57 Blood Components Transfusion

Sick neonates frequently receive transfusion of different blood components: packed red blood cells (PRBCs), platelet concentrates (PC), and plasma. Transfusion of blood products in the vulnerable neonates need to be strictly regulated to avoid the inherent risks of transfusion such as infections, retinopathy of prematurity (ROP), intraventricular hemorrhage and iron overload.

Packed red blood cells

PRBCs are prepared from the whole blood (WB) after centrifugation within 8 hours of collection. Either some of the plasma could be retained in the prepared red cells for storage or all the plasma could be separated with addition of a preservative solution to the PRBCs. Preservative solutions such as SAGM (saline, adenine, glucose and mannitol) gives an added advantage of increase in the shelf life of PRBCs to 42 days in contrast to 21 days or 35 days of storage with anticoagulant CPD or CPDA, respectively. PRBCs need to be stored at a temperature of 2 to 6°C irrespective of the preservative used.

PRBCs are sometimes subjected to further modifications to make PRBC transfusion safer:

- ***Leucocyte reduction***
  Leukocyte reduction could be achieved by a number of methods such as buffy coat removal, washing of red cells and leukofiltration. Leukofiltration reduces the concentration of leucocytes to less than $5x10^6$ per unit of RBCs. It reduces transfusion reactions and prevents non-hemolytic febrile transfusion reactions (NHFTR), HLA alloimmunization, transmission of leukotropic viruses (CMV, EBV and HTLV-1), and transfusion related acute lung injury (TRALI).
- ***Gamma irradiation***
  Gamma irradiation inactivates donor T cells, and hence reduces the risk of TA-GVHD. Cellular blood components

are required to be irradiated to prevent TA-GVHD in susceptible patient groups (preterm neonates <1200 g, cellular immune deficiency, immunosuppression by drugs or radiation, transfusion from blood relations, HLA/cross matched platelets). Gamma irradiation reduces the shelf life of PRBCs to 28 days and also causes leakage of potassium out of RBCs.Therefore,irradiated PRBCs should be used within 4 hours to avert the risk of hyperkalemia.

- ***Washed RBCs***
  Washing PRBCs with saline is done to remove plasma and to reduce potassium in the RBCs. Washed RBCs are recommended for IUTs, exchange transfusion and large volume transfusions (more than 20 mL/kg). Washing of red cells and platelets is also indicated if maternal red cells and platelets are used for the transfusion to fetus/neonate in hemolytic disease of newborn (HDN) and neonatal alloimmune thrombocytopenia (NAIT).

- ***CMV reduced RBCs***
  CMV is a concern in newborns, especially preterm neonates. CMV reduction can be achieved by either leucofiltration or by preselecting CMV negative donors. CMV-seronegative blood components are more efficacious in preventing transfusion-acquired CMV infection.

- ***Red cells for intrauterine transfusion (IUT)***
  Red cells are transfused *in-utero* to treat severe fetal anemia. In order to keep the volume transfused to a minimum, they are prepared in a way to achieve a high hematocrit of 0.70 to 0.90. Because of concern over the potential toxicity of adenine and mannitol in red cell additive solutions, red cells for IUT and exchange transfusion are prepared after removal of additive solution and addition of AB plasma so as to keep the hematocrit to 0.70 to 0.90 and 0.40 to 0.50, respectively. RBCs should be irradiated and leuco-filtered for both intrauterine and exchange transfusions.

Platelets

Random donor platelet (RDP) or whole blood derived platelet concentrates

Platelets can be producedfrom WB either by platelet rich plasma (PRP) method or buffy-coat method.

Single donor platelet (SDP) or apheresis derived platelet concentrates

SDP units are obtained by platelet pheresis wherein platelets are collected from a single donor and the RBCs and platelet poor plasma are returned to the donor.The SDP has high platelet concentration ($3x10^{11}$/unit) in comparison to RDP ($0.5x10^{10}$ per unit). In neonatal transfusion practice, RDP is generally adequate to treat thrombocytopenia. Platelets should be stored at 20 to 24°C with continuous gentle agitation for a maximum of 5 days from collection. 'Washed platelets' can be used in patients with anaphylactic reactions to the plasma component. Washed platelets have a shelf life of only 24 hours.

Fresh frozen plasma (FFP)

FFP is produced by rapidly freezing the plasma within 8 hours of collection in order to preserve the activity of coagulation factors V and VIII, which are relatively labile.FFP can be stored for up to 1 year at storage temperature below -30°C. Once thawed, FFP should be used immediately but can be stored for up to 24 hours at 4°C.

