

Clinical Guidelines For the use of Blood Products In South Africa

4th Edition 2008

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THE CLINICAL GUIDELINES FOR THE USE OF BLOOD PRODUCTS IN SOUTH AFRICA

4TH EDITION 2008

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1. Legal Aspects of Blood Transfusion

Blood Transfusion is a cornerstone of modern medical practice. It is an essential component in the medical management of patients in almost every field of clinical practice. Medical practitioners who order blood for their patients are faced with the challenge of managing the blood transfusion needs of the patient in an evidence-based approach and balancing the expected clinical benefit with the medical and legal risks inherent in the transfusion of blood.

Blood should only be ordered when there is an appropriate medical indication for a transfusion and practitioners must be able to justify all requests for blood products.

Blood transfusions are currently regulated by the Human Tissue Act (Act No. 65 of 1983) and will soon be regulated under the new National Health Act. Contravention of provisions of the Act, and/or the Regulations, constitutes an offence.

In the broad doctor-patient relationship, it is generally accepted that the doctor (and the blood transfusion service) owe a 'duty of care' to the patient. The doctor and the blood service are in a unique position to prevent harm. The blood service is required to act as a public protector and take responsible steps to make the blood supply as safe as possible. The attending doctor, who has a closer relationship with the patient, is responsible for assessing the clinical need for a blood transfusion, for informing the patient of the benefits and risks of treatment prescribed, and for obtaining informed consent.

1.1 Responsibilities of doctors who transfuse blood

The responsibility of the practitioner who orders and transfuses blood encompasses the following:

- Transfusing blood only when it is medically indicated.
- Warning patients of the potential risks inherent in blood transfusion.
- Obtaining and documenting informed consent.
- Correctly identifying the patient, and units of blood to be transfused.
- Ensuring that appropriate compatibility tests has been performed.
- Ensuring that the blood has been correctly handled prior to and during transfusion.
- Ensuring that the blood has not passed its expiry date.
- Permitting responsible persons to administer blood to the patient.
- Transfusing blood at the proper rate.
- Observing and monitoring the patient at the commencement of, and during the transfusion.
- Effectively managing any untoward transfusion reaction.
- Retaining blood samples as required.
- Reporting of untoward reactions or death.
- Tracing, counselling and testing recipients of blood transfusions identified through the transfusion transmissible infection 'lookback' programme.

1.2 Informed consent

As with any medical treatment, patients have a right to decide whether or not they want the treatment. As far as possible the patient should understand the treatment and agree that the benefits, risks and alternatives to transfusion have been explained and that they consent to the treatment. It is a process which must be acknowledged and documented.

The attending doctor must, in each case, consider alternatives to conventional transfusion therapy (and consider the risks of alternative therapy), and is responsible for discussing alternatives to allogeneic blood transfusion (such as autologous or directed donation) with the patient. The patient must be informed of the material risks inherent in blood transfusion and of alternatives to it. Failure to do this could amount to a failure to procure informed consent, resulting in legal liability for the doctor should the patient suffer adverse effects from the transfused blood component.

1.3 Assessing the benefits and the risks

While the residual risk of transmitting HIV, HCV and HBV infection in the era of individual donation nucleic acid testing is remote, doctors must nevertheless assess the benefits and risk in each case and must be able to justify all requests for blood transfusions. Clinicians must be aware of other infectious risks such as malaria, cytomegalovirus (CMV) and bacterial contamination (particularly of platelet concentrates), and of potential non-infectious adverse effects of transfusion such as red cell incompatibility, immune-modulation, transfusion associated graft versus host disease (TA-GVHD) and transfusion related acute lung injury (TRALI).

Practitioners are advised to keep up to date with international best practices in the field of transfusion medicine and adopt a high standard of care at all times. For example, clinicians need to be aware of the indications for, and the availability of, leukocyte depleted blood components and/or gamma irradiated blood components, know the appropriate clinical indications for blood components, be aware of the potential risks of transfusion and give consideration to alternative treatment. Swift corrective action must be taken when problems occur. Maintaining a good doctor-patient relationship and initiating private dispute resolution or mediation discussions with aggrieved parties is likely to result in a more favourable outcome.

The hospital or institution who employs doctors and other health care professionals (or permits them to practice in their facilities) also has a responsibility in the selection, education, retention and supervision of its medical staff, including the responsibility of the medical staff to obtain informed consent.

1.4 Delictual liability

Generally, delictual liability arises when some harm or damage is caused, either negligently or intentionally, to another, in an unlawful manner. In general, negligence is deemed to be present if the reasonable person would have foreseen harm to the plaintiff and would have taken steps to avoid such harm, and if the defendant failed to take such steps. In the case of experts and professionals, the conduct of the expert or professional is measured against the conduct of the reasonable expert or professional.

The basic elements of a negligence claim are: the defendant owed a duty of care to the plaintiff; the defendant breached the duty; the plaintiff's injury was directly or proximately caused by the breach; and the plaintiff suffered damages as a result.

It is generally considered that it may be difficult to prove that a blood transfusion service or medical doctor acted negligently in the administering of blood if they adhered to the legislation, regulations and standards for practice applicable at the time of the blood transfusion. However, those officials who compiled and/or sanctioned the standards could possibly be held liable if it were shown that the standards themselves were inadequate.

Since blood is a living tissue, inherently variable and incapable of being rendered uniform or completely safe, the standard of 'strict liability' generally does not apply and is not part of South African law.

1.5 Criminal liability

Apart from the statutory offences created by the Human Tissue Act and the Regulations, blood transfusions may give rise to criminal liability for the common law crime of culpable homicide and perhaps even assault. If a patient dies as a result of negligence on the part of the practitioner, or of the blood transfusion service, the individuals involved may be charged and convicted of the crime of culpable homicide – which entails the wrongful and negligent causing of the death of another person. A medical practitioner in South Africa (and, on a separate occasion, a blood transfusion medical laboratory technician) have previously been convicted of culpable homicide after

incompatible blood was administered to a patient. Assault may be deemed to have been committed if a blood transfusion is administered to a patient without the necessary consent.

Blood transfusions are an essential component of medical practice. They are frequently life-saving and dramatically improve survival rates and morbidity particularly in the fields of trauma and surgery and, for example, play a critical role in enabling treatment to be undertaken in medical disciplines such as haematology and oncology. As outlined above, practitioners who order blood for their patients must be cognizant of their legal responsibilities with regard to the administration of blood.

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2. Ordering and Administration of Blood

Procedures for the administration of blood may vary in different hospitals but safety is always the primary concern. As monitoring of the patient during transfusion is often a nursing responsibility, accurate and thorough guidelines should be available for all nurses.

In order to ensure the safety of transfusion, these guidelines should include:

- Preparation of the patient
- Correct identification and verification of the patient and the blood unit
- Correct aseptic technique
- Careful observation of the patient during transfusion
- Special precautions

2.1 Preparation of the patient

The preparation of the patient for transfusion involves documentation of informed consent. Informed consent for transfusion means a dialogue has occurred between the patient and the doctor. The significant risks, benefits and alternatives to transfusion including the patient's right to refuse the transfusion will have been discussed.

The length of time that consent is valid may range from a single prescription for an episode of care or as specified by the treating institution.

As a result of this discussion the patient should:

- Understand what medical action is recommended.
- Be aware of the risks and benefits associated with the transfusion.
- Appreciate the risks, and possible consequences of not receiving the recommended therapy.
- Be given an opportunity to ask questions.
- Give consent for the transfusion.

The consent shall be documented by a consent form or by documentation in the patient's hospital record.

In circumstances where it is not possible to obtain informed consent before proceeding with transfusion (e.g. life-threatening emergency, comatose patient, unaccompanied minor patient), it is acceptable to proceed without consent in the patient's best interests, provided such action is documented in the patient's hospital notes.

2.2 Identification and verification

The safe transfusion of blood products starts with the positive identification of the patient at the time of drawing a blood sample for compatibility testing. Identification is carried out by questioning the conscious patient or suitable responsible person. After taking the appropriate blood samples, these should be clearly labelled at the patient's bedside, with full names, date of birth, hospital number, date of sample withdrawal and ward identification. In the under age or unconscious patient the medical staff may assume the responsibility for identification.

The clinician must complete a requisition form outlining all the above information plus details of previous medical, obstetric, and transfusion history, the diagnosis, reason for transfusion, number and type of component required, and the date and time when the blood or blood components should be available. This information will assist the blood bank staff in identifying the recipient and in finding compatible unit. The blood bank will return all incomplete or illegible forms, and

improperly labelled samples. The transfusion service cannot accept any legal responsibility if they are not supplied with sufficient information to identify the patient.

Laboratory tests are carried out on the sample to determine the ABO and Rh status of the patient, to detect blood group antibodies and to test for serological compatibility with the requested component.

a. The unit

Inspect for leaks, especially in port areas, by inverting and applying light pressure to the unit. Observe for missing port covers and abnormalities. The colour of a red cell concentrate unit should not be significantly darker than the attached segments. Plasma in the unit should not be murky, purple, brown or red. Platelet units will be cloudy yellow/straw colour and should not contain grossly visible aggregates. Thawed fresh frozen plasma will be clear with the colour varying from yellow to straw. Cryoprecipitate will usually be a cloudy straw colour.

When you are ready to start the transfusion, perform the following verification process to help ensure the correct unit will be given to the correct patient. Most acute haemolytic transfusion reactions occur as a result of errors in patient or component identification.

- Recheck the physician's order against the component received to verify you have received the correct component type.
- Ideally two qualified individuals should verify the patient and unit identification at the patient's bedside. This process involves one individual reading the information out loud from one source and the other individual comparing the information to the other source. The blood unit is preferably verified by a medical practitioner and a registered nurse or by two registered nurses.

Staffing and other requirements do not always make this practicable; nevertheless, special care must be exercised in identification procedures. It should always be assumed that one has the wrong patient or the wrong unit, until all identification has been specifically checked.

The following guidelines should be adhered to:

- All identification is carried out at the patient's side.
- All information is read aloud by both attendants checking the blood.
- The recipient's name and identification number on the unit must be identical to that on the hospital record (folder).
- The identification number on the unit must correlate with the unit identification number on the requisition form and/or label.
- The donor's ABO and Rh groups must be recorded on the blood unit (and the transfusion requisition).
- Verification that a compatibility test between the donor and the recipient has been performed.
- If possible the patient's ABO and Rh groups should be confirmed from previous transfusion records in the patient's folder.
- The date and time of expiry of the unit must be checked. Expired blood must not be transfused.

If any abnormalities are noted, the component should NOT be transfused. It should be returned to the hospital's blood bank.

b. The patient

Asking for his/her full name, birth date and other relevant details identifies the patient. The questions should be phrased so that the patient gives a specific answer and not just 'yes' or 'no'.

For example “What are your full names?” and not “Are you Mr J Smith?”. The patient information must correlate with that on the blood unit (and requisition form).

Extra care must be taken in identifying the unconscious, anaesthetised or unidentified patient by checking identity bands, written records and requisition forms. ONLY if all identification is in order may the transfusion be initiated.

If the patient is to receive autologous or directed units, they should be administered first. If a patient has both autologous and directed units available, autologous units should be given before directed units. If a patient has both directed units and non-directed units available, directed units should be given before non-directed units.

2.3 Aseptic technique

Blood is usually transfused through a large needle or cannula, the size of which is selected according to the calibre of the patient's veins. Almost any peripheral vein is suitable for transfusion; however, those in the forearm are best, as the patient's movement will not be restricted. Meticulous skin care and aseptic technique cannot be over emphasized in transfusion therapy as blood acts as an ideal culture medium for bacterial growth. The proposed site for venepuncture should be cleaned with the recommended hospital antiseptic working from clean to dirty areas. Ideally, gloves and a sterile field should be used to position cannulae for transfusion, but most especially in the immunocompromised and long-term transfusion patients. The site should never be re-palpated after cleansing.

During transfusion the transfusion site should be visible through a transparent dressing so that any inflammation or infiltration may be seen immediately. The transfusion should be repositioned if the inflammation is observed.

