Blood components transfusion in neonates

Neonates receiving intensive care often receive transfusion of blood products. Preterm neonates comprise the most heavily transfused group of patients, and about 85% of extremely low birth weight newborns receive a transfusion by the end of their hospital stay.1,2

Blood components used in modern day practice include blood components such as red blood cell components, platelet concentrates, and plasma rather than whole blood. Transfusion of blood products in the vulnerable neonates need to be strictly regulated to avoid the inherent risks of transfusion such as transmission of infections.3

Donor identification and selection

Donor selection is done according to predefined criteria. Usually voluntary (nor replacement) donors who do not require any remuneration are preferred over paid donors. Donors should be provided with educational materials on the essential nature of blood, the blood donation procedure, blood components, and the important benefits to patients.

The donors should be given a questionnaire to identify any health risk factors which can be of concern to themselves and the recipients. Information on the protection of personal data, including confirmation that there will be no disclosure of the identity of the donor, of information concerning the donor's health and of the results of the tests performed also should be provided.4

Collection of blood:

About 450 to 500 mL blood is collected by puncturing vein in the antecubital area after appropriate antiseptic precautions. Blood is collected into bags prefilled with an anticoagulant which is comprised usually of citrate, phosphate and dextrose or other preservatives. The shelf life of the stored blood depends upon the nature of the preservative used.

Apheresis is a technique by which blood components are produced from whole blood donations by selectively collecting one or more components directly from donors and returning the rest to the circulation. Apheresis can be used to collect platelets, plasma, red cells or granulocytes from the donor. The main advantage of apheresis collections are that more than one dose of platelets or red cells can be collected from one donor per donation, thus reducing patient exposure to multiple donors.5

Testing of donated blood:
All donations are tested for mandatory microbiological markers (hepatitis B and C, HIV, and syphilis). A proportion of donations also undergo testing for other viruses (e.g. CMV) and additional typing, such as extended blood grouping and human leukocyte antigen (HLA) typing, for patients with specific requirements.4,6
Preservation and storage:

As there are very few clinical indications for transfusion of whole blood, vast majority of the blood is processed into its basic components: red cells, platelets and plasma. This is achieved by centrifugation of whole blood in the primary collection pack, followed by manual or automated extraction of the components into satellite packs.

The initial storage temperature of whole blood determines the nature of the components that can be produced from it. For platelet production, whole blood must be processed on the day of blood collection or stored overnight at 22°C. However, for the production of red cells, whole blood can be stored at 4°C for 48-72 hours prior to separation. Plasma is separated from whole blood on the day of collection or from blood that has been stored at 22°C for up to 24 hours.  

**PRESERVATION OF WHOLE BLOOD**

Whole blood was stored with acid citrate dextrose (ACD) as the preservative initially. Later less acidic citrate phosphate dextrose (CPD) was used. Both ACD and CPD conferred a shelf life of 21 days. Subsequently adenine was added to the preservative thus forming CPD-A which improved the ATP content of the stored blood and thus increased the shelf life to 35 days.

**PRESERVATION OF RED CELLS**

Additive solutions

With the advent of component therapy and preferential use of red cells for transfusion, preparation of red cell concentrates resulted in inadvertent removal of the preservatives thus resulting in decreased red cell shelf life. To circumvent this problem red cell additive solution were developed which allowed maximum recovery of plasma and preparation of red cell concentrate with a final hematocrit of 60%. Three types of additive solutions are available AS-1, AS-3 and AS-5.

This new blood collection system has a primary bag containing a standard anticoagulant (CPD) and a satellite bag containing an additive solution. Blood is collected in the primary bag containing anticoagulant solution. After the plasma is removed from the whole blood into another empty satellite bag, the additive solution is added to the red cells, thus providing nutrients to red cells for improved viability. The red cells can be stored for six weeks at 2-6°C. The additive solution should be added to red cells within 72 hours since phlebotomy. Additive solution having mannitol are not routinely used for exchange or neonatal transfusion.

