Guidelines

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National Guidelines on the Appropriate Clinical Use of Red Cell Concentrates in Pakistan

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"The best blood is the one that you have not transfused"

Blood transfusion is a critical component of modern healthcare. Human-derived therapeutic products, including blood, its labile components, and plasma-derived medicinal products, play a significant role in medical treatment.[1,2] Ensuring availability and equitable access to safe and high-quality blood is essential for achieving universal health coverage.

The demand for blood is rising due to two primary factors: (i) advancements in the diagnosis and treatment of complex diseases, and (ii) the growing number of aging populations with increased blood requirements. When used appropriately, blood transfusion can be lifesaving, but it may also pose risks such as acute or delayed transfusion reactions and the transmission of infectious agents, including HIV, hepatitis viruses, spirochetes, and malaria parasites.[3]

Ensuring an adequate, safe, and effective supply of blood and blood components requires attention to their clinical use. Achieving safety and clinical efficacy involves obtaining blood from healthy and regular donors and

conducting accurate, reliable, quality-controlled testing, and processing. This process demands substantial human and financial resources and involves a collaborative effort between blood transfusion services, prescribers, and administrative authorities to allocate sufficient resources for blood supply and its appropriate rational use.

Blood transfusion therapy relies on the availability of different blood components. The use of specific components, either separately or in combination, addresses the transfusion needs of most patients while minimizing risks. The clinical use of blood thus ensures that the right blood component is used for the right patient, at the right place, dose, time, and indication.[4]

Efficient utilization of blood and blood components is crucial to avoid its unnecessary use, as such practices can lead to shortages for those in real need while expose others to undue transfusion risks. Safety must be the priority for clinicians, patients, and their families. Blood should be used appropriately and only when clinically indicated, with clinicians prepared to manage any adverse events and hence, proper patient identification during sample collection and transfusion is essential.[5]

Red Cell Concentrates (RCC) or Packed Red Blood Cells (PRBC) transfusion is a life-saving procedure with primary objective of sustaining tissue and organ oxygenation in patients with massive bleeding or acute anaemia. RCCs for transfusion are routinely stored for up to 35 or 42 days, depending on the anticoagulant solution (CPDA-1 and SAGM).[6,7] This time limit has been determined mainly by the recovery and the lifespan of the RBCs in the circulation of recipients.[8-11]

Clinicians must discuss the benefits and risks of transfusion with patients and obtain informed consent. Measures to reduce adverse reactions should be implemented, including the use of modified components (e.g. leucoreduced cells) for patients requiring repeated transfusions.[12]

Alternatives to allogenic blood transfusion should also be considered, such as blood conservation techniques during surgery, autologous transfusion, or the use of pharmacological agents. Developing effective communication between blood providers and prescribers is vital to ensure: (i) that a sufficient and safe blood supply is accessible to all in need, and (ii) appropriate clinical use of blood and blood components.

Blood and its components play an essential role in modern healthcare. However, transfusion services constantly face challenges related to safety, cost, and the availability of blood. Despite strict processes and procedures designed to ensure safe transfusion practices, the risk of complications remains. This highlights the importance of ensuring that transfusions are appropriate. The responsibility for safe, efficient, and effective blood transfusion lies with both transfusion services and the prescribers. The safety and effectiveness of a blood transfusion mainly depend on five key factors:

- A sufficient supply of safe blood and blood components, accessible at reasonable cost and adequate to meet the national and local needs.
- Safety of blood and blood components, with blood adequately tested for the absence of infectious pathogens and for blood group antigens and antibodies as appropriate and necessary.
- Appropriate processing and safe handling of blood monitored by key quality indicators.
- The appropriate clinical use of blood and blood components. This comprises the assessment of anaemia and haemostasis of the recipient, and the use of measures that can reduce the transfusion of unnecessary blood products.
- Evaluation of benefits and risks related to blood transfusion prior to transfusion.

Appropriate blood transfusion is defined as the administration of safe blood and blood components to treat a condition that causes significant morbidity or mortality and cannot be effectively prevented or managed by alternative methods. Proper use of blood helps minimize the potential risks associated with transfusions.[13] Pertinence of transfusion now also comprises the use of the most appropriate blood components or derivative available when choices can be made, and in the correct dose, to meet the patient's specific need.[2] As if used appropriately, blood transfusion can save life and improve health. However, evidence from every region of the world indicates considerable variations in patterns of clinical blood use between different hospitals, diverse clinical specialties and even between different clinicians within the same team.[4] This suggests that the use of blood and blood components is often not been optimized, behind lack of apt information and/or education regarding the subject matter.

Haemovigilance

In transfusion medicine, the concept of haemovigilance has emerged during the last three decades. Haemovigilance is a set of processes that brings the entire

vein to vein chain of blood transfusion under examination to avoid any untoward events from donor end to the recipient end and to document it thus maximizing the donor recruitment and retention and making the provision of blood transfusion more efficient and safer.[14,15]

According to the International Haemovigilance Network (IHN), Haemovigilance is a set of surveillance procedures covering the entire transfusion chain, from the donation and processing of blood and its components to their provision and transfusion to patients and their follow-up. It includes monitoring, reporting, investigation, and analysis of adverse events related to the donation, processing, and transfusion of blood, and taking actions to prevent their occurrence or recurrence.[16]

Haemovigilance, at its core, is purely data record keeping and drawing conclusions from the results to correct any malfunction in the blood transfusion services. The data obtained also forms the basis for renovating systems, revising policies and strategies, refining standards, and practices all adding to the safety of the blood transfusion chain. Nearly four decades ago, i.e. in the 1980s, haemovigilance systems were triggered by the terrible experience with transfusion-transmitted HIV cases. The first reporting system of screening HIV as TTI was developed by France through a legislation in 1994.[17] Soon after, many other European countries stepped forward and passed similar legislation in line with the EU (European Union) directives.

The haemovigilance is no longer limited to patients getting a blood transfusion (recipients) but covers entire vein to vein transfusion chain including, (i) collecting information on adverse events/reactions associated with blood collection (donor haemovigilance); (ii) monitoring the frequency of transfusion-transmitted infections in blood donors, monitoring the processing and testing of donated blood; and (iii) authenticating the transfusion of blood components to recipients and collecting information on adverse events/reactions associated with transfusion of blood and blood components (recipient haemovigilance).