2.4 Monitoring the patient

A critical part of transfusion therapy is monitoring of the patient, whether by a nurse or a medical practitioner. The accurate and quick interpretation of adverse effects could prevent a fatal reaction. The unit number, date of transfusion, and the starting and finishing time of each unit transfused should be recorded in the patient's folder. Some services require additional signatures on accompanying forms. All this information should be permanently retained in the patient's folder.

Baseline observations of vital signs should be recorded prior to commencing the transfusion. The patient is then observed closely for the first 30 minutes of the transfusion to detect any untoward reaction, and to ensure that the desired rate of transfusion is maintained. In cases of major blood loss, ideally the CVP, pulse, BP, respiratory rate and urinary output should be monitored every 15 minutes throughout the transfusion. In less severe cases the recipient's vital signs should be checked every half hour after the initial 30-minute observation. Patients at risk for circulatory overload should be observed for 12-24 hours after transfusion.

If a transfusion reaction is suspected because the patient complains of symptoms or there are clinically significant changes in vital sign measurements, the transfusion must be stopped immediately, the drip set changed, and the vein kept open with a transfusion of normal saline.

The following actions must be undertaken:

- A member of the medical staff must be contacted immediately.
- The patient's temperature, pulse, respirations and blood pressure must be recorded.
- All clerical and identity checks must be repeated.
- Further management depends on the type and severity of the reaction.

All empty blood units should be returned to the blood bank. In any event, they must be retained for 48 hours following transfusion, at a temperature of 1-6 °C.

2.5 Special precautions

a. Rate of transfusion

The rate of the transfusion depends on the clinical condition of the patient. A patient in acute shock from massive blood loss will require rapid transfusion whereas a patient with chronic anaemia should not exceed 2ml per minute. A relatively slow rate of 5ml per minute is recommended for the first 30 minutes and if there is no sign of untoward reaction the rate can then be increased.

Blood transfusions must be completed within 6 hours of entry of the pack. Blood components that are not used immediately should be stored at the temperature specified by the blood bank. Blood components that are no longer required for a specific patient must be returned to the blood bank for correct storage (if still contained in the original packaging and no seals are broken) or disposal.

b. Filters

Red blood cells, whole blood, cryoprecipitate, FFP and WPBTS VIAHF (Factor VIII concentrate) are administered through a standard blood recipient set, or Y-type giving set. These sets have 170 – 240µm mesh filters to prevent the transfusion of clots or coagulation debris. The filter should be covered with blood to ensure that the full filtering area is used. A platelet giving set should preferably be used with platelets although the standard filter administration set may also be used in an emergency. The latter results in greater loss of the available platelets due to a larger surface area for adhesion.

The use of microaggregate (40µm) filters is not recommended.

The administration set should be changed:

- When there is a transfusion reaction, in order to prevent further potentially harmful blood entering the patient's system.
- Between red cells and other blood products, and between red cell transfusions of different ABO groups.
- Before infusing other fluids, e.g. Dextran, Ringers lactate.
- Every 12-24 hours in patients requiring long term transfusion.

c. Temperature of the blood

If cold blood is administered at a slow rate it does not appear to affect the circulatory system. However, in cases where rapid transfusion is necessary, complications such as cardiac arrhythmias can be avoided by warming the blood to not more than 37°C. Overheating of the blood can cause extensive haemolysis with renal damage and possible death. Blood should be warmed with a blood warmer specifically designed for this purpose. This apparatus should be equipped with a visible temperature-monitoring device and should have an audible alarm. The practice of warming blood in a sink of warm water is ineffectual, as only the outer red cell layers are warmed. It may also present an infectious hazard as the ports may become contaminated. Furthermore, overheating may occur with devastating haemolysis.

Under no circumstances should blood be heated in a microwave oven or similar device. This not only results in extensive haemolysis but also causes conformational changes and denaturation of proteins.

Blood warming is not routinely indicated and refrigerated blood may be transfused without harm over several hours.

Indications for warming are:

- Massive transfusion of more than 50ml/kg/h.
- Infants transfused at greater than 15ml/kg/h.
- Neonates receiving exchange transfusion or large volume transfusion.
- Patients with high titre cold haemagglutinins reactive in vitro at temperatures above 30°C.

d. Additives

No medications or other fluid should be added to the blood or blood products before or during a transfusion because:

- Bacterial contamination is a real hazard whenever any unit of blood is entered.
- A reaction could occur between drug and the anticoagulant or nutrient fluid in the blood, e.g. Dextrose solutions might cause lysis or aggregation of the red cells in the transfusion set.
- Because blood may be administered slowly therapeutic levels of a drug may not be achieved.
- If it is difficult to infuse medication through an alternative access site then a Y piece may be inserted near the junction of the insertion of the intravenous transfusion cannula.

The only fluids that can be given concurrently through the same IV device as a red cell transfusion are:

- Normal saline
- 4% Albumin
- Plasma protein fractions
- ABO – compatible plasma

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3. Red Cell Components

The transfusion of red cells has the ability to save lives and markedly improve survival rates and morbidity in patients being treated for a wide range of medical and surgical conditions. A review of patients who declined blood transfusion showed an increasing morbidity and mortality in proportion to reducing haemoglobin level below 8g/dl. Therefore, for each patient, depending on co-morbidities, a transfusion threshold for red cell transfusion should be determined.

The transfusion of blood should be managed in such a way that the most favourable outcome for the patient is achieved, using the optimal (minimal) amount of allogeneic red cells. Clinicians should focus on guideline-driven, appropriate use of banked blood, utilize pharmaceutical preparations that prevent, minimize, or control blood loss (particularly in the surgical setting), and employ other blood conservation methods whenever appropriate.

3.1 Indications for Red Cell Components

The primary indication for red blood cell (RBC) transfusion is the restoration of oxygen-carrying capacity. Whole blood or red cell concentrates are used to improve tissue oxygenation when this is impaired by haemorrhage or anaemia.

a. Acute blood loss

An acute blood loss of greater than 20% of blood volume (about 1000-1200ml of blood in an adult) will often result in the need for a red cell transfusion. There must be no delay in ordering blood in situations where blood loss is acute and rapid or where there is a possibility of recurrence or continuation of bleeding. Crystalloid solutions should be used initially in volume resuscitation.

b. General surgery

Consider transfusion if:

- The pre-operative haemoglobin level is less than 8g/dl and the surgery is associated with major blood loss (>500ml).
- The intra- or post-operative haemoglobin falls below 7g/dl. A higher haemoglobin level may be indicated in patients who are at risk for myocardial ischaemia or who are >60 years of age.

Pre-operative anaemia must be investigated in every case, as medical management to raise the haemoglobin level may be more appropriate than transfusion.

In surgical patients, the effect of plasma and blood volume expansion should be taken into account when determining the red cell transfusion threshold based on haemoglobin concentration only, and the limitations of the haematocrit level should be taken into account when assessing the need for red cell transfusion in hypovolaemic anaemic patients. In situations of massive transfusion, the number of red cell units transfused can be used as a surrogate for determining the transfusion requirements of fresh frozen plasma (FFP), platelet concentrate and cryoprecipitate.

c. Anaemia in Acute Coronary Syndromes (ACS)

In patients with ACS there is evidence that a haemoglobin level below 8g/dl may be deleterious. Transfusion to a haemoglobin level of 10g/dl is considered acceptable but the effect of each unit transfused must be evaluated for the risk of heart failure due to fluid overload.

d. Anaemia

The aetiology of anaemia should be investigated and, as far as possible, a definitive diagnosis should be made in every case. Medical management will be determined by the cause of the anaemia. Appropriate alternatives to blood transfusion must be considered. Consider transfusion in normovolaemic patients only if they are severely symptomatic e.g. shortness of breath at rest, angina, incipient cardiac failure.

Patients with a haemoglobin level below 7g/dl often require a transfusion. The target (post-transfusion) haemoglobin level will be determined by many factors, including the primary diagnosis. The target haemoglobin will be higher in individuals who require chronic red cell transfusions (such as patients with thalassaemia). In general, the target haemoglobin level will be higher in patients with a "medical" anaemia as apposed to patients with a "surgical" anaemia with blood loss. In the latter, the bone marrow is usually normal; whereas in the former, the bone marrow and other organs may be impaired. The patient's clinical condition should be reassessed after each unit transfused and the need to continue transfusion therapy should be evaluated. In many cases, transfusion can be stopped when a haemoglobin level is reached where the patient is asymptomatic.

e. Cardiac surgery

Pre-operative clinical variables have been identified that independently predict the likelihood of exposure to blood transfusion of patients undergoing cardiac surgery. These variables include: pre-operative haemoglobin, weight, female gender, age, non-elective procedure, pre-operative creatinine, previous cardiac surgical procedure, and non-isolated procedure (e.g. CABG and valve repair). They constitute the clinical predictive index (TRUST). Making use of this scoring tool enables clinicians to stratify patients according to their likelihood of exposure to blood transfusion. It provides patients with important information about their transfusion-related needs, helps the medical team anticipate the patient's transfusion needs, transfusion needs, and guides the clinician in the ordering of additional tests.

f. Obstetric haemorrhage

During an obstetric haemorrhage, red cells should be administered to maintain the patient free of signs and symptoms of inadequate tissue oxygen delivery. The haemoglobin should be maintained between 6 and 10g/dl during the resuscitation phase.

3.2 Red cell compatibility

Red cell transfusions must be ABO compatible. As far as possible, red cell transfusions should also be Rh-D compatible although, in an emergency, in situations of massive blood transfusion, or when there is a shortage of Rh-D negative blood, Rh-D positive blood may be transfused to Rh-D negative patients provided that the patient does not have preformed anti-Rh-D antibodies. Rh-D positive blood should also be avoided in females of childbearing age who are Rh-D negative. Antigen negative blood should always be transfused to patients with specific and clinically significant red cell antibodies. As far as possible, compatibility tests (a 'crossmatch') should be performed prior to transfusion of red cells.

3.3 Storage of red cells

Red cell products are preserved and stored at between 1° and 6 °C for up to 42 days. During the storage of banked blood, changes occur which may be clinically significant. The characteristics of stored blood should be taken into account when transfusing red cell products and the following are some of the impacting factors.

a. Anticoagulant

Donated blood is collected into a solution containing sodium citrate. Citrate is a stable, minimally toxic anticoagulant with pH buffering properties. Citrate is metabolized in the Krebs cycle of respiration and, after transfusion, is rapidly metabolized by most cells in the body, particularly in the liver, muscle and renal cortex. However, certain clinical conditions such as liver disease, hypothermia and hyperparathyroidism may place patients at risk for 'citrate toxicity' during rapid transfusion of whole blood or fresh frozen plasma. Newborns without adequate calcium stores, and with immature livers, are also at risk. In these circumstances, citrate has been considered to be the cause of cardiac arrhythmias due to its ability to decrease plasma ionized calcium through chelation. The flow rate of citrate determines the degree of toxicity. A rate corresponding to 0.04mmol/kg/min. is associated with a significantly increased plasma citrate level and a prolonged QT interval. This situation may arise in massive, rapid transfusion of whole blood especially and, to a lesser extent, red cell concentrates. If possible the ionized calcium levels should be monitored

and 10ml of 10% calcium gluconate administered intravenously (a rule of thumb is 10 ml for every 2 units whole blood given in under 10 minutes). Calcium and any other drug or solution should never be directly added to blood components.

b. 2,3 Diphosphoglycerate (2,3 DPG)

The concentration of erythrocyte 2,3 DPG decreases with storage. The function of 2,3 DPG is to facilitate oxygen transport. The binding of 2,3 DPG with deoxyhaemoglobin, and its interaction with oxyhaemoglobin, shifts the oxygen- dissociation curve to the right, decreasing oxygen affinity of haemoglobin and enhancing oxygen delivery to tissues. With significantly decreased 2,3 DPG levels, as occurs in stored blood after approximately one week of storage, the oxygen-dissociation curve is shifted to the left, decreasing oxygen delivery to tissues.