Frozen red cells

Frozen red cells are primarily used for autologous transfusion and the storage of rare group blood. Red cells which are less than 6 days old are frozen rapidly after addition of cryopreservative agent containing glycerol. Glycerol prevents damage to red cells when frozen by maintaining a liquid phase and also by preventing hypertonicity. Frozen red cells can be stored for 10 years. Frozen red cells have to be thawed and deglycerolized before use. Frozen red cells once thawed can be stored at 2-6°C for only 24 hours.
Special RBC preparations

Leucocyte depletion

Leukocyte depletion or reduction is done to reduce the concentration of leucocytes to less than $5 \times 10^6$ leucocytes per unit of RBCs by using special filters.

Leukocyte reduction helps in preventing non-hemolytic febrile transfusion reactions (NHFTR), HLA alloimmunization, transmission of leukotropic viruses (CMV, EBV and HTLV-1), transfusion related GVHD, and transfusion related acute lung injury (TRALI).⁴

Mukagatare and associates reported that leukocyte reduction significantly decreased the rate of all transfusion reactions from 0.49% to 0.31% ($P<0.001$), the rates of febrile non-hemolytic transfusion reactions from 0.35% to 0.24% ($P<0.002$), and the rate of allergic reactions from 0.05% to 0.01% ($P<0.001$).⁷

Implementation of universal WBC reduction has been found to decrease the incidence of bronchopulmonary dysplasia (OR, 0.42; 0.25 to 0.70), retinopathy of prematurity (OR, 0.56; 0.33 to 0.93) and necrotizing enterocolitis (OR, 0.39, 0.17 to 0.93).⁸

Gamma irradiation

Gamma irradiation of blood components is done to inactivate donor T cells, and the associated risk of transfusion associated graft versus host disease (TA-GVHD), which may occur in immunosuppressed patients, very small babies, in large volume transfusions and during intrauterine transfusions⁹ or when the donor is related.

Irradiation reduces the shelf life of RBCs to 28 days and also causes leakage of potassium out of RBCs.¹⁰ Irradiated RBCs should be used within 4 hours in neonates to avert the risk of hyperkalemia.

Irradiated RBC’s are recommended for babies with birth weight below 1.2 kg. It may be preferable for any transfusions till 4 months of age.

Washed RBCs

Washing RBCs with saline is done to remove plasma and to reduce potassium in the RBCs. Washed RBCs are recommended for intrauterine transfusions, exchange transfusion and large volume transfusions (more than 20 mL/kg). For patients with immunoglobulin A deficiency or severe allergic or anaphylactoid reactions to red cells, it may be necessary to remove >90% of plasma by washing and re-suspending red cells in saline.³

CMV reduced RBCs
CMV reduced RBCs reduce the risk of transmission of CMV infection, which may be a cause of considerable concern in newborns especially preterm infants. CMV reduction can be achieved by either leucoreduction of blood components, or by pre-selecting donors who are CMV negative.

A meta-analysis of the available controlled studies indicates that CMV-seronegative blood components are more efficacious than WBC-reduced blood components in preventing transfusion-acquired CMV infection.\textsuperscript{11}

\textit{Red cells for intrauterine transfusion:}

Red cells are transfused \textit{in-utero} to treat severe fetal anemia. In order to keep the volume transfused to a minimum, they are prepared by removing some of the plasma from whole blood to achieve a high hematocrit of 0.70 to 0.90. Because of concerns over the potential toxicity of adenine and mannitol in red cell additive solutions, red cells for IUT and exchange transfusion are prepared and stored in plasma.
PLATELETS:

Random donor platelet (RDP)

Platelets can be isolated from the whole blood donations or by apheresis. From whole blood, platelet can be produced either by platelet rich plasma (PRP) method or buffy-coat method. In the PRP method, whole blood is subjected to 'soft spin' initially which separates the whole blood into PRP and red cells. The PRP is then subjected to a 'hard spin' to remove plasma and concentrate the platelets. In the buffy-coat method, whole blood is subjected to a 'hard spin' and buffy-coat separated. The buffy coats from four to six donations are then pooled with a unit of plasma or platelet additive solution and then subjected to a 'soft spin' and the PRP removed.4,5

Single donor platelet (SDP)