Cryoprecipitate

It is prepared from FFP by thawing at 2 to 4° C. Undissolved cryoprecipitate is collected by centrifugation and supernatant plasma is aseptically expressed into a satellite bag. Cryoprecipitate can be stored for 12 months at -30° C or lower. Thawed cryoprecipitate can be stored for 6 hours at 2-6° C and pooled cryoprecipitate kept at 2-6°C should be used within 4 hours.

Indications for PRBC transfusion

In order to limit the number of transfusions and the number of donors as well, restrictive transfusion policy is recommended.

Restricted versus liberal blood transfusion in VLBW neonates: What is the evidence?

The cochrane review on using low versus high hemoglobin threshold for blood transfusion in VLBW neonates did not find any significant difference in the combined outcome of death or serious morbidity at hospital discharge (RR 1.19; 95% CI 0.95 to 1.49).

The guidelines for transfusion of PRBC according to age, level of sickness and hematocrit are as follows (Tables 57.1 and 57.2):

Table 57.1: Guidelines for PRBC transfusion thresholds in preterm neonates (<32 weeks)

Postnatal age	Suggested transfusion threshold Hb (g/dL)		
	Ventilated	On oxygen or CPAP/ NIPPV	No supplemental oxygen
First 24 hr	<12	<12	<10
Days 2 to 7	<12	<10	<10
Days 8 to 14	<10	<9.5	<7.5 – 8.5
Day 15 onwards	<10	<8.5	<7.5

British Committee for Standards in Hematology, Guidelines on transfusion for fetuses, neonates and older children 2016

Table 57.2: Guidelines for PRBC transfusion thresholds in term neonates

Condition	Hb (g/dL)
Severe pulmonary disease	<12
Moderate pulmonary disease	<10
Severe cardiac disease	<12
Major surgery	<10
Symptomatic anemia	<7

Practical issues

1. *Amount of transfusion to be given*

   It is recommended to transfuse 10 to 15 mL/kg in non-bleeding neonates. The transfusion should be administered at 5 mL/kg/h.[15] Top-up transfusions in excess of 20 mL/kg are not recommended because of risk of transfusion – associated circulatory overload (TACO).

2. *Properties of RBC products used in neonatal transfusion*
   a. Fresh RBCs (less than 7 days old) with high 2, 3-DPG levels ensure higher tissue oxygen delivery.They also reduce the risk of hyperkalemia.
   b. Multiple donor exposures in small and sick neonates can be prevented by reserving a bag of fresh PRBC for up to 7 days for each neonate and withdrawing small aliquots required as and when needed.
3. *Choosing the blood group for neonatal transfusions*
   a. For transfusions in infants <6 months, it is preferable to take samples from both, mother and the newborn, for initial testing prior to transfusion. Mother's sample should be tested for blood group and for any atypical red cell antibodies.
   b. ABO compatibility is essential while transfusing PRBCs. Though ABO antigens may be expressed only weakly on neonatal erythrocytes, the neonate's serum may contain transplacentally acquired maternal IgG anti-A and/or anti-B.
   c. The transfused blood must be compatible with both maternal and newborn's ABO and Rh group. For example, if both mother and newborn are A positive, then blood to be transfused should be either A positive or O positive depending on the availability. If mother is A positive and newborn is B positive, then O positive blood should be chosen for transfusion. In addition, the blood unit should also be compatible towards any atypical red cell antibody present in the maternal serum.
4. *Volume and rate of transfusion*
   a. Volume of packed RBC = Blood volume (mL/kg) x (desired minus actual hematocrit)/ hematocrit of transfused RBC
   b. The rate of infusion is 5 mL/kg/hr in absence of cardiac failure. Rate should not be more than 2 mL/kg/hour in the presence of cardiac failure.
   c. If more *volume is to be transfused, it* should be done in smaller aliquots.
5. *Expected response*:
   Each transfusion of 9 mL/kg of body weight should increase

hemoglobin level by 3 g/dL. Meticulous monitoring of input, output and vital signs are mandatory during blood transfusion.

Platelet transfusion

Thrombocytopenia is defined as platelet count less than 1.5 lakh/cubic mm. Thrombocytopenia has been observed in 1–5% of newborns at birth.