After transfusion, levels of 2,3 DPG are, however, regenerated in-vivo, with approximately 50% being regenerated within 7 hours, although full restoration of RBC 2,3 DPG can take up to 72 hours. In clinical situations of hypoxia and lactic acid production, and with decreasing pH, the oxygen dissociation curve is also shifted to the right, increasing oxygen delivery. Increased oxygen delivery also occurs with an increase in cardiac output. It is therefore generally considered that low 2,3 DPG levels in stored blood are not usually clinically significant. For example, fresh blood and aged stored blood have been shown to be equally efficacious in immediately reversing anaemia-induced brain oxygenation deficits in humans and lower 2,3 DPG red cell concentrations during the first 24 hours of intensive care are not associated with higher ICU mortality.

However, in certain clinical situations, such as in those patients in shock who cannot increase cardiac output to compensate, patients receiving large volumes of stored blood such as occurs in massive transfusion, or in patients undergoing red cell exchange procedures, transfusion of blood which has been stored for less than 5 days may be optimal.

c. Preservative solutions

Red cell concentrates (RCC's) are prepared by the removal of most of the plasma, and the removal of the buffy layer (which is rich in leucocytes and platelets), from a unit of whole blood. A preservative solution (111 ml volume) is added to the residual red cells. It contains adenine which helps maintain ATP levels during storage; glucose, which provides a substrate for RBC energy pathways plus saline and mannitol which reduces the haemolysis of the banked red cells during the 42 day storage period. Separating off the buffy layer results in the removal of approximately 70-80% of leukocytes present in the original whole blood donation and significantly decreases the occurrence of non-haemolytic febrile transfusion reactions. The volume of a unit of red cell concentrate is approximately 300-350ml (including the adenine additive solution) and the haematocrit is between 0.55 and 0.70. One unit of red cell concentrate (at a dose of 4ml/kg) can be expected to increase the haemoglobin level of an average (70kg) adult by approximately 1-2g/dl. Stored red cells experience loss of deformability and, on day 42 of storage, about 75% of red cells are viable.

Hyperglycemia has been observed in certain clinical situations such as massive transfusion in orthotopic liver transplantation, or following cardiac surgery in infants, and has been attributed to the high glucose concentration in red cell concentrates stored in adenine additive solutions.

d. Electrolyte changes

Red cell concentrates must be stored between 1° and 6 °C. At these temperatures, the sodium-potassium pump is essentially non-functional and intracellular and extracellular levels gradually equilibrate. Plasma potassium concentration increases nearly eightfold over 28 days of storage although, at expiry, the total potassium load in red cell concentrates is only about 5.5mEq. Therefore, the potassium load is rarely a clinical problem except in the setting of pre-existing hyperkalaemia. In these situations fresh (<5 days) or washed red cell concentrates should be used.

e. Plasticizer

The plasticizer di (2-ethylhexyl) phthalate (DEHP) has been shown to leach from the plastic

container into stored blood and, as storage time increases, the amount of DEHP detectable ranges from 6.8 to 36.5 µg/ml in red cell concentrates. The potential toxicity of transfused DEHP remains under investigation, but to date no studies have emerged indicating clinically significant effects.

3.4 Leucocyte depleted red cells

For characteristics and indications see guidelines for leucocyte depletion, Chapter 5.

3.5 Washed red cells

Washed red cells are prepared by the removal of plasma, and the buffer layer, from whole blood donations. The residual red cells are suspended in isotonic saline and centrifuged; the saline from the first saline 'wash' is then removed, and the red cells re-suspended in isotonic saline. Because washed cells are manipulated in an open system, with a possibility of bacterial contamination, they must be transfused within 24 hours of preparation.

a. Indications for washed red cells

- Patients who have experienced severe, recurrent, allergic transfusion reactions not prevented by antihistamines.
- Patients with known IgA deficiency who have formed anti-IgA antibodies. Patients with IgA deficiency may experience an anaphylactic reaction if transfused with blood products containing plasma (even minute amounts of plasma containing IgA protein).
- Patients with paroxysmal nocturnal haemoglobinuria (PNH). Traditionally, washed cells have been recommended for red cell transfusions in these patients. However, recent evidence suggests that transfusing washed cells in patients with a diagnosis of PNH is not necessary. Washing of red cells is therefore no longer recommended provided that donor red cells of the same ABO group as the patient are transfused.
- Neonates with T-activated red cells. Immune-mediated haemolysis may occur following transfusion of plasma-containing blood components to patients whose red cell T-crypt antigens have been exposed by bacterial infection. T-activation occurs when bacterial neuraminidase removes N-acetyl neuraminic acid and exposes red cell T-crypt antigens. These antigens are then susceptible to IgM anti-T which is prevalent in normal plasma, leading sometimes to severe haemolysis. This is particularly associated with necrotizing enterocolitis. However there is so little plasma in red cell concentrates that it is probably unnecessary to provide washed red cells as a routine to all patients with evidence of T-activation of red cells.
- Stored red cells which have been gamma irradiated. Plasma potassium concentrations increase significantly after 12 hours following a gamma irradiation dose of 25Gy. In patients where a high potassium concentration in transfused blood may be clinically significant, red cells which have been gamma irradiated can be washed shortly before transfusion. However, in practice, this can best be managed by ensuring that irradiated whole blood is transfused within 24 hours of irradiation.

3.6 Warming blood for transfusion

In general, blood should not be warmed when individual units are being transfused slowly (over a period of 2-4 hours per unit). Blood should be warmed to between 35 ° and 37 °C when large volumes of blood are being transfused rapidly.

Transfusing ice cold blood rapidly has been associated with an increased incidence of cardiac arrest. Blood should also be warmed when transfused to patients with identified, strongly reacting, cold agglutinins. The best method of warming blood is to use a heat exchanger in which coils of tubing are warmed by electric heating plates. Microwave ovens must never be used to warm blood for transfusion.

3.7. Whole blood

Whole blood is a complex tissue from which clinically appropriate components are processed. Many of the components, particularly platelets and clotting factors, deteriorate in whole blood within hours of donation. It is therefore necessary to physically separate the components soon after donation so that they are available for use in the appropriate clinical situation. The clinical indications for using whole blood are limited since red cell concentrates are more appropriate in most situations where O₂-carrying capacity needs boosting.

Indications:

- Exchange transfusion in neonates
- Massive haemorrhage

3.8 Massive transfusion

The replacement of the equivalent of the total blood volume in 24 hours with red blood cells and crystalloid and/or colloid solutions is defined as massive transfusion. Massive transfusion can also be defined as transfusion of 50% of total blood volume within 3 hours.

In massive transfusion, when blood loss is being replaced by red cell concentrates (packed cells), it may be necessary for red cell transfusions to be supplemented with fresh frozen plasma, cryoprecipitate and platelet concentrates. Whenever possible, the haemostatic profile of the patient should be monitored and the above components transfused only if there is a specific haemostatic defect.

Massively transfused patients manifest a profound haemostatic disorder as demonstrated by prolonged PT, APTT and thrombocytopenia less than $50 \times 10^9/\mu\text{L}$, which is, in part, due to haemodilution. Increases in PT or APTT greater than 1.5 to 1.8 times control values are associated with decreases in some coagulation factors, particularly fibrinogen, FV and FVIII, and should be treated with FFP, especially if there is active bleeding.

Although FFP contains fibrinogen, the amount provided in FFP is usually insufficient to maintain adequate levels and cryoprecipitate should be given early in the course of massive haemorrhage, along with FFP. In general, FFP and cryoprecipitate should be considered when more than 50% of blood volume has been replaced, and it is mandatory when more than 120%-150% of the blood volume has been replaced with red cell concentrate, crystalloid and/or colloid. In situations of massive transfusion, replacement of RBC's, FFP and platelets in a ratio of 1:1:1 is recommended.

3.9 Irradiated red cells

See guidelines for irradiated blood, Chapter 6.

3.10 Blood for exchange transfusion in neonates

For specifications and indications, see Chapter 8.

3.11 Blood for exchange transfusion in adults

Red cell exchange may be performed on those patients with malaria who have a high parasite load, and on patients in acute sickle cell crisis. Erythrocytes infected with plasmodium falciparum have been shown to have decreased 2,3 DPG activity. Because of the large volume of red cells transfused over a short period, it is recommended that, for exchange transfusion in adults, red cells that are no older than 5 days be transfused. The procedure is best managed using apheresis technology.

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4. Leucocyte Depletion of Blood Components

Leucocytes in blood components are responsible for a number of adverse effects associated with blood transfusion. The pathogenesis has not been precisely elucidated in many instances but it is likely that it is immunologically mediated. Potential mechanisms include clonal deletion or anergy, induction of suppressor cells, production of anti-idiotypic antibody and suppression of NK cell activity among others.

Accordingly, filters capable of removing leucocytes by several orders of magnitude have been developed and can effectively reduce the number of white cells in, for example, a red cell concentrate to $< 1 \times 10^6$. A less efficient but much more economical process for depleting components of leucocytes involves removing the buffy coat from red cell components and also using the buffy coats to prepare random donor platelet concentrates. This results in red cell and platelet components with residual leucocytes intermediate in number between filtered components and those with the buffy coat retained. The standard red cell concentrate prepared in South Africa is buffy coat reduced.

A number of countries have adopted a policy of universal pre-storage leucocyte depletion (ULR) while others have adopted a policy of selective leucocyte depletion of components. The costs associated with ULR are considerable e.g. in the USA it would amount to $> \$400m$ and in South Africa (based on 2002/2003 figures), the costs would amount to $\pm 24\%$ of the total annual turnover of all the services. Given the competing health priorities in South Africa, there should therefore be convincing evidence that such an intervention is clinically beneficial and cost effective.

The transfusion services in South Africa have reviewed the medical literature and conclude the following:

- There is good evidence to support the avoidance of febrile non-haemolytic transfusion reactions (FNHTR's) by leucocyte depletion.
- Leucocyte depletion of platelet concentrates will reduce the incidence of platelet refractoriness to platelet transfusions.
- Leucocyte depletion significantly reduces the risk of transfusion-transmitted CMV infection in susceptible individuals.
- The evidence for reduction in post-operative infection is not consistent.
- The evidence for reduction in cancer recurrence is not consistent.
- Although meta-analyses do not provide convincing evidence of a reduction in post-operative mortality for leucocyte depleted products, sub group analyses suggest a benefit for seriously ill and cardiac surgery patients.
- An association with reactivation of viral infections (HIV and CMV) and non-leucocyte depleted components has not been demonstrated.
- Sensitisation to transplant antigens can be ameliorated by leucocyte depletion where HLA allo-immunisation is important.
- Leucocyte depletion may reduce prions in blood components but there is as yet no evidence that leucocyte depletion will avoid transmission of vCJD by blood components.

A policy of selective leucocyte depletion of blood components is therefore recommended as follows:

- All standard red cell concentrates are buffy coat depleted.
- Random donor platelet concentrates are prepared from buffy coats.
- Single donor platelet concentrates collected by apheresis incorporate a leucocyte depletion process.
- Patients on chronic transfusion regimens should receive leucocyte depleted products.
- Patients at risk for CMV infection should receive leucocyte depleted products.
- Organ and stem cell transplant patients should receive leucocyte depleted products.
- Infants < 1 year old should receive leucocyte depleted products.

- Critically ill patients and patients undergoing cardiac surgery should receive leucocyte depleted products.
- Pre-storage (< 48 hours after donation) leucocyte depletion in blood processing laboratories is recommended. If this product is unobtainable it is recommended that freshest units available be filtered in the blood bank for immediate use. Bedside filters should only be utilised when neither of the former 2 options is available.

We emphasise that the above be regarded only as guidelines. If individual clinicians wish to use leucocyte-depleted products for patients that fall outside these guidelines they should request accordingly and the services will issue if the product is available. By continually monitoring the usage and gearing up accordingly, the services will be in a position to meet such demands. However, the cost of a leucocyte depleted component is considerably greater than a standard component.

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5. Gamma Irradiation of Blood Products

Transfusion-associated graft-versus-host disease (TA-GVHD) is a potential complication of the transfusion of any blood component containing viable T-lymphocytes. Under certain conditions these cells engraft and proliferate in the recipient. Cellular interaction between donor T lymphocytes and recipient cells leads to cellular damage (particularly the skin, thymus, gastrointestinal tract, liver, spleen and bone marrow) leading to clinical consequences which are often fatal. The risks of TA-GVHD are highest in immune deficient or immune suppressed recipients; while in immunocompetent individuals, sharing an HLA haplotype with the donor is a major risk factor.