SDP units are obtained by a process called plateletpheresis wherein multiple units of platelets are collected from single donor and the RBCs and platelet poor plasma are returned to the donor. The procedure is repeated 4 to 6 times, yielding 4 to 6 units of platelets from one individual. It is especially useful to prevent alloimmunization in multiply transfused patients. Both SDPs and RDPs are irradiated. The concentration of platelets is more in SDP than in RDP, with SDP having a platelet concentration of $3 \times 10^{11}$/unit and RDP having a concentration of $0.5 \times 10^{10}$ per unit. In neonatal transfusion practice, RDP is generally adequate to treat thrombocytopenia. SDP is required only if prolonged and severe thrombocytopenia is anticipated, requiring multiple platelet transfusions. Platelets should be stored at 22-24°C with continuous gentle agitation in platelet incubator and agitator. Maintenance of pH above 6.0 is essential and the function of platelets depends on the permeability of the storage bag to oxygen and carbon dioxide. Platelets stored in bags made of polyolefin have longer half life up to about 7 days. However it is recommended to store platelets in new bags for 5 days only from the date of collection of blood. Platelets are stored with agitation at 22±2°C for up to 5 days. ‘Washed platelets’ can be used in patients with anaphylactic reactions to the plasma component. Washed platelets have a shelf life of only 24 hours.

GRANULOCYTES

Granulocytes are normally collected by apheresis and contain mainly neutrophils but also significant numbers of lymphocytes, red cells and platelets. Granulocytes can also be prepared from buffy coats. Granulocyte transfusion should provide a dose of at least $1 \times 10^{10}$ neutrophils.

Granulocytes should be transfused as soon as possible after collection or preparation but can be stored at 22°C for up to 24 hours without agitation and are irradiated prior to transfusion to prevent transfusion-associated graft-versus-host disease (TA-GVHD). Post transfusion recovery of granulocytes in circulation and migration into inflammatory loci is better if transfused within 8 hours of storage than granulocytes stored for 24 hours.12

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.

Frozen-plasma components can be stored for up to 24 to 36 months depending on the storage temperature, which is usually below -30°C. Once thawed, FFP should be used immediately but can be stored for up to 24 hours at 4°C.\textsuperscript{13}

**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 -18°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.\textsuperscript{13}
Indications for PRBC transfusion in neonatal practice

PRBCs are the most commonly used blood product in neonatal transfusions. Preterm infants requiring intensive care are in need of repeated PRBC transfusion because of their immaturity, ongoing illness and the need for repeated sampling. Transfusion of PRBCs results in resolution of symptomatic anemia and improvement in tissue oxygenation. PRBC transfusion in preterm neonates should be restricted to minimum to prevent complications which are unique to them such as increased incidence of retinopathy of prematurity (ROP), CMV infection and even necrotizing enterocolitis (NEC). To achieve this, transfusion guidelines in neonates should ensure reduction in the number of transfusions and donor exposures.

Restrictive versus Liberal Transfusion

In order to limit the number of transfusions and the number of donors as well, restrictive transfusion policy is recommended. In general for young, mechanically ventilated preterm infants, the capillary
hemoglobin should not be less than 11.5 g/dl; for older, stable infants, the hemoglobin should not be allowed to fall below 7.5 g/dl.

The guidelines for transfusion of PRBC vary according to age, level of sickness and hematocrit are as follows (Table 1, 2).

Table 1: Guidelines for packed red blood cells (PRBCs) transfusion thresholds for preterm neonates