Table 57.3: Suggested thresholds for neonatal platelet transfusion

Platelet Count	Condition
<25,000 /cubic mm	Neonates with no bleeding (including neonates with NAIT if no bleeding and no family history of ICH)
<50,000 / cubic mm	• Neonates with bleeding • Evidence of coagulopathy • Before surgery • NAIT if previously affected sibling with ICH
<1,00,000 / cubic mm	Major bleeding e.g. significant IVH Major surgery

NAIT, neonatal alloimmune thrombocytopenia; ICH, intracranial haemorrhage. Adapted with permission from British Committee for Standards in Hematology: Guidelines on transfusion for fetuses, neonates and older children 2016.

Practical issues

1. Platelets should never be filtered through a micropore blood filter before transfusion, as it will considerably decrease the number of platelets. Each blood component should pass through a blood transfusion set with filter before transfusion. However, platelets should not be transfused through the same set, which has been used to transfuse other blood products. If it is necessary to transfuse multiple blood components through same set (without filter), platelets should be transfused first.
2. Female Rh-negative infants should receive platelets from Rh-negative donors to prevent Rh sensitization from the contaminating red blood cells.
3. It is also preferable to have ABO compatible platelets as far as possible (at least until one year of age).

4. The usual recommended dose of platelets is 1 unit of platelets per 10 kg body weight (unit volume = 45 mL), which amounts to 5 mL/kg. The predicted rise in platelet count from a 5-mL/kg dose would be 20 to 60,000/cubic mm. Doses of up to 10 to 20 mL/kg may be used in case of severe thrombocytopenia.
5. The recommended rate of infusion is 10-20 mL/kg/hr

Fresh frozen plasma

The valid indications for transfusing FFP in a newborn include

a. Disseminated intravascular coagulation (DIC)
b. Vitamin K deficiency associated bleeding
c. Neonates with clinically significant bleeding or prior to invasive procedures with a risk of significant bleeding and with abnormal coagulation profile (PT or aPTT significantly above the normal gestational- and postnatal-age-related reference ranges).

FFP should not be used for simple volume replacement/ expansion or enhancement of wound healing or routinely for prevention of IVH.

FFP should not be routinely used to correct abnormalities of the coagulation screen alone with no evidence of bleeding.Other rare indications include patients with afibrinogenemia, von Willebrand factor deficiency, congenital antithrombin III deficiency, protein C deficiency and protein S deficiency when specific factor replacement is not available. Typically, the transfusion volume is 15-20mL/kg at a rate of 10-20mL/kg/hr. Preferably ABO compatible plasma should be selected as far as possible. Group O plasma must only be given to O recipients.

Cryoprecipitate

Each unit of cryoprecipitate contains about 80 to 100 U of factor VIII, minimum 150 mg of fibrinogen and varying amounts of factor XIII. Volume of cryoprecipitate to be transfused is usually 5 to 10 mL/kg at a rate of 10-20 mL/kg/hr.

Indications for use of cryoprecipitate

1. Congenital factor VIII deficiency when recombinant and plasma derived factor VIII products are not available.
2. Congenital factor XIII deficiency with active bleeding or while under going an invasive procedure in absence of factor XIII concentrate
3. Afibrinogenemia and dysfibrinogenemia with active bleeding or while under going an invasive procedure

Table 57.4 Pediatric dosing of blood components

Component	Dose	Expected increment
Red Blood Cells	10-15 mL/kg	Hemoglobin increase 2-3g/dL
Fresh Frozen Plasma	10-15 mL/kg	15%-20% rise in factor levels (assuming 100% recovery)
Platelets (whole-blood-derived (WBD) or apheresis)	5-10 mL/kg or 1 WBD unit/10 kg (patients 10 kg)	50,000/μL rise in platelet count (assuming 100% recovery)

Transfusion associated risks

Blood transfusion reactions may be broadly classified as

1. Infectious
2. Non-infectious
   a. Acute
      i. Immunologic
      ii. Non-immunologic
   b. Delayed

Infectious complications

In India, it is mandatory to test every unit of blood collected for hepatitis B, hepatitis C, HIV/AIDS, syphilis and malaria. Even though highly sensitive serological tests as well as nucleic acid tests are available, there still remains the risk of transmission of HBV, HCV and HIV due to the window period of infections as well as mutant strains which evade detection in testing. In addition, there is risk of transmission of emerging infectious agents such as Zika virus for which testing is not available.

Non-infectious complications: These can be further subclassified as immune mediated and nonimmune mediated reactions, and as acute and delayed complications.