Gamma-irradiation is currently the only recommended method for the prevention of TA-GVHD and when indicated should be administered to all blood products containing significant numbers of white cells (whole blood, red cell concentrates and platelets).

Indications

- All transfusions from blood relatives.
- All HLA matched platelet concentrates.
- Intra-uterine transfusion (IUT).
- Exchange transfusion (ET) following IUT.
- Recommended for all exchange transfusions provided this does not lead to undue delay of the ET.
- Congenital immunodeficiency states (In some centres all blood for neonates is irradiated to avoid missing a congenital immunodeficiency)
- All recipients of allogeneic bone marrow transplants (BMT) or peripheral blood stem cell transplants from the time of initiation of conditioning chemo/radiotherapy. This continues while patient is on GVHD. prophylaxis or lymphocytes $> 1 \times 10^9/L$.
- Patients undergoing stem cell harvesting for later autologous re-infusion.
- All patients with Hodgkins Disease.
- Patients treated with purine analogue drugs.

Blood may be irradiated at any time up to 14 days after collection and thereafter stored for a further 14 days after irradiation. Where there is a particular risk from hyperkalaemia (IUT, ET), it is recommended that red cells (usually whole blood in these cases) be transfused within 24 hours of irradiation.

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6. Platelet Transfusion

Platelet transfusions are required for the treatment or prevention of bleeding due to reduced platelet numbers or function. In general, the risk of bleeding increases only when the platelet count falls to below $50 \times 10^9/l$ and spontaneous bleeding seldom occurs at platelet counts above $20 \times 10^9/l$.

Good transfusion practice

- Platelets should be transfused in accordance not only with clinical guidelines but also with reference to the individual patient's clinical status.
- Do not give prophylactic transfusions without verification of the platelet count on the peripheral smear.
- Ensure that the patient is not on drugs which might potentiate bleeding e.g. Aspirin.
- Consider the appropriate use of other measures such as antifibrinolytics, fibrin glue etc.

6.1 Indications for platelet transfusions

Transfusion of platelet concentrates is standard treatment for bleeding associated with thrombocytopenia and /or defective platelet function in conditions such as:

- Bone marrow failure e.g. aplastic anaemia, acute leukaemia.
- Massive transfusion with dilutional thrombocytopenia.
- Acute disseminated intravascular coagulation.
- Congenital disorders of platelet function.

The role and clinical efficacy of prophylactic platelet transfusions is less well defined. Spontaneous bleeding is unusual at counts higher than $5 \times 10^9/l$.

The following transfusion triggers are widely accepted:

- Threshold of $10 \times 10^9 /l$ for adult stable patients.
- Threshold of $20 \times 10^9 /l$ for patients at increased bleeding risk: -
 - Anatomic lesions e.g. peptic ulcer. -
 - Fever/sepsis. -
 - Recent severe haemorrhage or bleeding from mucous membranes.
 - Anticoagulant therapy. -
 - On drugs affecting platelet function. -
 - Severe anaemia.
- For patients with chronic stable thrombocytopenia e.g. aplastic anaemia, prophylactic transfusions are generally not indicated.
- Platelet transfusion is not required for bone marrow aspirate or biopsy. Application of local pressure is sufficient.
- Threshold of $50 \times 10^9 /l$ for most surgical procedures e.g. laparotomy, liver biopsy.
- Threshold of $100 \times 10^9 /l$ for CNS surgery, ocular surgery.
- For massive transfusion maintain platelet count at $>50 \times 10^9 /l$.
- In situations of multiple trauma and head injury, maintain platelet count at $> 100 \times 10^9 /l$.
- Cardiopulmonary bypass - transfuse only in the presence of microvascular bleeding and platelet count $< 100 \times 10^9 /l$.

6.2 Contraindications to platelet transfusions

Platelet transfusions are generally contraindicated in patients with immune causes of thrombocytopenia unless there is severe life threatening haemorrhage.

- Immune Thrombocytopenic Purpura (ITP): Transfused platelets will be destroyed by the autoantibodies.

- Thrombotic Thrombocytopenic Purpura(TTP): Platelet transfusion may potentiate thrombotic tendency.
- Heparin Induced Thrombocytopenia(HIT): May potentiate thrombosis.

6.3 Platelet products

a. Random donor pooled platelets

- Prepared from the buffy layers of whole blood donations within 8 hours of collection.
- Stored with continuous agitation for up to 5 days at 22 °C.
- Adult dose consists of platelets from 5 individual donations pooled together to produce 1 platelet concentrate.
- Each unit contains a minimum of $>2.4 \times 10^{11}$ platelets with a volume of 200-300mls.
- Random donor platelets are indicated for patients with acute causes of thrombocytopenia e.g. DIC and who are unlikely to require long term platelet transfusion therapy.

b. Single donor apheresis platelet concentrates.

- Complete dose derived from 1 donor with minimum yield of $2,4 \times 10^{11}$ platelets and volume of 200 - 300ml.
- Leucocyte reduction occurs during apheresis procedure; therefore recommended for patients who experience febrile reactions as a result of sensitisation to leucocyte antigens.
- Reduced donor exposure and therefore reduced risk of alloimmunisation to HLA antigens.
- Recommended for patients who are on long term therapy e.g. leukaemia.

6.4 Compatibility

- It is recommended that, as far as possible, group specific platelet concentrates be administered. However, not infrequently, clinical demands and stock availability dictates that patients receive platelet transfusions that are not ABO matched. A good clinical outcome is usually attained as ABO antigens are weakly expressed on platelets.
- Platelet concentrates may contain a small number of red cells. Therefore Rh-D negative platelets should be given to Rh-D negative women with child bearing potential. If this is not possible, administration of anti-D immunoglobulin should be considered, once the platelet count is corrected.

6.5 Administration

- Platelets should be transfused through a platelet giving set over a period of 15-30 minutes. Transfusion through a standard red cell giving set will reduce the number of platelets received.
- Dose: In South Africa the services provide buffy coat derived platelets (5 donors per pool) suspended in plasma. This is equivalent to one adult dose. Apheresis (single donor) platelets are given as a single adult dose. Platelets for paediatric use are subdivided into aliquots from a single apheresis unit and a recommended dose for neonates and infants is 5-10 ml/kg.

6.6 Expected increments

The platelet count should increase by $20-40 \times 10^9$ /l per standard adult dose. The increment will vary, however, and be lower in patients with:

- Splenomegaly
- DIC
- Septicaemia

6.7 Platelet refractoriness

An increment of less than 10×10^9 /l on more than one occasion may be due to development of antibodies to HLA and/or platelet antigens. Consult with the transfusion service regarding provision of matched platelets.

6.8 Adverse effects of platelet transfusion (See Chapter 10)

As with other blood products adverse reactions may occur. Febrile reactions are the most common and may be treated symptomatically. For subsequent transfusions leukocyte depleted preparations are indicated. In addition, the risk of **bacterial contamination** is greater with platelet transfusions because of room temperature storage.

6.9 Irradiation (See Chapter 5)

Platelets may be irradiated as indicated with no loss of function.

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7. Paediatric Transfusion Practice

The field of transfusion medicine for children shares most of the same principles as that of adults but it has distinctive features which need separate consideration. Those children who require blood products are also among the most intensively transfused of all patients. Because they are likely to have a long lifespan following transfusion, minimising adverse events is of great importance.

For the purpose of these guidelines, neonates are considered to be infants within 4 weeks of the normal gestational age (40 weeks) and infants are children within the first year of life.

7.1 Intra-uterine Transfusion (IUT)

This should only be done by specialised units. It is most commonly indicated for correction of foetal anaemia caused by red cell allo-immunisation. Intra-uterine platelet transfusions are rarely indicated and are essentially used only to correct foetal thrombocytopenia caused by platelet allo-immunisation. However, the use of intravenous immunoglobulin in mothers with allo-immunisation has largely replaced foetal platelet transfusions.

Red cell products for intra-uterine transfusions are specially prepared by the blood transfusion service on request by the clinician. They are usually group O, Rh-D negative (preferably also Kell negative), crossmatch compatible with maternal serum, < 5 days old, leucocyte depleted and irradiated.

7.2 Neonatal Transfusion

a. Exchange Transfusion

Exchange transfusion may be used to manage severe anaemia at birth and to treat severe hyperbilirubinaemia, usually caused by haemolytic disease of the newborn (HDN). The aim in exchange transfusion is to remove Rh-D positive red cells, reduce bilirubin levels and remove maternally derived anti-D. The bilirubin level at which an exchange transfusion is indicated varies according to the weight and gestational age of the baby and the South African Neonatal Academic Hospitals' Consensus Guidelines should be followed. (S Afr Med J 2006;96: 819--824). The early administration of intravenous immunoglobulin (1 g/kg) to Coombs positive infants with neonatal jaundice significantly reduces the level of exchange transfusions for hyperbilirubinaemia.

The red cell component used for exchange transfusion varies nationally and internationally. Some centres use unmodified whole blood while others plasma reduce whole blood to a haematocrit of 0.5-0.6 l/l. Some centres, particularly in the USA, reconstitute red cell concentrates with fresh frozen plasma but it increases donor exposure and is not recommended. The unit should be group O (or ABO compatible with maternal and neonatal plasma), Rh-D negative, crossmatch compatible with maternal plasma, < 5 days old, irradiated (must be transfused within 24 hours of irradiation) and leucocyte-depleted. It should not be transfused directly from cold storage and should be warmed during the procedure with care taken to avoid overheating. In normal term infants the routine use of calcium gluconate is unnecessary. However, in sick, preterm neonates monitoring of ionized calcium is advisable.

b. Small volume red cell transfusions

Most neonatal transfusions are small volume (10-20 ml/kg). It should be noted that during the first 4 months of life, blood bank pre-transfusion testing differs from adults. If there are no clinically significant red cell antibodies in the infant or maternal plasma, and the direct antiglobulin test is negative, a full crossmatch is not necessary, although the ABO and Rh-D group should be re-confirmed prior to each transfusion.

Suggested transfusion thresholds for infants < 4 months of age are listed below:

- Anaemia in the first 24 hours Hb <12g/dl (Hct c 0.36 l/l)
- Neonate receiving mechanical ventilation Hb < 12g/dl
- Acute blood loss = 10% blood volume lost
- Oxygen dependent (not ventilated) < 8-11g/dl
- Late anaemia, stable patient (off oxygen) Hb < 7g/dl

The age of the unit does not matter for small volume top-up transfusions, but large volume transfusions (exchange transfusion or acute blood loss) should be < 5 days old in order to avoid hyperkalaemia and reduced 2,3 DPG levels with poorer oxygen release. Leucocyte depleted products are also recommended for infants < 1 year.

Neonatal units should arrange with their local blood banks that those neonates with extended transfusion needs are placed on a "limited donor exposure" programme where the transfusion requirements of one infant are met by reserving units bled from one donor for a specific infant. This ensures minimum infectious risk and red cell antigen exposure.

c. Specific paediatric products for neonates and infants

The use of an adult red cell concentrate unit, fresh frozen plasma (FFP) or platelet concentrate for infants and small children will result in significant wastage since the volumes required are generally small. The services therefore prepare special products for paediatric use in the following volumes.

- Red cell Concentrates
 - Infant: 120-140ml
 - Neonate: 50-80ml
- FFP: 130ml
- Platelets: 50-60ml volume; usually aliquoted into 5-6 units obtained from a single apheresis unit

d. Platelet transfusion

Thrombocytopenia is common in sick pre-term infants and is associated with an increased risk of severe periventricular haemorrhage. The guideline thresholds for platelet transfusion are:

- Consider in all neonates: < 30 x 10⁹ /l
- Consider if increased bleeding risk: < 50 x 10⁹ /l
 - <1000g and < 1 week old
 - Clinically unstable (e.g. labile blood pressure)
 - Previous major bleeding
 - Current minor bleeding
 - Coagulopathy
 - Planned surgery or exchange transfusion
- Major bleeding: < 100 x 10⁹ /l

ABO group specific platelets are recommended.