The haemovigilance reporting can be ‘hot’ if the adverse events or reactions are immediately reported, or it can be ‘cold’ when the reporting is periodical, e.g. annual reports with data analysis and recommendations. Haemovigilance is also a critical element of quality control in a blood system, allowing remedial and preventive actions, and for the continuous advancement of the quality and safety of blood, blood components and the transfusion process.[18] Therefore, haemovigilance forms an essential part of quality management in blood transfusion services. It can be compared with the 'check' step of the PDCA cycle (plan – do – check – act), which is a four-step management technique applicable to the control and perpetual improvement of processes. The characteristics of a haemovigilance system include:

- Confidentiality
- Professionally owned
- Not punitive (no punishment)
- Voluntary/mandatory
- Sufficient detail to make effective recommendations
- Focus on improved safety and outcomes

The haemovigilance can be successfully implemented and maximum benefit obtained if the data analysis and resulting conclusions are mutually shared with the stakeholders including hospital transfusion services, blood centre, clinical faculty, quality department, infection control department, nursing department, hospital transfusion committee (HTC), and blood transfusion authority (BTA).[19] The ultimate aim of a strong haemovigilance network is to identify the problem areas as well as successful interventions and linking the data globally for a more coherent approach in the blood transfusion services. The basic requirements of a haemovigilance system include (but not limited to):

- Awareness of the clinical staff regarding the need to monitor adverse reaction
- System for reporting incidents
- Guidelines, training, and refreshers
- Hospital transfusion committees (HTC)
- Regular analysis of transfusion practices
- Ensure implementation of appropriate preventive measures
- Traceability of all products from donor to patient
- The system for the recall implicated donations/products/donors
- Robust no blame approach - participants feel free to report incidents without fear
- Ongoing assurance that the focus of the programmes is only on the improvement of patient care

The haemovigilance system can be ‘centralized’ or ‘decentralized’. For a ‘centralized’ haemovigilance model, which is taken as the best method internationally, there is a central haemovigilance headquarter that collects data from all the blood centres and hospitals responsible for managing the adverse event(s) in blood donors or recipients. Reports of the data analysis with feedback and

recommendations are made available to all stakeholders nationally. While in the 'decentralized' haemovigilance model, there is no central body to gather data instead it may be organized at a lower level, e.g. province-wide or at state-level. However, it is pertinent to mention here that regardless of the model adopted by a country, it must be simple, confidential, and quick.[20] In addition to 'donor and process haemovigilance', a key aspect of haemovigilance is the 'patient or recipient haemovigilance' where transfusion reactions and adverse events in recipients are investigated by the clinical team and reviewed by HTC.[21]

In Pakistan, the 'National Guidelines for Quality Control in Transfusion Medicine' were formulated in 2007 and later revised in 2017 and 2020 by the Safe Blood Transfusion Programme of Pakistan's National Health Ministry to ensure the maximum safety of all procedures for donors, recipients, and staff involved in transfusion services. This document includes a chapter on haemovigilance with a basic introduction and key forms to be filled in for reporting an adverse event both in the donors and the recipients.[22] We strongly encourage our readers to fully utilize this document when implementing haemovigilance in blood centers and hospital settings.

The establishment of an effective haemovigilance system is a dire need of Pakistan because substantial risks with regards to blood donation and transfusion of blood and blood components exist and cannot be denied. Haemovigilance can help quantify these risks and qualify them, leading to changes and improvement of quality and safety all along the blood chain, to the benefit of donors, patients, and staff.[23]

Physiology of Red Blood Cells

The normal daily production of red blood cells (RBCs) in a healthy adult is about 0.25 mL/kg and the average lifespan of the cells is about 120 days, whereas that of transfused RBCs is about 50-60 days and can be significantly shorter in the presence of factors reducing their survival.[24]

The storage of RCCs leads to a series of metabolic, biochemical and molecular changes, defined globally as the storage lesion; the extent of these changes is related to the duration of the period of storage.[25-27] Depletion of 2,3-diphosphoglycerate (2,3-DPG) occurs within a few days of the start of storage and is completed within 1 or 2 weeks. This alteration is reversible: 50% of the 2,3-DPG is restored by 8 hours after starting the transfusion, while 24 - 72 hours are necessary for complete recovery. This can be clinically relevant in patients who require massive transfusions.[28-30]

Informed Consent Before a Transfusion

To uphold the principle of autonomy or self-determination, it is essential to obtain informed consent from the recipient or their relative prior to transfusion. The key elements of informed consent include:

- Informing the patient about the necessity of the transfusion, the associated risks of both undergoing and forgoing the procedure, and any available alternatives.
- Obtaining the patient's written consent in the language they best understand after providing the necessary information. Ensure that the consent form is signed by the patient.
- For minors under the age of 18, unconscious patients, or those individuals' incapable of making decisions, consent must be provided by a parent or the next of kin.

Guidelines for Obtaining Informed Consent

Obtaining informed consent before a blood transfusion involves specific considerations to ensure that patients (or representative) fully understand the process, its risks, and benefits. Using non-technical terms to describe the transfusion and its implications is recommended and then asking the patient to repeat or explain back the information back in their own words to confirm comprehension. Key steps include:

- Allowing the patient to ask questions and address their concerns.
- Documenting the obtained consent by completing a transfusion consent form.
- Clearly recording the reason for the transfusion in the patient's medical chart.
- Whenever feasible, discuss consent for the transfusion early enough to consider alternative blood management strategies.
- If the patient refuses the transfusion, documenting this refusal, including the patient's signature and a witness.
- While respecting the patient's decision, ensuring they are informed about all available alternative strategies to blood transfusion and also being offered.