<table>
<thead>
<tr>
<th>SN</th>
<th>Levels of respiratory support</th>
<th>Oxygen requirement</th>
<th>&lt;28 days</th>
<th>≥28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Assisted ventilation</td>
<td>( \text{FiO}_2 \geq 0.3 )</td>
<td>&lt;40</td>
<td>&lt;12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \text{FiO}_2 &lt; 0.3 )</td>
<td>&lt;35</td>
<td>&lt;11</td>
</tr>
<tr>
<td>2</td>
<td>CPAP</td>
<td>Any ( \text{FiO}_2 )</td>
<td>&lt;30</td>
<td>&lt;10</td>
</tr>
<tr>
<td>3</td>
<td>Spontaneously breathing</td>
<td>Symptomatic anemia*</td>
<td>Any Age</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td></td>
<td>( \text{FiO}_2 \geq 0.35 )</td>
<td>&lt;35</td>
<td>&lt;11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \text{FiO}_2 &gt; 0.21 \sim 0.34 )</td>
<td>&lt;30</td>
<td>&lt;10</td>
</tr>
<tr>
<td>b</td>
<td>Oxygen therapy</td>
<td>( \text{FiO}_2 &gt; 0.21 )</td>
<td>&lt;25</td>
<td>&lt;8</td>
</tr>
<tr>
<td>c</td>
<td>Room air</td>
<td></td>
<td>&lt;20</td>
<td>&lt;7</td>
</tr>
</tbody>
</table>

*Symptomatic anemia as defined by more than 9 apneic and bradycardic episodes in 12 hours or 2 or more requiring bag and mask ventilation in 24 h while on adequate methylxanthine therapy or HR>180/min or RR >80/min sustained for 24h or weight gain less than 10 g/day for 4 days on 100 kcal/kg/day or requiring surgery

Table 2: Guidelines for packed red blood cells (PRBCs) transfusion thresholds for term neonates

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hb (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe pulmonary disease</td>
<td>&lt;13</td>
</tr>
<tr>
<td>Moderate pulmonary disease</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Severe cardiac disease</td>
<td>&lt;13</td>
</tr>
<tr>
<td>Major surgery</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Symptomatic anemia</td>
<td>&lt;8</td>
</tr>
</tbody>
</table>
Practical Issues

1. **Amount of transfusion to be given**: It has been seen that transfusion with PRBC at a dose of 20 mL/kg is well tolerated and results in an overall decrease in number of transfusions compared to transfusions done at 10 mL/kg. There is also a higher rise in hemoglobin with a higher dose of PRBCs.\(^{17}\)

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 a newborn and withdrawing small aliquots as and when needed.

3. **Choosing the blood group for neonatal transfusions\(^{18}\)**
   a. 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, neonate’s serum may contain transplacentally acquired maternal IgG anti-A and/or anti-B.
   c. Blood should be of newborn’s ABO and Rh group. It should be compatible with any ABO or atypical red cell antibody present in the maternal serum.
   d. In exchange transfusions for Rh hemolytic disease of newborn, blood transfused should be compatible with mother’s serum. Ideally Rh negative blood of the baby’s ABO group has to be used after cross matching with maternal serum. If compatible ABO group is not available then group O and Rh negative blood can be used.

4. **Volume and rate of transfusion**:
   a. Volume of packed RBC = Blood volume (mL/kg) \times (desired minus actual hematocrit)/hematocrit of transfused RBC
   b. Rate of infusion should be less than 10 mL/kg/hour in the absence of cardiac failure.
   c. Rate should not be more than 2 mL/kg/hour in the presence of cardiac failure.
   d. 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. Presence of thrombocytopenia leads to an increase in risk of bleeding. Dysfunctional platelets in the presence of normal platelet counts may also cause bleeding tendency. Thrombocytopenia has been observed in 1–5% of newborns at birth. Severe thrombocytopenia defined as platelet count of less than 50,000/cubic mm may occur in 0.1%–0.5% of newborns. In NICU, there is a higher incidence; with thrombocytopenia being observed in up to 22% to 35% of all babies admitted to NICUs and in up to 50% of those admitted to NICUs who require intensive care. Significant proportions (20%) of these episodes of thrombocytopenia are severe. Thus a large number of neonates are at risk of bleeding due to thrombocytopenia in NICU.