In neonatal allo-immune thrombocytopenia, HPA-compatible platelets are required. In an emergency, use of maternal platelets is an option when the count is < 30 x 10⁹/l.

Dosage: Platelets for neonates are usually prepared from single donor apheresis/ procedures: a dose of 5-10 ml/kg is recommended.

e. Fresh Frozen Plasma (FFP)

ABO group specific plasma (or AB plasma) is recommended. Group 0 FFP should not be given to neonates who are not group 0 owing to the potential risk of the infusion of significant amounts of anti-A and -B.

FFP should never be used for volume replacement. It should be reserved for neonates with a significant coagulopathy {INR or activated partial thromboplastin time (APTT) ratio > 1.5 and significant risk of bleeding} or who are about to undergo an invasive procedure, at a dose of ± 15 ml/kg.

f. Transfusion in necrotising enterocolitis (NEC)

Infants with NEC may be infected with neuraminidase-producing organisms such as *Clostridium* sp. Neuraminidase can strip sialic acid residues from red cell sialoglycoproteins exposing the T-cryptantigen (so called "T-activation"). T-activation can easily be detected by screening the affected red cells with a lectin (*arachis hypogea*). Adult plasma invariably contains anti-T, a potentially haemolytic IgM antibody. Although there have been well described cases of haemolysis following transfusion in patients with NEC, it is controversial whether T-activation in NEC is predictive for clinically significant haemolysis. As a result, different centres have different policies. It is probably reasonable to provide platelets, FFP and cryoprecipitate with low titre anti-T. Washed red cells are not recommended as a routine as they contain minute volumes of plasma. If unexplained haemolysis occurs the use of washed red cells may then be considered.

7.3 Irradiation

The indications for irradiation are outlined in Chapter 6. Note that while irradiation is recommended prior to exchange transfusion, it should not be unduly delayed as a direct result of the irradiation process.

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8. Plasma Components and Derivatives

There is a wide range of plasma products available with specific indications for their use. For the purpose of clarity, products produced by the component processing laboratories and relying on purely physical separation techniques will be defined as plasma components (e.g. fresh frozen plasma, cryoprecipitate). Those products derived from plasma pools and subjected to more complex chemico-physical processing (e.g. Kistler and Nistchmann alcohol fractionation method) will be referred to as plasma derivatives (e.g. albumin). The various products, usage guidelines and recommended dosage schedules are outlined below. Clinicians should be aware that all the products are antigenic and potentially capable of causing allergic or anaphylactic reactions. The patient should therefore be observed as for cellular products during the initial 15 minutes of any transfusion. The information is provided as a guideline only. For further information please refer to the Medicines Control Council approved package inserts for plasma derivatives.

8.1. Plasma Components

a. Fresh Frozen Plasma (FFP)

Plasma for FFP is separated from anticoagulated whole blood within 18 hours of donation. This is done by centrifuging whole blood in a closed sterile system and freezing the plasma to below -18 °C. It contains all the coagulation factors at normal physiological levels. During the past 5 years, the transfusion services have in most areas introduced a donor plasma retest quarantine program (also for cryoprecipitate and cryo-poor plasma) to minimise the risk of a window period infection. In areas where this program is not in place, only plasma from regular donors is used. No pathogen transmissions have been reported since the introduction of the program. However, patients likely to receive large or repeated doses may benefit from pathogen inactivated plasma (see pp 29-30).

Table 1

Product	Volume	Content	Dosage
Fresh Frozen Plasma	Approx 280 ml	Physiological levels of all coagulation factors	15-20 ml/kg as an initial dose. Further therapy is dependent on clinical response and laboratory monitoring.

Table 2: Coagulation factor levels in FFP

Factor	Average Levels
Fibrinogen	200mg per unit of FFP
Factor II	1.03 IU/ml
Factor V	0.64 IU/ml
Factor VII	1.21 IU/ml
Factor VIII	0.85 IU/ml
Factor IX	0.95 IU/ml
Factor X	1.25 IU/ml
Factor XI	0.79 IU/ml
Antithrombin III	104 IU/ml
Plasma pseudo-cholinesterase	3000-10 000 IU/ml

An average unit of FFP will also contain solutes of the anticoagulant from the original unit of whole blood.

Table 3: Solute in FFP

Solute	Average Levels
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Glucose	24.8 mmol/L
Potassium	3.2 mm/L
Sodium	165 mmol/L
Chloride	79 mmol/L
Osmolarity	322 mmol/L
pH	7.9

Caution: FFP is hyperosmolar due to the solutes listed. In elderly and very young patients, care should be taken not to precipitate pulmonary oedema if cardiopulmonary function is compromised and tissue oedema is present. Hyponatraemia and hypokalaemia may occur if large volumes are transfused.

Table 4: Clinical Indications for FFP

Indications	No justification for use of FFP
Replacement of inherited single factor deficiencies (if single factor concentrate not available).	Hypovolaemia
Multiple Coagulation factor deficiencies (DIC, massive blood transfusion, liver disease) in presence of active bleeding and abnormal coagulation screening tests.	Plasma Exchange procedure (except TTP)
Thrombotic thrombocytopenic purpura (TTP) (preferably cryo poor plasma).	Nutritional support and protein losing states
Reversal of Warfarin if active bleeding: preferable to use Prothrombin Complex Concentrate (PCC) e.g. Haemosolvex Factor IX	
Vitamin K deficiency associated with active bleeding	
Scoline Apnoea	
Paediatric use: Haemorrhagic Disease of Newborn: use FFP and intravenous Vitamin K	

FFP must be administered through a blood giving set after thawing at 30-37 °C. The unit should be transfused as rapidly as possible (15-20 minutes per unit) with a recommended maximum delay after thawing of up to 4 hours, as labile coagulation factors deteriorate within a few hours of thawing or reconstitution. The first choice is to administer FFP of the same ABO blood group as the patient. If not available, a different ABO group can be given provided the anti-A and B titres are low. Blood group O FFP should preferably be given only to group O patients. Group O should especially be avoided in non group O neonates since this may result in haemolysis from passive infusion of anti-A and B.

b. Cryoprecipitate

This is the cold insoluble fraction of FFP and is obtained by thawing FFP at 0-4 °C. It is stored at <-18 °C for up to 1 year and the mean volume is 0-15ml.

It contains the following proteins in concentrated amounts:

- Factor VIII and von Willebrand Factor ± 100 IU per unit
- Fibrinogen 150-250 mg per unit
- Fibronectin
- Factor XIII

It is indicated primarily for treating hypofibrinogenaemia (acquired or congenital) and is usually administered in pools of 10 units and is given through a standard blood administration set. It may also be used for treating hereditary Factor XIII deficiency.

c. Cryosupernatant (cryo-poor FFP)

This is the component available following extraction of cryoprecipitate. It is stored in limited quantities and is the component of choice in many haematology units for the treatment (with or without plasma exchange) of thrombotic thrombocytopenic purpura (TTP). For protocol guidelines, please refer to the nearest specialist haematology unit.

8.2. Plasma Derivatives

a. Bioplasma FDP (Fresh Human Plasma: lyophilised powder for IV infusion)

Bioplasma FDP (from National Bioproducts Institute - NBI) is produced from pooled fresh human plasma from non-remunerated, volunteer donors. It undergoes a pathogen inactivation procedure using a solvent detergent treatment process which inactivates lipoprotein-coated viruses such as HIV, hepatitis B and hepatitis C. After reconstitution with water for injection, each 100 ml contains 4-6 g plasma proteins and a minimum of 0.4 IU/ml of each coagulation factor. Bioplasma FDP has the same clinical indications as FFP at the same recommended dosage. This product is available either as a 50 ml or 250 ml pack size and infused through a standard blood administration set. It can be stored at room temperature (below 25 °C). This product contains no antimicrobial agent or preservatives.

Table 5: A comparison of standard fresh-frozen plasma (FFP) with solvent detergent-treated FFDP

	Standard FFP	Solvent detergent FDP
Source	Single unit format. Voluntary, non-remunerated donors	Voluntary non-remunerated donors; pools of up to 220 L
Donation screening Serology Genomic	HIV, HBV, HCV, Syphilis HIV, HBV, HCV	HIV, HBV, HCV, Syphilis HIV, HCV, HCV
Volume	±250 ml	200 ml; 50 ml
Coagulation factor content	Physiological levels, variable between units (see Table 2)	Constant within batch. All factors > 0.4 IU/ml.
Residual additives	Solutes as per Table 3	Residual Levels of solvent detergent not toxic.
Allergic reactions	May be reduced by leucocyte depletion	Probably less frequent than FFP but no data.
Red cell	Tested for high titre anti- A,B. If > 1/64 - not used for FFP	High titre Anti-A,B not a problem since donations pooled. Screen out high titre anti-A,B
Cellular content	No need to Rh-D match.	No need to Rh D match
Product licence	Not required	Licensed, batched product
Indications	See Table 4	As for FFP – see Table 4

b. Coagulation Factor Concentrates

Haemosolvate Factor VIII 300 IU/500 IU

This is an intermediate purity Factor VIII concentrate produced by NBI and prepared from freshly frozen plasma pools. It is reconstituted into 10 ml volumes for direct intravenous injection and is clinically indicated for the treatment of Haemophilia A and von Willebrand's Disease (vWD). It undergoes a viral inactivation step using a solvent-detergent process which

inactivates lipid-enveloped viruses such as HIV, hepatitis B and hepatitis C. See Table 6 for further details and also refer to the package insert.

Haemosolvex Factor IX

This is a prothrombin complex concentrate produced by NBI and prepared from fresh plasma and contains prothrombin, factor VII, factor X and factor IX. It is reconstituted to a volume of 10 ml for direct intravenous injection. It is indicated in the management of haemophilia B and the treatment of warfarin induced bleeding. It undergoes a viral inactivation step using a solvent-detergent process which inactivates lipid-enveloped viruses such as HIV, hepatitis B and hepatitis C. Refer to Table 6 and the package insert for further details.

VIAHF

This is an intermediate purity Factor VIII concentrate produced by Western Province Blood Transfusion Service (WPBTS) from small pools (5-6 bags) of cryoprecipitate. It is reconstituted into 50 ml volumes with sterile water for injection and is administered through a standard blood administration set. It is indicated for the treatment of Haemophilia A and vWD. It undergoes a viral inactivation procedure (80 °C heating for 72 hours) that has been shown to inactivate HIV, hepatitis B and C viruses.

Table 6: Coagulation factor concentrates

Product	Content	Units	Volume
VIAHF 250 (WPBTS) (Paediatric)	Factor VIII/vWF	250 IU	50 ml after reconstitution with sterile water
VIAHF 500 (Adult) (WPBTS)	Factor VIII/vWF	400 – 600 IU	As above
Haemosolvate Factor VIII 300 IU (NBI)	Factor VIII/ vWF	factor VIII:C 300 IU; factor VIII:vWF - >300 IU;.	10 ml after reconstitution with sterile water for injection
Haemosolvate Factor VIII 500 IU (NBI) Two pack sizes: 500 IU and 2 x 500 IU	Factor VIII/ vWF	factor VIII:C 500 IU; factor VIII:vWF - >500 IU	10 ml after reconstitution with sterile water for injection
Haemosolvex Factor IX (NBI)	Factor IX (also contains II, VII and X)	factor IX 500 IU (50 IU/ml), factor II > 400 IU, factor VII>65 IU and factor X > 400 IU	10 ml after reconstitution with sterile water for injection

c. Dosage schedules and treatment guidelines

For details refer to your local haemophilia centre. It is important that all haemophiliacs or any patient with an inherited bleeding disorder be registered with the South African Haemophilia Foundation and referred to the nearest haemophilia centre.

Haemophilia A

The levels of Factor VIII should be monitored throughout therapy. However, in an emergency or in remote areas dosage schedules may have to be empirically applied.

For major surgery in haemophilia and treatment of severe haemorrhage it is strongly recommended that this be undertaken under the supervision of a practitioner experienced in haemophilia care and with reliable laboratory monitoring.

Factor VIII has an average half-life of 12 hours. Treatment should therefore be given every 8-12 hours for the first 24 hours and then approximately 12 hourly. After major surgery Factor VIII infusions may be required for up to 10 days post-operatively. The dosage (in units of Factor VIII) can be estimated as follows:

Required dose (IU Factor VIII) = body mass (kg) x 0.5 x desired FVIII increase (% of normal).