Pre-transfusion Sample Collection

Pre-transfusion testing is essential to prevent the transfusion of incompatible donor red cells, which could lead to an immune-mediated haemolytic transfusion reaction. It is important that blood transfusion requests include sufficient information to accurately identify the recipient and avoid potential errors. For sending blood samples to the blood bank with requisition form, the following should be considered.[31,32]

- If one unit of blood is required, a 3-5 mL blood sample in an EDTA (ethylene diamine tetraacetic acid) vial should be submitted.
- For each additional unit, an extra 1 mL of blood in a plain vial should be sent.
- For infants under four months of age, send EDTA samples from both the mother and the infant: 5-cc of clotted blood from the mother and 1-cc of EDTA blood from the infant. For repeated transfusions, only a sample from the mother is needed.
- For double volume exchange transfusion (DVET), submit a 3 mL sample from the mother along with a neonatal EDTA sample.
- Blood samples for crossmatching should be collected no more than three days before the transfusion.
- When requesting plasma components or platelet concentrate, if the blood group has not been previously checked, include a blood sample with the request.
- In true emergency situations, telephone requests are acceptable, but they must be followed by a written request.
- For investigations related to transfusion reactions, send a 5-cc post-transfusion clotted blood sample, an EDTA sample, urine sample to evaluate haematuria, a completed adverse reaction notification form along with any remaining implicated blood unit.
- Deliver the sample and the requisition form to the blood bank.
- The blood bank laboratory will perform antibody screening and compatibility tests. If issues arise during crossmatching, the blood bank may need additional time to locate a compatible blood unit.

Considerations Before Prescribing Blood[33]

- Can you minimize the patient's need for transfusion?
- Are there specific clinical or laboratory indications for blood transfusion?
- Is there any other alternative treatment you could consider before giving blood - such as IV fluids and any drugs that achieve haemostasis?
- Are you likely to achieve any improvement in the patient's clinical condition?
- What other options are there if blood for transfusion is not available in time?
- Will a trained person monitor this patient during transfusion and respond immediately if any acute transfusion reactions occur?
- Have you recorded the decision and reasons for transfusion on the patient's chart and the blood request form?
- Do the benefits outweigh the risks of this transfusion?
- Will you use blood transfusion for yourself or your dear one in this condition?

Receipt of Blood and Instructions for Administration[34,35]

- Blood for transfusion should be collected just before the transfusion begins. Use a clean, cool box to transport the blood bag from the blood bank to the hospital/ ICU/OT/ward.
- Blood or blood components should never be stored in unmonitored domestic refrigerators, as proper storage conditions cannot be guaranteed.
- Inspect the blood bag for signs of haemolysis, discolouration, clots, turbidity, and leaks. When the bag reaches the hospital, the distinct separation between red cells and plasma may not be visible, but a red colour with a metallic sheen indicates haemolysis.
- A completely haemolyzed RCC unit can be identified by a colour change from red to black.
- Saline-washed red cells prepared using an open system should be used within six hours.
- Administer blood within 30 minutes of issue from the blood bank. If there is a delay, return the blood unit to the blood bank within 30 minutes, ensuring the blood bag is not damaged. Avoid non-medical reasons for delays in starting a transfusion.
- Except in emergencies, blood transfusions should be avoided at night.
- Use 18G needles for routine transfusions and 23G scalp vein sets for paediatric transfusions.
- Administer blood or blood components using a disposable transfusion set with a filter.
- Record the patient's blood pressure, pulse rate, and temperature before, during, and after the transfusion.

- The infusion rate should be adjusted based on the patient's condition. It is recommended to start the infusion slowly for the first 15 minutes, at approximately 100 mL/hour or 1-6 mL/minute (24 drops). If no adverse reactions occur after 15 minutes, the rate can be increased. RCCs should typically be infused within two hours, while whole blood transfusions should be completed within four hours. Rapid transfusion may be necessary for patients with congestive heart failure.
- Observe the patient for any signs of transfusion related adverse events, such as febrile reactions, haematuria, oliguria, or hypotension.
- In the event of a transfusion reaction, stop the blood transfusion immediately and inform the attending physician and the issuing blood bank.
- In case of mild reactions, the transfusion may be temporarily paused and resumed at a slower rate after evaluating the patient's condition.
- If signs and symptoms are severe, then send the remaining blood unit or blood component, along with a 5-cc post-transfusion clotted blood sample, an EDTA sample, urine sample and a completed adverse transfusion reaction notification form to the blood bank for further investigation.
- If the transfusion is completed without any complications, document the time the transfusion finished and the exact volume of blood transfused.

Indications

The following clinical parameters are to be evaluated when considering a transfusion:[36-39]

- Age and gender
- Signs and symptoms of anaemia
- Speed and volume of blood loss
- Cardiac function
- Lung function
- Ischaemic heart disease
- Pharmacological treatments

General Indications for Surgical / Gynaecological Patients[40]

The general indications for surgical patients are sub-divided into pre-operative, per-operative and post-operative indications.

Pre-Operative Indications

Pre-operative screening should be done with history, physical examination, blood CP, and alloantibody screening. Antiplatelet drugs should be stopped seven days before planned surgeries. Reversible causes of anaemia should be treated before surgery to raise the level of haemoglobin (Hb) to 10 g/dL. All surgeries can be performed on all the patients with Hb $\geq$ 10 g/dL.[41-44] The pre-operative indications for transfusions are, (i) if Hb is < 8g/dL, transfusion is required,[45-48] and (ii) in the presence of heart or lung disease, maintain Hb of > 8g/dL.[49]

Per-operative Indications

The amount of blood loss and oxygen saturation drives the decision to transfuse. About 10% of blood volume may be taken as allowable blood loss, that can safely be replaced with crystalloids.[50] Blood loss of up to 750 mL (15% blood volume) can be replaced by crystalloids and requires no transfusion unless blood loss is superimposed on preexisting anaemia, or the patient is unable to compensate for it due to preexisting cardiovascular or pulmonary compromise.[51,52] Blood loss of 800-1500 mL (15-30% blood volume) in the presence of pre-existing anaemia, cardiovascular or lung disease should also be replaced first by crystalloids unless blood loss is superimposed on preexisting anaemia, or the patient is unable to compensate for it due to preexisting cardiovascular or pulmonary compromise. In case of blood loss between 1,500-2,000 mL (30-40% blood volume), replace with crystalloids, however, blood transfusion is required in most of the cases. A blood loss of more than 2,000 ml (> 40% blood volume) requires confirmed blood transfusion, and this also holds true for post-partum haemorrhage.[53-56] Medical conditions where the amount of blood lost cannot be assessed, vital signs guide the decision to transfuse.