**Table 3: Indications for platelet transfusion in nonimmune thrombocytopenia in newborns**

<table>
<thead>
<tr>
<th></th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Platelet count less than 30,000/cubic mm: transfuse all neonates, even if asymptomatic</td>
</tr>
<tr>
<td>2</td>
<td>Platelet count 30,000 to 50,000/cubic mm: consider transfusion in</td>
</tr>
<tr>
<td></td>
<td>a. Sick or bleeding newborns</td>
</tr>
<tr>
<td></td>
<td>b. Newborns less than 1000 gm or less than 1 week of age</td>
</tr>
<tr>
<td></td>
<td>c. Previous major bleeding tendency (IVH grade 3-4)</td>
</tr>
<tr>
<td></td>
<td>d. Newborns with concurrent coagulopathy</td>
</tr>
<tr>
<td></td>
<td>e. Requiring surgery or exchange transfusion</td>
</tr>
<tr>
<td>3</td>
<td>Platelet count more than 50,000 to 99,000/cubic mm: transfuse only if actively bleeding</td>
</tr>
</tbody>
</table>

**Practical Issues**:

1. Platelets should never be filtered through a micropore blood filter before transfusion, as it will considerably decrease the number of platelets.
2. Female Rh-negative infants should receive platelets from Rh-negative donors to prevent Rh sensitization from the contaminating red blood cells.
3. The usual recommended dose of platelets for neonates is 1 unit of platelets per 10 kg body weight, 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 10-20 ml/kg may be used in case of severe thrombocytopenia.

**Granulocyte transfusion**

Granulocyte concentrates have limited therapeutic effectiveness in general except for bacterial sepsis or disseminated fungal infection unresponsive to antibiotics in infants. The concentrate should be CMV...
seronegative and be irradiated as it contains large number of lymphocytes but leukofilters should not be used for granulocyte transfusions. The usual dose is 1-2 x 10 neutrophils/Kg body weight, in a volume of 15 ml/Kg. Cochrane review on the effect of granulocyte transfusion on suspected or confirmed sepsis with neutropenia did not find any reduction in mortality when compared to placebo (RR 0.89, 95% CI 0.43 to 1.86).26

**Fresh frozen plasma**

FFP has traditionally been used for a variety of reasons, including volume replacement, treatment of disseminated intravascular coagulopathy (DIC), during the treatment of a bleeding neonate, for prevention of intraventricular hemorrhage, and in sepsis.3 It has not been shown to have any survival benefits in most of these conditions and currently the only valid indications for transfusing FFP in a newborn include

1. Disseminated intravascular coagulopathy
2. Vitamin K deficiency bleeding
3. Inherited deficiencies of coagulation factors

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. It is also used for reconstitution of blood for exchange transfusion.

**Cryoprecipitate**

Cryoprecipitate contains about 80 to 100 U of factor VIII in 10-25 mL of plasma, 300 mg of fibrinogen and varying amounts of factor XIII.13

**Indications for use of cryoprecipitate:**

1. Congenital factor VIII deficiency
2. Congenital factor XIII deficiency
3. Afibrinogenemia & dysfibrinogenemia
4. von Willebrand disease

**Practical Issues:**

1. FFP should be group AB, or compatible with recipient's ABO red cell antigens
2. Volume of FFP to be transfused is usually 10–20 mL/kg
3. Volume of cryoprecipitate to be transfused is usually 5 mL/kg

**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. However, transfusion transmitted infections are still a considerable risk, because of the relative insensitivity of screening tests, and several other organisms besides those tested for, which may be transmitted through blood.

1. **Viral infections**: Transmissible diseases can be caused by viruses like human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV & HCV), and cytomegalovirus (CMV). Other uncommon viruses like hepatitis G virus and human herpes virus-8 have also been detected. Viral infections contaminate platelet products more commonly than RBC products due to a higher temperature used for storage of platelet products. Though screening for HIV, HBV and HCV is mandatory in blood banks, other viruses still present an unaddressed problem. Insensitivity of pathogen testing is also an issue, and risk of viral infections with blood transfusions remains real. Risk of post transfusion hepatitis B/C in India is about 10% in adults despite routine testing because of low viremia and mutant strain undetectable by routine ELISA. HIV prevalence among blood donors is different in various parts of the country.

   **CMV**: Transfusion related CMV infections in newborns were initially identified in the year 1969, and since then transfusion associated CMV transmission is a well known entity. It has been reported that there is a seroconversion rate of 10-30% in preterm newborns transfused with CMV positive blood. Leukodepletion and selection of CMV negative donors decreases the risk of transfusion transmitted CMV.