SA Haemophilia Foundation recommendations:

Dose depends on severity of bleeding

- Minor Bleed : 15-25 IU/kg
 - Major Bleed : 40 IU/kg
- Expected response: 1 IU/kg = 2% rise in Factor VIII level
Major bleeds often require laboratory monitoring.
- Round off dose to nearest vial/container, do not discard excess concentrate.

Transfusion of factor concentrates should be rapid. Patients should be observed for any adverse reactions, particularly those of an allergic nature.

Continuous infusion regimens have also been utilised and may well provide more consistent haemostatic levels.

Approximately 10% of haemophilia A patients acquire antibodies (inhibitors) to Factor VIII and may not respond to therapy. Emergency referral to a haemophilia centre is required.

von Willebrand Disease (vWD)

Haemosolvate Factor VIII and VIAHF concentrates are the treatment of choice when DDAVP (a vasopressin analogue) is not indicated or ineffective. Both concentrates contain high molecular weight multimers.

Dosage recommendations vary and the best methods of monitoring the response are clinical assessment and measurement of Factor VIII levels. Initial dosage recommendation is 30 IU Factor VIII concentrate per kg body weight. Laboratory monitoring should be every 24 hours with regular interim clinical observation.

If significant bleeding persists despite Factor VIII infusions, cryoprecipitate and platelet concentrates may be efficacious.

Haemophilia B

The clinical picture of haemophilia B (Factor IX deficiency) is identical to that of haemophilia A. The levels required are similar to those for Factor VIII, although slightly lower levels of Factor IX are usually adequate for normal haemostasis. Factor IX has a longer half-life (16-30 hours) and therefore once daily dosage is often sufficient.

The dosage (in units of Factor IX) can be estimated as follows: Required dose (IU) = body weight (kg) x desired FIX increase (%) x 1.2

SA Haemophilia Foundation recommendation:

- Minor Bleed : 15-25 IU/kg
 - Major Bleed : 40 IU/kg
- Expected response: 1 IU/kg = 1.5% rise in Factor VIII level
Severe bleeds often require laboratory monitoring

If therapy with high doses for >5 days treatment is required, the patient should be carefully monitored for development of thrombosis, which has been reported in some prothrombin complex concentrates. Thrombosis, however, has never been reported in association with Haemosolvex.

d. Plasma volume expanders

Albumin

- Albusol 4% Manufactured by NBI
- Albusol 20% Manufactured by NBI
- WPBTS 20% Albumin Manufactured by WPBTS

Protein Solution

- Stabilised Human Serum (SHS) Manufactured by WPBTS

All the above are prepared from pooled human plasma from volunteer, nonremunerated donors. Each donation has been individually tested by serologic and nucleic acid amplification technology for HIV, hepatitis B and hepatitis C and is non-reactive for these tests. Albumin solutions are prepared by ethanol fractionation which further reduces the risk of viral transmission. The albumin solutions are sterilised by filtration and finally pasteurised by heat for 10 hours at 60 °C, a process validated and shown to inactivate HIV, hepatitis B and hepatitis C viruses. SHS is prepared by selective absorption of lipoprotein, coagulation proteins and complement components. Potential viral pathogens are reduced by this process and ultra violet irradiation plus a heat treatment step validated as a viral inactivation procedure for HIV.

Albusol 4% is a sterile solution containing 4% m/v human plasma albumin and is available in 200ml volumes (8 g/200 ml). It is stabilised with 0.16 mmol sodium caprylate per gram protein and 3% m/v dextrose. The solution is at pH 7.0 and each litre contains less than 130 mmol sodium, less than 2 mmol potassium and less than 4 mmol citrate.

Albusol 20% is a sterile solution containing 20% m/v human plasma albumin, available in 50 ml (10 g/50 ml) and 100 ml (20 g/100 ml) volumes. It is stabilised with 16 mmol/l acetyl tryptophanate and 16 mmol/l sodium caprylate. The solution is at pH 7.0 and contains less than 100 mmol/l sodium, less than 10 mmol/l potassium and less than 20 mmol/l citrate.

WPBTS'S 20% albumin is a sterile solution containing 20% m/v human plasma albumin and available in 50 ml (10 g/50 ml) and 100 ml (20 g/100 ml) volumes. It is stabilised with sodium caprylate and is at pH 7.0. It contains less than 130 mmol/l sodium and less than 10 mmol/l potassium.

SHS is a stable protein solution containing IgG, IgA and IgM antibodies, albumin and transport proteins. It is available as a 5% solution (50 g/l protein) in 50 ml and 250 ml volumes. The solution is at pH 7.5 and contains 130 mmol/l sodium, 3.5 mmol/l calcium and 130 mmol/l chloride.

Clinical Indications

- *Blood volume expansion:*

Fluid resuscitation in acute clinical conditions associated with hypovolaemia (e.g. trauma) remains controversial. It is not the intention of this guideline to provide a comprehensive review of the subject but the following is a short summary of current opinions and practice.

- The initial resuscitation fluid of choice for volume expansion is a crystalloid solution, probably a balanced salt solution, although an ideal solution does not exist.

- If further therapy is required after 2-3 L of crystalloids have been infused, it is appropriate to continue with a colloid solution. Which colloid to use depends to some extent on the duration of effect required and cost considerations.
- An ideal colloid should have a molecular weight of ± 70 kDa (MW albumin 69 kDa; gelatin 30 kDa; HES 60-70 kDa; Dextrans 40-70 Kda).
- Adverse reactions should be minimal; a meta-analysis published in 2004 showed that albumin proved to be the safest of 4 colloids reviewed (albumin, dextrans, HES, gelatine).
 - Costs: synthetic colloids are cheaper than plasma colloids.
- Since there are no clinical trial data to support a clear cut therapeutic advantage for either crystalloids or colloids, the final choice of fluids for resuscitation is ultimately influenced by individual clinician experience and cost considerations.

- *Replacement fluid following Paracentesis:*

- Albumin is beneficial in preventing acute complications of hyponatraemia and renal impairment.

- *Therapeutic plasma exchange:*

Albumin is the replacement fluid of choice for most procedures. The exception is TTP, where FFP or cryosupernatant are indicated.

- *Burns:*

Often used after the first 24 hours in severe burns but there is a lack of randomised clinical trials.

- *Nephrotic Syndrome:*

May have a short term limited role in combination with diuretics for the Control of oedema, where diuretics alone have failed.

Refer to package inserts for dosing guidelines.

Albumin solutions appear to have no useful role in malnutrition, cirrhosis and chronic nephrotic syndrome.

The above protein solutions should not be given to any patient with a known sensitivity or allergy to human proteins.

e. Immunoglobulins

Immunoglobulin is the antibody-containing fraction of human plasma obtained by fractionation of pooled plasma units. Each unit has been individually tested and found non-reactive for hepatitis B, HIV and hepatitis C using both serological and nucleic acid amplification technology.

Products

- Polygam 1 g/3 g/6 g/12 g:

This is a concentrated IgG immunoglobulin for intravenous use prepared by cold ethanol fractionation and pH 4.0 pepsin treatment. The pH 4.0 pepsin process has been validated and shown to be effective against enveloped viruses such as HIV, HBV and HCV. It is available as a lyophilised powder and is reconstituted to a 50 ml volume (1 g/50 ml 2% solution); a 100 ml volume (3 g/100 ml 3% solution); a 200 ml volume (6 g/200 ml 3% solution) and a 400 ml volume (12 g/40 ml 3% solution).

Clinical Indications (see Table 7)

- Replacement therapy in primary antibody deficiency syndromes - Myeloma or chronic lymphocytic leukaemia with severe hypogammaglobulinaemia and recurrent infections
- Children with congenital AIDS and recurrent infections
- For immunomodulation in:
 - Idiopathic thrombocytopenic purpura (ITP) in children and adults
 - Kawasaki Disease Guillain Barré Syndrome

- Allogeneic bone marrow transplantation

Polygam should be given with caution to patients with antibodies to IgA or selective IgA deficiency, as the small amount of IgA present in Polygam may cause sensitisation. This could lead to a severe allergic reaction and anaphylaxis or subsequent reactions to other IgA containing products.

- Immunoglobulins for intramuscular injection (see Table 8 for Clinical Indications): These are produced from the same donor pool as above and screened in identical fashion. There are various preparations available, mostly hyperimmune globulins with high titres for specific antibodies for passive immune prophylaxis.

Table 7: Intravenous Immunoglobulin (Polygam)

Dosage:

The dose and dosage regimen is dependent on the indication and the *in vivo* half-life of the IgG molecules in the individual patient. The following intravenous dosage regimens are given as a guideline only:

Replacement Therapy in Immunodeficiency		
Indication:	Dose:	Frequency of Infusions:
Primary immunodeficiency:	Starting dose: 0,4 – 0,8 g/kg – thereafter: 0,2 – 0,8 g/kg	every 2 – 4 weeks to obtain IgG trough levels of at least 4 – 6 g/l
Secondary immunodeficiency:	0,2 – 0,4 g/kg	every 3 – 4 weeks to obtain IgG trough levels of at least 4 – 6 g/l
Children with AIDS:	0,2 – 0,4 g/kg	every 3 – 4 weeks
Immunomodulation:		
Indication:	Dose:	Frequency of Infusions:
Idiopathic Thrombocytopaenic Purpura:	0,8 – 1 g/kg or 0,4 g/kg/day	on day 1, may be repeated once within 3 days or for 2 – 5 days. May be repeated if relapse occurs
Kawasaki Disease:	2 g/kg or 1,6 – 2 g/kg	as a single dose in conjunction with aspirin or in divided doses for 2 – 5 days in conjunction with aspirin
Guillain Barré Syndrome:	0,4 g/kg/day	for 3 – 7 days
Allogeneic bone marrow transplantation:		
Indication:	Dose:	Frequency of Infusions:
Treatment of infections and prophylaxis of graft versus host disease:	Starting dose: 0,5 g/kg	every week starting 7 days before transplantation and up to 3 months after transplantation
Persistent lack of antibody production:	0,5 g/kg	every month until antibody levels return to normal

Table 8: Intramuscular Immunoglobulin Preparations

Product	Composition	Indication	Dose
Hebagam® IM (Human hepatitis B immunoglobulin solution for IM injection)	100 IU/ml 2ml ampoule	Needle-stick injury Mucosal exposure Sexual exposure	>10 years : 500 IU 5-9 years : 300 IU < 5 years : 200 IU Treat preferably within 48 hours, and not more than 7 days after exposure. Repeat after 28 days unless recipient has been shown to be immune or has received hepatitis B vaccine.
		Newborn babies born to HBsAG positive mothers (especially those who are HBeAG positive).	200 IU Treat preferably at birth, or within 48 hours after birth. First dose of hepatitis B vaccine must be administered at the same time.
Intragam® 2ml /5ml (human normal immunoglobulin for IM injection)	16% gammaglobulin 2ml and 5ml ampoules	Hepatitis A Prophylaxis Pre-exposure prophylaxis: Travellers to endemic areas Visit < 3 months Visit > 3 months Measles prophylaxis Within one week of contact Susceptible immuno-compromised children Replacement Therapy Congenital Immunoglobulin deficiencies Transient hypogamma-globulinaemia	0,02 ml/kg 0,06 ml/kg every 4-6 months 0,02 – 0,04 ml/kg 0,2 – 0,25 ml/kg (maximum 15ml) 0,5 ml/kg (maximum 15ml) 0,2 – 0,5 ml/kg repeat every 4-8 weeks 0,2 – 0,5 ml/kg repeat when necessary

Product	Composition	Indication	Dose
Rabigam® IM (Human rabies immunoglobulin solution for IM injection)	150 IU/ml 2ml ampoule	Indicated for all persons known or suspected to have been exposed to the rabies virus and is used in conjunction with the rabies vaccine (active immunisation) Rabies immunoglobulin must be given for any mucous membrane exposure to saliva i.e. licks, and all single and multiple bites or scratches inflicted by a suspected rabid animal, especially if associated with any signs of bleeding, irrespective of the interval between exposure and initiation of treatment.	20 IU/kg Administered at the same time, but at a different anatomical site, as the vaccine. This dose is applicable to both children and adults. Infiltrate the entire dose of Rabigam IM into the depth of and around the wound if anatomically possible. Administer the remainder of the dose by deep into muscular injection at a site separate from that used for the vaccine. Ensure that the wound has been adequately infiltrated with immunoglobulin locally before suturing, if suturing is necessary.
Rhesugam IM (Human anti-D(Rh ₀) immunoglobulin solution for IM injection)	500 IU (100 µg) per 2 ml ampoule	Antenatal prophylaxis Prophylaxis following potentially sensitising events, including abortions Postnatal prophylaxis	500 IU (100 µg) is given at 28 and/or 34 weeks gestation. 250 IU (50 µg) is recommended for events up to 20 weeks. For events occurring after 20 weeks, a dose of 500 IU (100 µg) is recommended. 500 IU (100 µg) is recommended.
Tetagam IM 250 IU and Tetagam IM 500 IU (Human tetanus immunoglobulin solution for IM injection)	125 IU/ml 2 ml ampoule 500 IU/ml 1 ml ampoule	Prophylaxis: High risk injuries to non-immune and immune patients. Treatment: Clinical tetanus	250 IU patients 10 years and older (500 IU if 24 hours have passed since injury or if there is a risk of heavy contamination) 3000 IU – 6000 IU as a single dose.