Post-operative Indications

Post-operative blood transfusions are often indicated to manage or prevent complications arising from significant blood loss or reduced oxygen-carrying capacity. Some degree of haemodilution can be expected in patients who have lost blood during a procedure. For this reason, an Hb level performed postoperatively is very likely to be lower than the preoperative level. This alone is not an indication for a blood transfusion, and the decision to transfuse should only be made following careful assessment of the patient. The objective is to maintain a Hb between 8-10 g/dL.[58] Consideration should be given to the general condition of the patient and to coexthe isting cardiopulmonary disease, signs of inadequate tissue oxygenation, and continued blood loss.[59]

General Indications

Reversible (treatable) Anaemias

The first line therapy is treatment with hematinic, blood transfusion should be kept as a last resort. In the presence of iron deficiency anaemia, megaloblastic and reversible haemolytic anaemia, the decision to transfuse should rest on patient's clinical condition. Minimum Hb of 6 g/dL is acceptable for well compensated chronically anaemic patients.[60,61] If a heart or lung disease is present or the patient is more than 65 years old, maintain a haemoglobin of ≥ 8 g/dL.[62] For pregnant females, the following indications apply for transfusion of RCCs:[63,64]

- Hb of 5.0 g/dL or below, even without clinical signs of cardiac failure or hypoxia[65]
- Hb between 5.0 and 7.0 g/dL and in the presence of the following conditions:
  - established or incipient cardiac failure or clinical evidence of hypoxia
  - pneumonia or any other serious bacterial infection
  - malaria
  - pre-existing heart disease, not causally related to the anaemia[66]

Irreversible Anaemias

Congenital

Thalassaemia Major: Transfuse when the Hb is < 9 g/dL.[67-71]

Sickle Cell Disease: Do not transfuse till the Hb is < 7 g/dL, maintain Hb between 7-10 g/dL. If surgery is planned, maintain Hb between 10-12 g/dL, HbS is to be reduced to less than 30%.[72-76]

Other Congenital Anaemias: In cases of pure red cell aplasia, congenital dyserythropoeitic anaemias, haemoglobinopathies, enzymopathies and membrane disorders, the decision to transfuse should rest on patient's clinical condition.[77,78]

Acquired

Chronic Renal Failure: Maintain haematocrit (HCT) at ≥ 30%.[79,80]

Myelodysplastic Syndrome, Aplastic Anaemia: The decision to transfuse should rest on patient's clinical condition.[81,82]

Chemotherapy, Neoplasia: Maintain Hb of ≥ 8 g/dL.[83,84]

Massive Transfusion

Experimental evidence suggests that HCT as high as 35% may be required to sustain haemostasis in this context.[85,86]

Burns

Anaemia and hypoproteinaemia commonly develop following extensive burns. These can be minimized by ensuring that burns patients receive a high-protein, high-calorie diet. Vitamin supplements and hematinic should also be administered. Blood transfusion should only be considered when there are signs indicating inadequate oxygen delivery.[87-90]

Indications for Modified Red Cell Concentrates

Leucodepleted RCCs

Used mainly for the prevention of febrile non-haemolytic transfusion reactions (FNHTR) caused by the presence of antibodies to white blood cells, other indications are:[91-94]

- patients with recurrent FNHTR
- patients who need prolonged transfusion support
- reduction of the incidence of CMV infections in:[95-97]
  - CMV-negative patients with congenital or acquired immunodeficiency[98]
  - CMV-negative recipients of a BMT (bone marrow transplant) from a Cytomegalovirus (CMV) negative donor[99,100]
- reduction of the risk of rejection in candidates for haematopoietic stem cell transplantation[101]
- prevention of refractoriness to platelet transfusion
- intrauterine transfusion
- preterm babies
- neonates, and paediatric patients up to one year old, if there is a prior history of intrauterine transfusion[102-105]

Irradiated RCCs[106]

Irradiation, at the dose of 25 Gy (and not > 50 Gy), is currently the only method available for preventing transfusion-related graft-versus-host disease (GvHD). The only unfavourable effect of irradiating RCCs is hyperkalaemia, due to the accelerated release of potassium from the RBCs. This effect is of little significance in adults but can cause serious problems in the case of intrauterine transfusions or exchange transfusions.[107-109] The main indications are:[110-113]

- intrauterine transfusions
- immunosuppressive agents therapy
- transfusion in neonates with a birth weight of ≤ 1,500 g and/or gestational age ≤ 30 weeks
- congenital cellular immunodeficiency
- transplant candidates
- relatives as blood donors, who are also future potential BMT donors
- chemotherapy with purine analogs

Washed RCCs[114-117]

- indicated in patients with IgA deficiency
- prevention of allergic reactions not sensitive to antihistamine drugs
- post-transfusion febrile reactions, present even when leucodepleted RCCs are used
- paroxysmal nocturnal haemoglobinuria

Frozen RCCs

These are indicated in patients with complex immunohaematological profiles in the absence of compatible donors, e.g.:[118]

- rare blood groups
- multiple alloantibodies
- IgA deficiency

Blood Warming

In elective transfusions where a unit of blood is administered over 2-4 hours, there is no need to warm the blood. Routine transfusions do not require blood warming, as maintaining the patient's body temperature is more crucial than warming the infused blood, because blood gradually attains body temperature as it flows drop by drop during the transfusion. It is a common misconception that non-warmed blood infusions cause febrile reactions, additionally, warming blood can lead to increased red cell metabolism, a reduction in 2,3-DPG levels, and an elevated risk of bacterial growth.[119-121]

Warming of blood is useful when rapid transfusion of components is required, especially in trauma [122] or surgery settings because infusion of cold blood/components can cause hypothermia and cardiac complications, increasing morbidity and mortality for the patient.[123] Transfusion at rapid rates (100 mL/min) for 30 minutes of refrigerated blood can lower the temperature of the sino-atrial node to below 30°C and cause ventricular arrhythmias and cardiac arrest. Blood should only be warmed in a blood warmer, which should have a visible thermometer, an audible warning alarm and be properly maintained. Blood should not be warmed by placing it in a microwave, on a heat source, or in unmonitored hot water or by using other devices not specifically approved for blood warming.[124] Warmed blood is mostly required in:[125,126]

- large volume rapid transfusions:
  - adults: greater than 50 mL/kg/hour
  - children: greater than 15 mL/kg/hour
- transfusions to neonates
- exchange transfusion in infants
- patients with clinically significant cold agglutinins

Dosage of RCC

Calculate the number of units by the increment in Hb needed. In general, apart from cases of acute haemorrhage, transfusion of only one unit of red cell concentrate/day is recommended.[127] The dosage needs to be modified on an individual basis to prevent transfusion associated circulatory overload (TACO).[128-130]

Adults

In adults, the dose is 10-20 mL/kg body weight. In the presence of cardiac failure, this is reduced to 3-5 mL/kg. The rate of transfusion is 3-5 mL/kg/hour. As a rough estimate, one unit of RCC increases Hb by 1 g/dL in adults.

