agitation of the bag.
- Typing: Platelet specific antigen and antibody testing has bearing on the management of alloimmune thrombocytopenia but it is not readily available. All platelet packs are contaminated with some RBCs, plasma and leucocytes, theoretically leading to ABO and Rh group incompatibility if similar group is not used. Ideally, therefore, group specific platelets should be used. However, unless repeated transfusions are required, different group platelets may be used in an emergency.
- Dosage: One unit of random donor platelets per 10 kg body weight increases the platelet count by 40-50 x 10^9/L. This can be achieved by infusion of 5-10 ml/kg of standard donor platelets.
- The goal of platelet transfusion is to raise the platelet count to 100 x 10^9/L.
- Frequency of transfusion: Normal half life of stored platelets is 3-5 days. In vivo life span is shorter, especially if there is platelet consumption. A repeat platelet count should be performed after 12 hours of transfusion.

5.Fresh frozen plasma

- Preparation & characteristics: FFP is made by freezing plasma obtained by centrifugation of fresh whole blood. It contains albumin and factors II, VII, X and XI. Antibodies and Factors V, VIII and XIII are also present, but in insignificant quantities, thus precluding the use of FFP as replacement for these substances.
- Storage and viability: FFP is stored at -20°C. After thawing it should be used immediately as there is a rapid fall in the concentration of clotting factors.