Product	Composition	Indication	Dose
Vazigam® IM (Human varicella-zoster immunoglobulin solution for IM injection)	100 IU/ml 2ml ampoule	<p>High risk patients for whom passive immunisation should be considered are:</p> <ul style="list-style-type: none"> * Premature neonates of less than 28 weeks gestation or with a birth weight of 1000g or less, who have had exposure to the varicella-zoster virus * Neonates if exposure to varicella-zoster virus occurred 5 days or less before delivery or within 48 hours after delivery * Bone marrow transplant recipients despite a history of chickenpox, who have had exposure to the varicella-zoster virus * Immunocompromised patients, who have had exposure to the varicella-zoster virus, including: <ul style="list-style-type: none"> – Patients currently being treated with chemotherapy or generalised radiotherapy or within 6 months of terminating such therapy – Patients who have received high dose steroids in the preceding 3 months – Symptomatic HIV-positive patients who have no history of chickenpox – Patients who have received an organ transplant and are currently on immunosuppressive treatment. 	<ul style="list-style-type: none"> * 2ml for patients up to 5 years; * 4ml for those aged 6 to 10 years; * 5ml for those aged 11 to 14 years; * 6ml for those aged 15 years and older.

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9. Alternatives to allogeneic transfusions

There are a number of alternatives to allogeneic blood transfusion. Some of these options are conventionally offered by the blood transfusion services themselves, whereas others such as acute normovolaemic haemodilution and autotransfusion of recovered blood are largely the domain of the anaesthetist and surgeon. The same is true for the use of hemostatic drugs and agents. This section will therefore focus on transfusion service controlled alternatives and the reader should refer to other texts for more detail regarding pharmacologic or autorecovery strategies.

It is also important to note that many of the measures outlined below require careful planning, and are not possible in emergency settings at short notice. Since there is a lot more time and attention required for the extra clerical requirements, special handling (additional labels, separate storage in the blood bank etc.) and the fact that blood that is not transfused is generally wasted, the costs for autologous and similar procedures are significantly higher than for standard allogeneic components.

9.1. Pre-operative Autologous Donations (PAD)

This is an option for patients who are undergoing elective surgery and whose intra-operative blood requirements can be reasonably accurately predicted (e.g. knee and hip joint arthroplasty). The patients should be in good general health and fall broadly within the criteria required for allogeneic blood donors.

Suitable candidates must be able to tolerate the standard donation withdrawal of 450-500ml of blood and the longer term reduction in haemoglobin levels. They must weigh >50kgs, have a haemoglobin level of 11 g/dl or more (lower level than allowed for allogeneic donors) and be between 16 and 70 years of age. Older or younger patients may be accepted after consultation and examination by the medical staff.

It is theoretically possible to collect up to 5 autologous units in a healthy donor, but in practice it is seldom that more than 2 units are collected. Autologous donations may be collected up to 72 hours pre-operatively and all donors are given iron supplementation during and after the collection process.

Contra-indications to admission to the autologous programme include severe cardiac disease, severe pulmonary disease and bacteraemia. Conditions such as insulin dependent diabetes mellitus and other systemic disorders will be assessed carefully in consultation with the referring physician.

The patient's practitioner should initiate requests for autologous donations and refer the patient to the local blood transfusion service in good time before the operation. Autologous donations are reserved exclusively for the patient who donates the unit and will not be made available for another patient. All autologous donations are also tested for markers of transfusion transmissible infections.

9.2. Designated Donations

This is not, strictly speaking, an allogeneic transfusion alternative as it is itself allogeneic. Also, the donation comes from the general population and theoretically

would carry the same statistical risk as the general donor population. Furthermore, with family and friends there may be subtle exertion of pressure by the prospective recipient with negative effects on the self-deferral process. Nevertheless, in a country where there is a high prevalence of viral disease with potential transfusion transmission, the motivation to have a known family member or friend as a donor is difficult to refuse and the services provide designated donor options.

All designated donors must conform to the accepted voluntary allogeneic donor criteria. Since blood from family members may have the same HLA haplotypes as the recipient there is a greater risk of transfusion-associated graft-vs-host disease (TA-GVHD) (See Chapter 6). Therefore all blood from family donors must be gamma-irradiated prior to transfusion.

9.3. Acute Normovolaemic Haemodilution (ANH)

This entails the removal of blood from a patient before or shortly after induction of anaesthesia and simultaneous replacement with appropriate volumes of acellular fluid (crystalloid/colloid) followed by the return of the blood as dictated by the intra-operative blood loss. ANH is the responsibility of the anaesthetist and the transfusion service will have little role to play other than possibly provision of suitable blood collection systems.

9.4. Blood Recovery (Autotransfusion)

a. Intra-operative

Suitable for any surgical procedure associated with significant blood loss from clean wounds e.g. cardiac and vascular surgery, orthopaedic procedures. The most commonly used technique is to employ so-called cell savers that aspirate the shed blood, saline wash the blood and return it to the patient. If topical haemostatic agents such as thrombin or microfibrillar collagen have been used, recovered blood from these sites should not be used as microthrombi may embolise to critical organs. Other adverse effects of intra-operative salvage that have been reported include air embolism and coagulation disturbances such as disseminated intravascular coagulation.

b. Post-operative

Blood may be collected from the mediastinum or joint spaces, usually limited to the first 6 hours post-operatively. Various bag systems are available e.g. Sorensen system.

9.5. Pharmacologic interventions

There are topically applied agents and systemically administered drugs that may in specific settings, decrease blood loss.

Examples are:

- Collagen haemostat pads, thrombin sprays and fibrin glue
These products are applied directly to the wound (sprayed or in powder form).
- Desmopressin (DDAVP)
This is a vasopressin analogue classically used to increase Factor VIII in mild haemophilia A and von Willebrands disease (vWD). Trials of DDAVP in reducing blood loss in cardiac surgery have given mixed results.

- Aminocaproic acid and tranexamic acid
A couple of trials have been published demonstrating efficacy in reducing blood loss post-cardiac surgery when these antifibrinolytic agents have been administered.
- Aprotinin
This is a serine protease inhibitor and has been used successfully to reduce blood loss in cardiac surgery in a number of clinical trials.
However, there are toxicity and other safety problems and careful monitoring is required.
- Haemoglobin-based oxygen carriers (HBOC)
Despite 2-3 decades of development, the number of products that have reached clinical trials status is limited. Hemopure (a polymerized bovine haemoglobin) is registered in South Africa for the treatment of surgical anaemia in adults for the purpose of eliminating, delaying or reducing the need for allogeneic red cells. It has been used successfully in a number of patients in an uncontrolled surveillance program.

Safety in pregnant women and in children has not been established. Reported adverse events include increases in blood pressure requiring pharmacologic intervention, and severe rebound anaemia, although in the latter, timing of dosage may have been a factor. Following infusion, the plasma and total haemoglobin (Hb) concentrations increase but the haematocrit may decrease as a result of haemodilution. Haematocrit measurements should therefore not be used to assess red cell O_2 -carrying capacity.

Red colourisation of the plasma or serum by infused Hemopure may lead to colourimetric interferences with serum chemistry and communication with the pathology laboratory is important. Hemopure has a short half-life (16-24 hours), however, and is therefore useful as an O_2 bridge in acute blood loss situations. It may also be considered for patients who for religious reasons will not accept blood transfusions.

Hemopure can be stored at room temperature for up to 3 years and is universally compatible. Cost is a consideration as it is relatively costly.

- Erythropoietin
It is the recommended treatment for the anaemia of renal disease; also effective for the anaemia induced by anti-retroviral agents and has been used widely for chemotherapy-induced anaemia, but there have been recent safety concerns.
- Recombinant Factor VIIa (rVIIa)
○ rVIIa is registered and approved for use in haemophiliacs with inhibitors and for Factor VII deficiency.
○ In addition a number of clinical trials have shown efficacy in:
○ Intracranial haemorrhage in premature neonates.
○ Post partum haemorrhage.
○ Cardiac surgery.
○ Trauma with massive blood loss.
○ It is, however, extremely costly.
- Parenteral Iron Preparations

It needs to be remembered that in patients who have documented iron deficiency but who, for various reasons, cannot take or tolerate oral iron compounds, the option of parenteral iron is available before resorting to transfusion. There are two registered preparations: an iron polymaltose compound for intramuscular injection and an iron sucrose compound for intravenous use. Both can cause allergic reactions including anaphylaxis.

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10. Risks of Transfusion / Adverse reactions to transfusion

It is imperative that the information required on the blood specimen tube and on the blood request form is completed fully and accurately for every blood request.

Transfusion of blood or blood products involves the doctor in the evaluation of the risk/benefit ratio to the patient. All blood products carry a risk of adverse effects, ranging from sensitisation to donor cells or proteins, to transmission of disease, including HIV infection. The transfusion services endeavour to minimise major risks in the following manner:

10.1. Transmissible Disease and Donor Selection

- **Health screening**

All donors are screened by means of a written questionnaire for evidence of any past or present infection that might be transmitted to the patient. This screening includes questions about behavioural patterns that may identify a risk of HIV and other infections. In addition the donor may be further questioned verbally prior to being selected for the donation process.

- **Testing**

All donated units are individually screened for laboratory evidence of Syphilis, Hepatitis B and C, HIV 1 and 2. The tests used are internationally validated and are subject to stringent quality control. The specific tests are those for Hepatitis B surface antigen, Hepatitis C antibody, HIV 1 and 2 antibodies, Syphilis, and nucleic acid amplification testing for HIV 1, HBV and HCV. All reactive units are removed from quarantine and carefully disposed of. Further confirmatory tests are performed to confirm reactivity and the donors are subsequently notified and deferred. The addition of nucleic acid testing has significantly reduced the window period for HIV, HBV and HCV.

Only units that are negative for the above markers are accepted for transfusion or for further processing.

Given the strict adherence to international standards of donor deferral and extremely sensitive test systems the risk of hidden infection is low, but recipients must be informed about the risk.

Look back programme

This programme was initiated in 1985 by the blood transfusion services of South Africa to assess the incidence of transfusion-transmitted infection.

This programme traces any patient who received HIV and Hepatitis negative blood from a donor whose subsequent donation is found positive for either infection. Patients are contacted through the hospital or their private physician and are offered counselling and testing.

Contacting the recipient is obligatory and may help prevent secondary spread to others through sexual contact. Ultimately the doctor who ordered the

blood transfusion is responsible for counseling and testing the recipient and for managing and treating the patient, or for referring the patient to a specialist, where appropriate.

10.2. Additional safety measures

Where the applicable technology exists, the blood product is further treated to inactivate any latent infection.

Currently the following products undergo viral inactivation procedures or include steps as part of the manufacturing process that have been documented as viral reduction steps: Albumin, Stabilised Serum, Factor VIII and IX concentrates, immunoglobulins and fresh dried plasma (FDP).