Acute immune mediated reactions

1. ***Immune mediated hemolysis:*** Acute hemolytic transfusion reactions are rare in neonates. Newborns do not form red blood cell (RBC) antibodies till 4 months of age and all antibodies present in newborns till 4 months of age are maternal in origin.

   Newborns must be screened for maternal RBC antibodies, including ABO antibodies even if O RBCs are to be given as the first transfusion. Maternal serum/plasma may be tested for any atypical red cell antibodies as it may not be possible to obtain sufficient sample from the newborn.

   Neonates are at a higher risk of passive immune hemolysis from infusion of ABO-incompatible plasma present in PRBC or platelet concentrates. Smaller quantities of ABO-incompatible plasma (less than 5 mL/kg) may be generally well tolerated. Unlike adults, in neonates an acute hemolytic event may be present as increased pallor, presence of plasma free hemoglobin, hemoglobinuria, increased serum potassium levels, and acidosis. Results of the direct antiglobulin (Coombs) test may confirm the presence of an antibody on the RBC surface. Treatment is mainly supportive and involves maintenance of blood pressure and kidney perfusion with intravenous saline bolus of 10 to 20 mL/kg along with forced diuresis with furosemide. Enforcing strict guidelines for patient identification and issue of blood, and minimizing human errors are essential in preventing immune mediated hemolysis.
2. ***TRALI (transfusion related acute lung injury):*** It refers to noncardiogenic pulmonary edema complicating transfusion therapy. It is a common and under-reported complication occurring after therapy with blood components. It has been associated with all plasma-containing blood products, most commonly whole blood, packed RBCs, fresh-frozen plasma, and platelets. The most common symptoms associated with TRALI are dyspnea, cough, and fever, associated with hypo- or hypertension. It

occurs most commonly within the initial 6 hours after transfusion. The absence of any signs and symptoms suggestive of acute lung injury before the transfusion should raise the suspicion. Presence of anti-HLA and/or anti-granulocyte antibodies in the plasma of donors is implicated in the pathogenesis of TRALI. Diagnosis requires a high index of suspicion, and confirmation of donor serum cross-reacting antibodies against the recipient. Treatment is mainly supportive.

3. ***Febrile nonhemolytic transfusion reactions (FNHTR)*** are suspected in the absence of hemolysis with an increase in body temperature of less than 2°C.

4. ***Allergic reactions***
   Allergic reactions are caused by presence of preformed immunoglobulin E antibody against an allergen in the transfused plasma, and are a rare occurrence in newborns.

Acute non-immune reactions

1. ***Fluid overload*****:** Neonates are at increased risk of fluid overload from transfusion because the volume of the blood component issued may exceed the volume that may be transfused safely into neonates. Care should be taken to ensure that, in the absence of blood loss, volumes infused do not exceed 10 to 20 mL/kg. There is no role for routine use of frusemide while transfusing newborns.
2. ***Metabolic complication*****:** These complications occur with large volume of transfusions like exchange transfusions.
   a) *Hyperkalemia*: In stored blood, potassium levels tend to be high after storage for around 42 days, potassium levels may reach 50 mEq/L. Though small volume transfusions do not have much risk of metabolic disturbances, large volume transfusions may lead to hyperkalemia. Washing PRBCs before reconstituting with FFP before exchange transfusion helps in preventing this complication.
   b) *Hypoglycemia:* Blood stored in CPD blood has a high content of glucose leading to a rebound rise in insulin release 1-2 hours after transfusion. This may lead to

hypoglycemia and routine monitoring is necessary, particularly after exchange transfusion, after 2 and 6 hours.

c) *Acid- base derangements*:Metabolism of citrate in CPD leads to late metabolic alkalosis. Metabolic acidosis is an immediate complication occurring in sick neonates who cannot metabolize citrate.

d) *Hypocalcemia and hypomagnesemia* are caused by binding of these ions by citrate present in CPD blood.

Delayed complications

1. ***Alloimmunization:*** Alloimmunization is an uncommon occurrence before the age of 4 months, and is caused by transfusion of blood products with are mismatched for highly immunogenic antigens like Rh.[35]
2. ***Transfusion associated graft versus host disease (TA-GVHD):*** Newborns are at risk for TA-GVHD if they have received intrauterine transfusions, exchange transfusions, or are very small, or immunocompromised. Unchecked donor T cell proliferation is the cause of TA-GVHD, and it can be effectively prevented by irradiation of the transfused blood products in at risk patients.

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