Children

In children, the transfusion of 10-20 mL/kg body weight increases the Hb concentration by about 1 g/dL.[131,132]

Neonates

The generally recommended dose of RCCs is 5-20 mL/kg body weight.[133] In case of exchange transfusion in neonates, for a term infant the dose is 80-160 mL/kg, whereas for a preterm infant it is from 100-200 mL/kg body weight.[134,135]

Transfusion Yield

As a rough guide, in the adults, one unit of RCC increases the Hb concentration by 1 g/dL and the HCT by about 3%.[136-140] In children, the transfusion of 5 mL/kg increases the Hb concentration by about 1 g/dL.[141,142] In the case of a lower-than-expected transfusion yield, conditions causing the loss, sequestration or destruction of red cells should be looked for. Such conditions include:

- Occult bleeding

- Repeated blood sampling (particularly in children)
- Fever
- Hypersplenism
- Primary and secondary immunological causes
- Mechanical or other types of haemolysis

Rate of Transfusion

For the first 15 minutes of a transfusion, administer blood at a slow rate of approximately 25-50 mL. If no adverse reaction occurs, the rate can be increased based on the recipient's haemodynamic status. All blood transfusions should be completed within a 4-hour time frame. In a haemodynamically stable patient, the transfusion can typically be completed within two hours. However, for a haemodynamically unstable patient, the process may extend for up to four hours.[143,144] If the recipient's medical condition necessitates a longer transfusion period, request the blood bank to divide the unit into aliquots and transfuse each aliquot over four hours to mitigate the risk of bacterial contamination. For elderly patients and those with congestive heart failure, adjust the rate and volume of the transfusion to avoid cardiac overload, and consider the use of diuretics as needed.

When rapid transfusion is required, avoid using a blood pressure cuff for external pressure on the blood bag, as it may cause barotrauma and haemolysis. If a cuff is used in an emergency, keep the pressure between 100-150 mmHg. The preferred method for regulating and monitoring the rate is a commercially available in-line infusion pump, when available.

Blood Group Compatibility

The criteria for blood-group compatibility for the transfusion of RCC are reported in Table 1:

Table 1: ABO phenotype of RCC units to transfuse

ABO phenotype of the recipient	ABO phenotype of units to transfuse (in order of preference)
O	O
A	A, O
B	B, O
AB	AB, A, B, O

Addition of Drugs and Medications to Blood Bag / Blood Set

Except for normal saline, no drugs should be added to a blood bag. Use only 0.9% sodium chloride injection to dilute RCCs and reduce viscosity. If saline needs to be added, this should preferably be done in the blood bank.

Avoid using an IV line that has been used for any intravenous solution other than normal saline or 5% albumin for blood transfusion. Do not use 5% dextrose or Ringer Lactate for diluting RCCs, as these solutions cause red cell haemolysis. The simultaneous administration of 5% dextrose leads to haemolysis, while Ringer Lactate causes blood clotting in the tubing.[145] Adding drugs to blood bags can change the pH and ionic composition, which may lead to reduced drug effectiveness and a higher risk of bacterial contamination. In the event of a reaction, identifying the exact cause becomes challenging, making it difficult to discern whether the reaction was due to the blood itself or the added substances.

Documentation

Documentation of every step is a legal requirement as per blood safety acts promulgated in all confederating units. All documentation should be kept confidential. The following information should be recorded to prove appropriate use of blood:

- reason for transfusion
- tests done to decide regarding need for transfusion
- screening tests done on blood before use
- number of units transfused and observations during transfusion
- patient's health before and after transfusion
- tests done to record post transfusion improvement

Fresh Blood

Blood collected within the last 24 hours is often referred to as "fresh" as it contains all blood components.[146] However, clinicians are advised not to prescribe fresh blood for the following reasons:[147,148]

Testing Limitations: Providing blood less than 24 hours old is impractical if thorough and reliable testing for transfusion-transmissible infections is to be conducted.

Component-Specific Needs: The demand for fresh whole blood as a source of coagulation factors, platelets, and white blood cells is unwarranted, as specific components can be administered individually.

Modern Practice: In many countries where blood component therapy is available, the use of fresh blood has become obsolete, with only the specific blood component needed for treatment being transfused.[149]

Efficacy for Anaemia: There is no added benefit to using fresh blood over stored blood for correcting anaemia.

Safety of Stored Blood: Many infectious agents, such as spirochetes (causing syphilis), malarial parasites, and bacteria, do not survive storage temperatures after a few days, making stored blood safer.

Resource Management: The unjustified use of freshly collected blood can lead to the unnecessary wastage of other units due to expiration, making it preferable to follow the first-in, first-out (FIFO) policy.[150,151] The use of whole blood is discouraged as it can deplete the supply of blood components. Transfusing components that are not needed increases the risk to the patient and is less efficient in resource management.

Special Cases

Newborns: Blood less than five days old is recommended for exchange transfusions to prevent hyperkalemia and to provide red cells with adequate 2,3-DPG content.

Hepato-Renal Patients: Blood less than 10 days old is suitable for patients with hepatic or renal issues to avoid complications from storage-related metabolites such as potassium, ammonia, and hemolysis.

Multi-Transfused Patients: Patients who require frequent transfusions should receive blood that is less than 10 days old to minimize the need for repeated transfusions.

General Use: For all other cases, blood up to its expiration date is effective for increasing haemoglobin levels.