Plasma products such as cryoprecipitate and fresh frozen plasma (FFP) carry a similar risk to cellular products; however, a virally inactivated lyophilised FDP (Bioplasma FDP) is produced by National Bioproducts Institute (NBI). Also, in many centres quarantined donor re-tested FFP is available.

10.3 Transfusion reactions

Most of these can be avoided by crossmatch and compatibility testing and strict attention to details of patient name, number, and identification procedures at point of issue. The medical practitioner ordering blood should ensure strict specimen identification of patient name, hospital number, and folder and crossmatch protocol.

Haemovigilance programmes throughout the world (including South Africa) have identified administration of blood to the incorrect patient as one of the leading causes of error (and mortality) in transfusion medicine. See section on "Ordering and Administration of Blood" (Chapter 2).

Patients must be monitored at the start of the transfusion and every 15 minutes thereafter. Transfusions should be stopped immediately should there be any signs of an untoward reaction.

a. Definition

A transfusion reaction may be defined as "any potentially adverse sign or symptom which occurs after the start of any transfusion of blood or blood products". It stands to reason therefore that in order to notice any adverse effect, the patient's condition prior to, during and after the transfusion must be monitored.

Bearing in mind that "caution saves lives", it is good medical practice to be suspicious and to take action fast. The steps to be taken if there is any sign that a reaction may be occurring are simple and apply in all instances.

- Stop the transfusion immediately.
- Maintain venous access with normal saline in a new drip set.
- Contact the transfusion service for advice.

Whilst the investigation of the transfusion reaction proceeds, venous access should be maintained with a crystalloid solution for:

- Further transfusion therapy if required.
- Suitable therapy to combat the effects of the reaction.

b. Monitoring

The basic monitoring of the patient prior to the initial transfusion and during subsequent transfusion should cover:

- Pulse.
- Blood pressure.
- Temperature.
- Respiration rate.
- General visual observation.
- Verbal enquiry as to the patient's well being.

Any abnormal symptoms existing at the start of transfusion should be noted e.g. dyspnoea, chills, oliguria, etc. Changes in intensity of these symptoms may also indicate the potential for a transfusion reaction and should be assessed clinically.

In cases of severe haemorrhage the rate of transfusion precludes monitoring individual units at specific intervals, and the effect of one unit may only be seen at the time of the transfusion of the second or third unit. These patients are however usually closely monitored for changes in their primary condition and transfusion reactions are readily detected.

Extra care must be taken in the unconscious patient to monitor and react to changes in vital signs. Excessive oozing from the operative site or venous access points and unexplained hypotension may indicate that a haemolytic transfusion reaction is occurring.

Signs and symptoms that are highly suggestive of a serious transfusion reaction:

- Chills/rigors
- Tachycardia/bradycardia
- Hypertension/hypotension
- Chest/flank pain
- Haemoglobinuria
- Agitation
- Fever/sweating
- Dyspnoea/bronchospasm
- Urticaria/pruritus
- Nausea/vomiting
- Oliguria/anuria
- Jaundice

c. Investigation

The investigation of a reaction is primarily to exclude severe or life threatening situations. The transfusion service has a specific set of instructions for investigating reactions and it is the legal responsibility of the clinician to assist in this undertaking.

Send appropriate samples which are clearly labeled; a minimum requirement will include:

- Clotted blood sample.
- EDTA tube.
- Post transfusion urine sample depending on the nature of the reaction.
- Return the suspect unit/s and drip set to the nearest blood bank. If it is suspected that the reaction is due to bacterial contamination ensure that blood bank is informed so that cultures and gram stains are performed. Obtain blood for blood culture from the patient.
- Complete the reaction report form specifying patient details, reason for transfusion, pre- and post transfusion signs and symptoms.

d. Transfusion reaction classification

The list of potential reactions is lengthy, and there are many different ways of classification. Reactions include those due to incompatibility, transmissible disease, bacterial contamination and storage lesions due to the age of the transfused blood products. However, for most practical purposes, the following are the most serious or the most frequently observed and are described fully

(see Table 9.)

Table 9: Potentially life threatening reactions

Acute Haemolytic Reactions Intravascular Haemolysis	Signs / Symptoms	Management
<p>Caused by exposure of patient to incompatible donor red cells (usually ABO mismatched blood)</p> <p>Apparently similar reaction can result from incorrectly heated / stored red cell products</p> <p>NOTE:</p> <p>In the case of an acute haemolitic reaction, the transfusion service's medical officer on-call will be informed and will immediately communicate with the patient's physician,</p>	<p>Usually abrupt in onset and within 15-20 minutes after initiation of any red cell containing blood product.</p> <p>Fever, chills, nausea, vomiting, pain-flank, back, chest, dyspnoea, hypotension, tachycardia, unexpected degree of anaemia, renal failure, DIC.</p> <p>Abnormal bleeding and hypotension may be the only signs in the unconscious patient.</p> <p>Further signs: Haemoglobinuria Haemoglobinaemia</p>	<p>Stop the transfusion, change the transfusion set and filter. Maintain venous access with crystalloid.</p> <p>Notify the blood bank for (a) clerical check i.e. patient/ donor ID numbers (b) send unit/tubing to laboratory with the urine specimen, blood samples and reaction report. Monitor vital signs, including in some instances the pulmonary arterial pressure or CVP. Measure urinary output, observe for abnormal bleeding, especially if the patient is in post operative stage. Maintain intravascular volume and urinary output with crystalloid/colloid solutions. Prevent/treat renal failure with furosemide i.v. 120mg (and manitol 1 gram). Vasopressors (e.g. dopamine) may be required. Monitor patient closely consult Renal Physician with a view to starting haemodialysis to reduce plasma haemoglobin and prevent acute renal failure. Consult Haematological/Renal Dept for further assessment of coagulation profile and renal functions.</p>

Bacterial Contamination	Signs / Symptoms	Management
<p>Caused by any contaminated blood products</p>	<p>Usually rapid onset, about one hour post transfusion. Chills, fever, abdominal cramps, vomiting or diarrhoea. Renal failure, flushed dry skin, hypotension and shock.</p>	<p>Stop the transfusion. Change filter and tubing. Maintain venous access with crystalloid or colloid solution.</p> <p>Notify blood bank, send blood samples, unit and tubing/ filter to the blood for gram stain and culture.</p> <p>Monitor vital signs and administer broad spectrum antibiotics, vasopressors, steroids, fluids and electrolytes.</p>
Anaphylactic Reactions	Signs / Symptoms	Management
<p>Severe, usually due to antibodies to IgA immunoglobulin or severe reactions to other plasma proteins.</p>	<p>Sudden onset. Symptoms include dyspnoea, hypotension/shock, facial and/or glottal oedema plus explosive gastro-intestinal symptoms. May lead to cardiac arrest/death.</p>	<p>Stop the transfusion. Maintain venous access, maintain IV volume and BP with crystalloid or colloid solutions.</p> <p>Give adrenaline, dopamine, steroids and oxygen. Monitor vital signs</p> <p>Prevention: Patients may be IgA deficient and require assessment of immunoglobulin profile. Further therapy must be with washed red cells that are plasma free.</p>

Transfusion Related Acute Lung Injury	Signs / Symptoms	Management
Severe, usually caused by leucoagglutinins in the plasma of the donor. Generally under-recognised and under-reported	Dyspnoea, hypotension, fever, bilateral pulmonary oedema usually occurring within 4 hours of a transfusion.	Should be initiated as soon as possible and consists of fluid support to maintain blood pressure and cardiac output. Ventilation support may be required. Diuretics should not be used as they may have a deleterious effect.
Delayed transfusion reaction Extravascular haemolytic reaction	Signs / Symptoms	Management
Caused by exposure to incompatible red cells in the presence of an atypical IgG antibody such as anti Kell, anti Duffy etc. Severity variable ranging from mild to severe.	Signs and symptoms may appear within hours in a severe reaction (often anti Kell) and is characterized by a drop in haemoglobin and jaundice. In some cases there may be additional complications such as renal failure and DIC. However most cases are mild and are only noticed some 2-10 days after the transfusion with mild jaundice and anaemia. Often the "reaction" goes unnoticed.	The severe reactions should be managed with supportive measures appropriate to the patient's condition. In cases with renal failure measures such as haemodialysis should be implemented and most cases resolve completely. If there is a bleeding diathesis then appropriate transfusion therapy should be given. In most cases the reaction is mild and no particular interventions are required.
Transfusion associated Graft vs Host Disease (TA-GvHD)	Signs / Symptoms	Management
This extremely rare condition results from the transfusion of lymphocytes that share an HLA haplotype with the recipient. Characteristically the donor lymphocytes are	The reaction is often florid and occurs 10-14 days after the transfusion. The patient presents with severe jaundice, a maculopapular rash, pancytopenia and	This condition carries an extremely high mortality rate. Therapy is directed at eliminating the clone of engrafted lymphocytes by chemotherapy.

<p>homozygous for a particular HLA haplotype where as the recipient is a heterozygote. The condition is more likely to occur in situations where blood relatives of the patient are the donors and can be prevented by irradiation of the blood at 25-30 Gy. Leucodepletion is not considered to be adequate to prevent TA-GvHD.</p>	<p>diarrhea.</p>	<p>This should be done by a specialist oncology unit.</p>
<p>Post Transfusion Purpura</p>	<p>Signs / Symptoms</p>	<p>Management</p>
<p>This rare condition results from recipient alloantibodies directed donor platelet antigens. The antibodies are usually directed against HPA1a or HPA5a and since most individuals have these antigens, antibodies are rare. In most cases the recipient is female.</p>	<p>This condition is characterized by a florid thrombocytopenia occurring some 9-10 days after transfusion. The recipients own platelets appear also to be destroyed in this reaction by unknown mechanisms.</p>	<p>This potentially lethal reaction is treated ideally with intravenous Gammaglobulin (2g/kg over 2 to 5 days). Platelet support (if possible HPA compatible) may be necessary but this often requires high doses in the presence of appropriate immunosuppressive therapy (e.g. Steroids) In some cases plasma exchange may be successful.</p>
<p>Febrile Non Haemolytic Transfusion Reaction</p>	<p>Signs / Symptoms</p>	<p>Management</p>
<p>Cause: Usually recipient leucocyte or platelet antibodies to transfused donor cells.</p>	<p>Onset usually within 1-2 hours after start of transfusion. Headache, myalgia, malaise, fever, chills, tachycardia and hypertension. Commonly found in multiparous or multi-transfused patients.</p>	<p>Stop the transfusion. Maintain venous access with crystalloid/colloid solution. Notify blood bank and send urine, post transfusion samples and pack to blood bank. Must be differentiated from early acute haemolytic transfusion reaction. Administer antipyretics.</p>

		Further management: If it recurs on further transfusion, then transfuse with leucocyte depleted blood. If latter not available, then give a ntipyretics and filter red cell products with a bedside leucocyte depletion filter.
Allergic	Signs / Symptoms	Management
Cause: Allergens to plasma proteins	Usually mild. NO FEVER. Itching, hives, urticaria, erythema. Limited to skin only.	Stop the transfusion. Keep IV open. Notify the blood bank and send post transfusion samples, urine and packs. Administer antihistamines. Commence transfusion with a new unit once blood bank has ascertained that this is not a haemolytictransfusion reaction.

e. Transfusion reaction reports

The transfusion service should complete and send out a preliminary report of the reaction as soon as possible after receiving the specimens. A full report will be dispatched after completion of serological and/or bacteriological investigation, and will include advice for further transfusion therapy. The report must be inserted into the patient's file.

f. Haemovigilance Programme

Beginning in 2000 the blood transfusion services have followed a formal haemovigilance program. The aim of the program is to gather in a structured manner information and reports on adverse events associated with the transfusion of blood products and to analyze and distribute the results. This enables the services and clinicians to direct action to the areas of greatest concern. Haemovigilance is therefore a quality assurance process with the aim of increasing the safety of blood transfusion. Reporting adverse transfusion reactions/effects by hospital staff is thus mandatory for the success of the program. The blood banks will supply forms for reporting such events and this is fed back to a haemovigilance officer at SANBS who collates and analyzes the national data.

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