2. **Bacterial infections**: Bacteria in donor blood are derived from either asymptomatic bacteremia in the donor, or from inadequate skin sterilization leading to bacterial contamination of the blood. Platelets are at a higher risk of causing bacterial infection than other blood components, as they are stored at room temperature, leading to rapid multiplication of infectious organisms. The highest fatality is seen when the contaminating organism is a gram-negative bacteria. In case of a febrile non-hemolytic reaction post transfusion, bacterial contamination always remains a possibility. It generally causes a higher rise in temperature than other febrile transfusion reactions.

3. **Parasites**: Plasmodium, trypanosome, and several other parasites may be transmitted through blood, depending on the endemicity of the area. Transfusion transmitted malaria is not uncommon in India, and may occur in spite of blood bag testing, as the screening tests for malaria are insensitive.

4. **Prions**: Variant Creutzfeldt Jacob Disease (v CJD) is an established complication of blood transfusion and has been reported since 2004. It is thought to have an incubation period of approximately 6.5 years. There is no easy test as yet to detect the presence of prions. It is not
very clear whether leuko-reduction prevents transmission of CJD\textsuperscript{28}. Restricted transfusions and avoidance of transfusions unless essential, are the only ways currently to prevent transmission.

**Noninfectious complications**: These can be further sub classified 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 a common cause of transfusion related fatality in adult patients, but these are rare in neonates. Newborns do not form red blood cell (RBC) antibodies; all antibodies present are maternal in origin.
   
   (1) Newborns must be screened for maternal RBC antibodies, including ABO antibodies if non-O RBCs are to be given as the first transfusion.
   
   (2) If the initial results are negative, no further testing is needed for the initial 4 postnatal months.

   Infants 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) are generally well tolerated. Newborns do not manifest the usual symptoms of hemolysis that are observed in older patients, such as fever, hypotension, and flank pain. 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 error is 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. It has also been reported after the transfusion of cryoprecipitate and IVIG. 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 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 in this self-limiting condition.\textsuperscript{31,32}

3. **Febrile nonhemolytic transfusion reactions (FNHTR)** are suspected in the absence of hemolysis with an increase in body temperature of less than 2°C. For reactions associated with a temperature rise of greater than 2°C or with hypotension, bacterial contamination also should be suspected and a Gram stain and microbial culture performed on the remaining blood product.
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. In some cases, release of residual cytokines or chemokines (eg, RANTES) from stored platelets also may cause allergic reactions. These reactions are generally mild, and respond to antihistaminics. Severe anaphylactic reactions are rare.

**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 complications**: These complications occur with large volume of transfusions like exchange transfusions.

   a) **Hyperkalemia**: In stored blood, potassium levels tend to be high. It has been seen that after storage for around 42 days, potassium levels may reach 50 mEq/L in a RBC unit. 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, to ensure that this complication does not occur.

   c) **Acid-base derangements**: Metabolism of citrate in CPD leads to late metabolic alkalosis. Metabolic acidosis is an immediate complication occurring in sick babies 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.
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 leucoreduction of the transfused blood products in at risk patients.

Research issues: Research issues relevant to Indian context are outlined in Table 4.

<table>
<thead>
<tr>
<th>Research question</th>
<th>Subjects</th>
<th>Study design</th>
<th>Intervention</th>
<th>Outcomes to be measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is the effect of implementation of strict transfusion guidelines in the transfusion practices in NICU?</td>
<td>All neonates admitted in NICU receiving transfusion.</td>
<td>Before and after intervention trial</td>
<td>Implementation of strict transfusion criteria</td>
<td>Number of transfusions, donor exposure, transfusion associated complications.</td>
</tr>
<tr>
<td>2. What is the effect of lower cut off for PRBC transfusion on the growth parameters of VLBW infants at discharge?</td>
<td>All VLBW neonates admitted in NICU receiving transfusion.</td>
<td>Randomized trial</td>
<td>PRBC transfusions at two different cut off levels</td>
<td>Growth parameters such as weight, length and OFC at birth and discharge; Time taken to discharge.</td>
</tr>
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</table>
REFERENCES