Shelf life

The shelf life of red cell concentrates is 35 days in CPD A-1 anticoagulant. It is increased to 42 days with the addition of an additive solution (e.g. SAGM).[152,153] When the RCCs are washed with saline they should be used immediately. If storage is unavoidable, it must not exceed 24 hours of washing.[154] The shelf life of irradiated red cell concentrates is reduced to 14 days from the day of irradiation, the maximum shelf life is 28 days. In cases of intrauterine transfusions, exchange transfusions and transfusions in neonates with a birth weight of ≤ 1,500 g and/or gestational age ≤ 30 weeks, irradiated blood must be transfused within 48 hours of irradiation to prevent hyperkalaemia.[155,156] Frozen red cells, if stored at -60 to -80 °C, can be stored for up to 10 years.[157,158]

Duration

The blood must be transfused immediately without undue delays, to prevent mortality and morbidity. Transfusion can be administered faster in individuals with acute blood loss or slower/in smaller aliquots in persons with congestive heart failure. The transfusion in all cases must be completed within four hours of issuance of blood. In addition, the following must be borne in mind:[159-162]

- Do not keep the blood bag in ice
- Do not let the blood bag fold
- Do not press the blood bag to expedite transfusion
- Do not add any medication to the blood bag
- Do not transfuse if there is any fault, damage or leakage in the container
- Do not cover the blood with a towel for warming
- Warming of blood bags is only required in cases of transfusion at a rate of > 100 mL/kg/hour. The temperature of blood warmer should be at 37°C. If blood warmers are not available, then blood can be warmed in a water bath. The blood bag should, however, not come in direct contact with the water bath and be placed inside a tubing.[163]
- Do not give blood transfusion through the saline I/V line[164,165]

Common Misuses of Blood[166-168]

- Anaemia with Hb above 10 g/dL (in the absence of specific risk factors related to the patient's clinical characteristics
- To replace hematinics (iron, vitamin B_{12}, folates)
- For re-constituent purposes
- To accelerate the healing of wounds
- To expand circulatory volume

Adverse Transfusion Reactions

Adverse blood transfusion reactions are described as an unfavourable response by the body to blood or blood components during or after a transfusion. These reactions can range from mild to severe and various frameworks

have been developed (e.g., International Haemovigilance Network [IHN] / International Society of Blood Transfusion [ISBT], Serious Hazards of Transfusion [SHOT], Transfusion and Transplantation Reactions in Patients [TRIP] data or National Healthcare Safety Network [NHSN]), that serve as excellent resources for background data and structured definitions on adverse transfusion reactions.[169] Four terminologies used are:

- *Adverse event* is an undesirable and unintended occurrence before, during or after transfusion of blood. It may be the result of an error, or an incident and it may or not result in adverse reaction.[170,171]
- *Incident* is a case where the patient is transfused with a blood component which did not meet all the requirements for a suitable transfusion for that patient, or that was intended for another patient. It thus comprises transfusion errors and deviations from SOPs that have led to mistransfusions. It may or may not lead to an adverse reaction.
- *Near miss* is an error or deviation from standard procedures or policies that is discovered before the start of the transfusion and that could have led to a wrongful transfusion or to a reaction in a patient / recipient.

Table 2: Signs and Symptoms of Adverse Transfusion Reactions (ATRs)[169,204]

Sign/Symptom	Type of Reaction	Comment
Fever (temperature of ≥ 38°C AND rise of 1-2 °C from baseline)	FNHTR, AHTR, TRALI (respiratory symptoms), and bacterial contamination, can be unrelated to blood transfusion	Can co-exist with other signs such as chills, rigors, myalgia, nausea or vomiting, dyspnoea, hypotension (≥30 mmHg below the baseline) and tachycardia (HR > 40 bpm above the baseline)
Urticaria, hives, pruritus	Allergic transfusion reaction, anaphylaxis	Can be mild and localized or more severe with generalized urticaria
Angioedema	Allergic transfusion reaction	May be preceded by tingling around the face and lips
Dyspnoea or hypoxia	TRALI, TACO, TAD, Severe Allergic transfusion reaction,	Severe dyspnoea without shock may occur in TRALI or TACO. TAD is a diagnosis of exclusion, and patients should be assessed for other causes of dyspnoea before making diagnosis
Stridor, bronchospasm	Allergic/anaphylaxis	
Pulmonary oedema	TACO, TRALI	
Hypotension (fall in systolic &/or diastolic BP by greater than 30 mmHg AND systolic blood pressure of 80 mm or less)	AHTR, severe allergic reaction, anaphylaxis, bacterial contamination, TRALI, Hypotensive reaction (Bradykinin mediated hypotension), can be unrelated to transfusion	Patients on ACE inhibitors are at risk. Risk is higher with bedside leukofiltration. Isolated hypotensive reactions are a diagnosis of exclusion, and occur within an hour of transfusion, in the absence of allergic or anaphylactic symptoms. These reactions usually require no/minor intervention.
Pain	FNHTR (generalized aches), AHTR (pain at the infusion site, abdomen, chest, loins), Anaphylactic reaction (chest pain)	

Severe anxiety or 'feeling of impending doom'	AHTR, bacterial contamination	Mild anxiety is common in patients on transfusions, especially for the first time. However, patients should be assessed for any transfusion reaction if anxiety develops.
Bleeding diathesis with acute onset	DIC can be associated with AHTR, bacterial contamination or massive transfusion	

*This list can be used as a guide and may not be inclusive. DIC: Disseminated Intravascular Coagulation, FNHTR: Febrile Non-Haemolytic Transfusion Reaction, AHTR: Acute Haemolytic Transfusion Reaction, TRALI: Transfusion Related Acute Lung Injury, TACO: Transfusion Associated Circulatory Overload, TAD: Transfusion Associated Dyspnoea

- *Adverse reaction* is an undesirable response or effect in a patient temporally associated with the administration of blood or blood components. It may, but need not, be the result of an incident.[172]

Immediate Immunological Mechanisms[173-175]

- Acute haemolytic reactions[176,177]
- Febrile non-haemolytic transfusion reactions (FNHTR)[178-180]
- Allergic reactions (anaphylaxis, urticaria)[181]
- Acute non-cardiogenic pulmonary oedema (transfusion-related acute lung injury - TRALI)[182,183]

Delayed Immunological Mechanisms

- Delayed haemolytic reactions[184-186]
- Graft-versus-host disease (GvHD)[187-188]
- Post-transfusion purpura[189]
- Alloimmunisation[190-192]

Immediate Non-immunological Mechanisms

- Reaction to bacterial contamination[193-197]
- Circulatory overload (TACO)[198,199]
- Non-immunological haemolysis

Delayed Non-immunological Mechanisms

- Iron overload[200-203]

Post-transfusion Infections (e.g.)

- HBV, HCV, HIV
- Treponema pallidum
- Malarial Parasite

Special Clinical Situations

This section includes special clinical situations which are relevant only to the health facilities having the suitable infrastructure and provision of services.

Transfusion Support for Haemoglobinopathies

The transfusion support for haemoglobinopathies should ideally be:[205-209]

- Leukocyte depleted
- Preceded by an extended red cell phenotype
- ABO compatible
- Be matched for Rh and K antigens
- Be tested for HbS
- Preferably irradiated
- Not be from relatives who are potential bone marrow transplant donors

Transfusion of RCCs in BMT Patients

The need for RCC transfusions in BMT recipients varies greatly from patient to patient. All the patients who are candidates for BMT must be transfused only with leucocyte-depleted RCCs that are preferably of the same group and phenotype.[210-213] Blood components filtered with the latest generation filters, able to reduce the leucocyte content by 99.9%, are a valid alternative to cytomegalovirus negative blood components.[214-216] Transfusion support is required till engraftment is complete or longer if pure red cell aplasia or delayed haemolytic transfusion occurs, with an aim of always maintaining ≥ 8g/dL Hb. CMV negative blood components are required only for CMV negative patients.

Transfusion of RCCs in Infants

Less than 4 Months of Age

Reverse grouping is not required for infants less than four months of age.[217] The RCCs should preferably be:

- Leucocyte-depleted, of the same group and phenotype
- CMV-negative
- Irradiated

The thresholds for transfusion are as follows:

- Hb <13 g/dL in first 24 hours of life[218]
- Cyanotic heart disease, Hb < 13 g/dL[219]
- Clinical manifestations of anaemia (e.g., apnea, tachycardia, poor weight gain), Hb < 10 g/dL

- Acute blood loss and not responsive to other forms of therapy
- Late anaemia, stable patient Hb < 7 g/dL
- Hypoxia or on ECMO, ECLS Hb < 12 g/dL
- Surgery with Hb ≤ 10 g/dl
- Clinical shock or severe decrease in BP, Hb < 10 g/dL

More than 4 Months of Age

For infants more than four months of age, the indications for transfusion are as follows:[220-222]

- Acute blood loss >15% of blood volume, or anticipation thereof, or hypovolemia not responsive to other forms of therapy
- Hb < 8g/dL in peri-operative period
- Postoperatively with signs of anaemia Hb < 10 g/dL
- Severe cardiopulmonary disease, Hb < 13 g/dL
- Patients receiving chemotherapy or irradiation, or patients with chronic anaemia not responsive to medical therapy, Hb < 7 g/dL (symptomatic patients may be transfused at a higher haemoglobin level)
- Clinical shock or severe decrease in BP, Hb < 10g/dL

Transfusion of RCCs in Neonates

In the case of neonates, units of smaller volume (pedipacks) should be used (25-100 mL) to prevent multiple donor exposure. The RCC should be:[223]

- Leucodepleted, irradiated, and CMV negative

Exchange Transfusion

Neonates

The indications for exchange transfusion[224-227] in neonates are severe anaemia, heart failure, and hyperbilirubinaemia usually caused by HDN.

Sickle Cell Anaemia

The indications for exchange transfusion in sickle cell anaemia are vaso-occlusive crisis, acute chest syndrome, and priapism.[228]

Malarial Parasite

Exchange transfusion is required when infestation with Plasmodium falciparum is >5%.[229,230]

Intrauterine Transfusions (IUT)

RCC preparations for IUT should be group O or ABO identical, and RhD negative, K-negative.[231,232] If the mother is negative for allo-antibodies and the blood group of the mother and the baby are the same, maternal transfusion can be given. If the blood group of the baby is not known, O-negative blood should be given.

Autologous RCC Transfusions

The indications for autologous RCC transfusions are the absence of compatible blood donors, e.g., rare blood groups, multiple alloantibodies, IgA deficiency, haptoglobin, C1 esterase inhibitors deficiency.[233] Various techniques for preparing autologous RCCs are available globally. These are:[234-236]

- Blood collected and stored prior to an anticipated surgical or other need (pre-deposit)
- Blood salvaged intra- and post-operatively from surgical wounds and from cardiovascular bypass and extracorporeal membrane oxygenation (ECMO) circuits.
- Haemodilution technique where blood is collected perioperatively, after the patient is anaesthetized and simultaneous replacement intravenous fluid is given.

Quality Control of RCCs

Ensuring a safe and efficacious supply of blood and blood components requires applying the principle of quality assurance to all aspects of components collection, preparation, testing, storage and transport. All QC procedures provided here are according to the National Guidelines for Quality Control in Transfusion Medicine, 2020.[22]

All procedures and equipment in use must be validated prior to their implementation and periodically monitored thereafter. The contents of final blood components should be periodically assessed to make sure they meet the QC standards of blood components. 1% of the total components prepared should be checked for their quality. If the workload is < 500 donors per month then a minimum of four per month should be checked for components quality.

The RCCs should be discarded if the collection exceeds 15 minutes. Components should be prepared and stored within eight hours of the blood collection time.[237,238] This usually happens in blood camps, so ensure that the components are prepared within time. The HCT of RCCs must be 55-79% to ensure sufficient nourishment and anticoagulant is available to keep the red cells viable for 35 days. QC should be checked of those components which have completed their shelf life. For RCCs collected in CPDA-1, the QC should be checked on the

35 or 36 days of their shelf life. If in-date units are selected, they must be given a final disposition and documented as 'used for quality control'. For RCCs, a segment is required after a thorough mixing from each blood unit with the appropriate segment number (segments must be made after the preparation of the RCCs, before making the segment strip the tubing by mixing blood and remaining plasma very well).

Procedure for QC Testing[22]

- Every 100th bag (1% of the collected blood donations) should be checked or a minimum of four bags per month should be checked for quality control.
- For RCCs haematocrit testing, detach one segment (newly made from RCC not the original segment made from whole blood) from three or four donor units of different types, made on different shifts if possible.
- Take the contents of each segment and place into a 12" x 75" test tube which is properly labeled with each unit number and mix well.
- Run these samples on the haematology analyzer and record the results on the QC form (Table 3).

Table 3: RCC Quality Control Record Form

Parameter	Specification	Result
Volume	230-250 ml	
HCT	55-79%	
Haemolysis	< 0.8%	
Sterility	Sterile	
Clot	Absent	

- Specific gravity of packed red cells is 1.080.
- Acceptable results for RCCs QC: at least 100% of units tested should have HCT percentage less than 80% when collected in CPDA-1.
- For leucodepleted RCCs, all specifications are the same except residual WBC count which should be < $5x10^6$/L.
- Store at 2-6°C for up to 35 days (with CPDA-1).
- Visually inspect RCCs for physical haemolysis, clots, grossly lipemic (milky white colour) or signs of bacterial contamination of units by observing colour (brownish/purplish/murky or greyish) and consistency. Further, bag segments should also be looked for signs of haemolysis (pinkish or reddish colour plasma).
- Record results on RCC Quality Control form as shown in Table 3 and included in the National Guidelines for Quality Control in Transfusion Medicine, 2020.

Hospital Transfusion Committee

Every hospital and health care facility responsible for the transfusion of blood components should have a transfusion committee in place. Hospital Transfusion Committees (HTCs) play a pivotal role in promoting safety and efficiency in blood transfusion therapy.[19] The HTC is a key clinical governance element for oversight and delivery of safe transfusion within the hospital.[21] They formulate appropriate local policies and procedures in accordance with the National Blood Policy and Clinical Use of Blood (CUB) Guidelines, regularly review and revise them and monitor hospital transfusion practices against them. HTC establishes and diffuse guidelines for requisition, handling, issuing, storage, and transfusion of blood and components as well as their traceability. HTC are a watchdog for promoting safe and appropriate transfusion of blood and components.

HTCs are an organizational concept and structure which can be set up with the proper resources of the hospital. They provide leadership and advocacy for good transfusion practices. Corresponding to the complexity of blood transfusion, HTCs are a multi-disciplinary team, involving all departments prescribing and providing blood products. They develop indicators of good practice at local level.

Hospital Transfusion Committees are a part of the Quality System for the management of the transfusion of blood and blood components. They are the moral authority at hospital for the implementation of good transfusion practices, haemovigilance and all required corrective actions within the hospital.[22]

The HTC concept was born in the USA at the end of the 1970s, when quality management strategies began to be introduced for the management of health care units and hospitals. From the start, HTC was a quality tool to implement, at the hospital level, quality standards and practices in routine blood transfusion practices. HTC must promote the establishment of:

- Rules of governing good transfusion practices at the hospital level,
- Policies, guidelines, and procedures covering all the aspects of the day-to-day practices in transfusion medicine.
- Initial and continuous training of all staff regarding safe blood transfusion practices.
- Audits to follow up on the implementation of safe blood transfusion practices.

HTC has also been the structure through which the haemovigilance concept has been put to practice, and promoted, among all the health care units where blood transfusions are prescribed and used.[23] Thus, HTC is the best way to implement, at the hospital level, quality and safety in the blood transfusion. This also forms the basis of the WHO recommendation that a Transfusion Committee should be established in every hospital to, (i) implement the national blood policy, standards and guidelines; and (ii) monitor the use of blood and blood components at the local level.

Patient Blood Management

Patient Blood Management (PBM) is a relatively new concept in transfusion medicine. Prof. James Isbister, a haematologist from Australia first used the terminology 'Patient Blood Management' in 2005.[239] PBM is a personalized, patient-focused approach now implemented globally across various clinical practices. PBM programmes are designed to encompass comprehensive patient care, covering preparation for procedures, surgeries, or obstetric management.

PBM aims to improve clinical outcomes for individual patients by managing and optimizing the patient's own blood as a standard of clinical care.[240] While PBM is essentially rooted in basic clinical best practices, it often challenges long-standing habits and default transfusion approaches that have evolved over time.[241] PBM has been described, especially in the elective surgical setting, to include main components:[242]

- Enhancing the patient's red blood cell mass
- Reducing blood loss
- Managing and optimizing the patient's tolerance to anaemia

These strategies help minimize transfusion needs and improved patient outcomes. PBM is also increasingly applied to various medical conditions.[243]

PBM programmes aim to limit excessive blood sampling for laboratory tests and line flushing, promoting alternative solutions such as small-volume sample tubes and rationalizing blood test frequency.[244] These measures help decrease the incidence and impact of iatrogenic anaemia and reduce the costs associated with frequent pathology testing.[245,246] The World Health Organization (WHO) has published a policy brief titled 'The urgent need to implement patient blood management,' which provides comprehensive insights into PBM. This document emphasizes the importance of integrating PBM into healthcare systems to enhance patient outcomes and safety. For detailed information and guidance, the document can be accessed from the WHO website.[247]

Conclusion

In conclusion, these guidelines, developed by the BBMT-Pakistan's Working Group, provide a comprehensive framework to promote safe, efficient, and appropriate transfusion practices for the clinical use of RCCs. By adhering to these guidelines, healthcare providers can enhance patient outcomes, reduce risks associated with transfusions, and optimize the use of blood resources. The structured approach outlined ensures that transfusions are administered only when clinically necessary, upholding the highest standards of patient care and safety.

They emphasize the importance of informed consent, pre-transfusion protocols, and adherence to quality standards in handling and administering RCCs. These guidelines also underscore the necessity for collaboration between clinical teams, blood banks, and hospital transfusion services to maintain an adequate, safe blood supply while minimizing risks. The emphasis on patient-centred care involves detailed protocols for monitoring, documentation, and the management of adverse transfusion reactions, ensuring transfusions are only conducted when truly indicated. The incorporation of haemovigilance practices provides a mechanism for continuous quality improvement and error prevention across the transfusion chain. Recognizing the dynamic nature of medical practices and advancements, these guidelines are designed to be a living document, subject to regular reviews and updates. This ongoing revision will ensure alignment with current research, technology, and best practices, thereby maintaining the highest safety standards for both patients and healthcare providers.

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