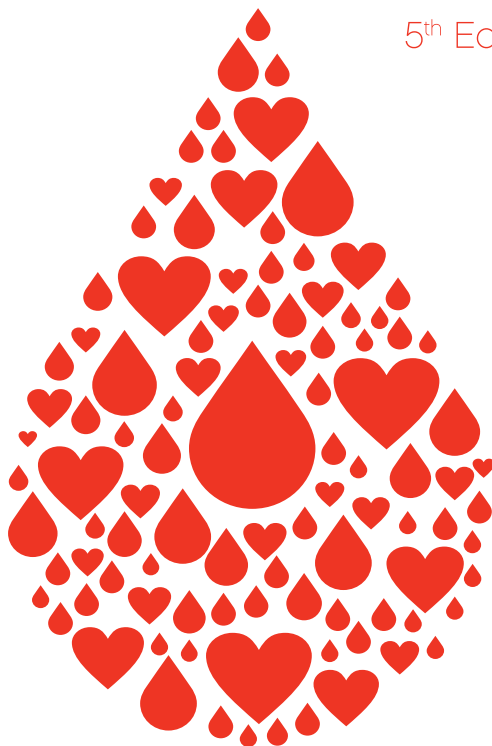


CLINICAL GUIDELINES FOR THE USE OF BLOOD PRODUCTS IN SOUTH AFRICA

5th Edition (2014)



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Donors and recipients are our priority whilst we manage the entire process of blood collection, component processing, testing, storage and distribution. We use the latest technologies and research to ensure blood product safety, and to excel in the science of transfusion. Each year we collect more than 165 000 units of blood that are used to save or improve the lives of more than 490 000 people. Our quality

management system ensures that we maintain consistently high standards of service. We operate according to strict standards based on those of the World Health Organisation (WHO) and other international and national expert bodies. We also comply with all relevant legislation, and are accredited by the South African National Accreditation System (SANAS).

our MISSION

Western Province Blood Transfusion Service is a community-based regional health organisation formed by an association of **voluntary** blood donors, dedicated to providing the **safest** possible blood products and efficient service to the community, while operating at the highest professional and ethical standards and remaining a viable organisation.

our VISION

To maintain a Blood Transfusion Service that is appropriate to the needs of the South African community; to be prepared for wider Regional and National needs and to provide leadership in Transfusion Practice.

our VALUES

we
are
caring
professional
remarkable
responsible
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teamwork



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FOREWORD/INTRODUCTION

Patient Blood Management (PBM) is an evidence-based, multidisciplinary approach to optimising the care of patients who might need transfusions and has become an important part of transfusion medicine. This 5th Edition of the Clinical Guidelines for the use of Blood Products in South Africa has taken into account the evidence-based guidelines that were released by AABB in 2010 and 2012, respectively. As noted in the foreword to the 4th Edition, blood transfusion is the cornerstone of therapy for many serious and common diseases. Without the ready availability of blood components it would be difficult to implement modern treatment regimens for many malignant diseases and complex surgical procedures.

The South African National Blood Services (SANBS and WPBTS), as organisations of voluntary, non-remunerated blood donors, aim to provide all patients with sufficient, safe, quality blood products and medical services related to blood transfusion, in an equitable, cost-effective manner. This commitment remains our key priority and as such the blood services benchmark at an international level to ensure blood safety by adopting guidelines that are in place by the World Health Organisation (WHO). This international standard, together with continuous research and investigation on how best we can adjust guidelines which are relevant to the South African community, have allowed us to maintain a safer blood supply for the country.

South Africa is self-sufficient in blood products. However, we live in a country severely affected by HIV/AIDS and also Hepatitis B, both of which are risks to the safety of the blood supply. The approach to ensuring safety therefore has to be comprehensive. First, we need to focus on the donor and ensure that our donor selection policies are stringent and identify, through education and deferral criteria, donors at low risk for spreading transfusion transmitted infections.

Second, the donated product requires to be carefully screened and in South Africa we are in the enviable position of using the latest genomic amplification technology to screen for HIV and hepatitis viruses.

Third, all the above strategies will go to waste if blood is used indiscriminately. The aim of this booklet is to complete a third tier of safety by providing guidelines for the appropriate use of blood components.

This 5th Edition of the Clinical Guidelines is the result of a co-operative project by Western Province Blood Transfusion Service (WPBTS) and the South African National Blood Transfusion Service (SANBS). Its aim is to provide useful basic information about blood products available to South African clinicians and brief guidelines for their optimum use. Hopefully it is ultimately to the benefit of the patients. Thanks are due to the following clinicians who assisted with the review of this edition of the Clinical Guidelines:

- Dr Juanita Makan
- Dr Elmin Steyn
- Professor Alan Davidson
- Dr Sandi Holgate
- Emeritus Professor Mike James
- Dr Neo Moleli
- Dr Karin van den Berg
- Dr Petro Wessels
- Dr Solomuzi Ngcobo
- Dr Robert Crookes
- Professor Johnny Mahlangu
- Professor Moosa Patel

In particular, we also thank Dr Arthur Bird (retired CEO/Medical Director of WPBTS) who coordinated the review of this edition, reviewed several individual chapters, compiled the reading list and consolidated the final draft document for printing.

For further information readers are referred to the references at the end of this booklet. These guidelines are also available on WPBTS and SANBS websites – www.wpblood.org.za and www.sanbs.org.za respectively.

Finally, thanks must go to the National Bioproducts Institute for supplying relevant information about their products and to Adcock Ingram Critical Care for sponsoring the publication and distribution of the Clinical Guidelines.

Dr Charlotte Ingram – Medical Director, SANBS

Dr Greg Bellairs – CEO/Medical Director, WPBTS

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 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 National Health Act (2003) and its associated Regulations. Contravention of provisions of the Act and/or the Regulations, may constitute 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 take reasonable 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.

RESPONSIBILITIES OF DOCTORS WHO TRANSFUSE BLOOD COMPONENTS

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 and informing them of the available alternatives.
- Obtaining and documenting informed consent.
- Correctly identifying the patient, and units of blood to be transfused.
- Ensuring that appropriate compatibility tests have 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 'look back' programme.

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.

ASSESSING BENEFITS AND 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 that employs doctors and other health care professionals (or permits them to practise 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.

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 claim based on negligence 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.

CRIMINAL LIABILITY

Apart from the statutory offences created by the National Health Act, and the Regulations, blood transfusions may give rise to criminal liability for the common law crime of culpable homicide and perhaps 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. In South Africa, a medical practitioner 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 cognisant of their legal responsibilities with regard to the administration of blood components.

FURTHER READING

- National Health Act No. 61 of 2003
- Regulations Relating to Blood and Blood Products (2012)

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 component to be transfused
- Correct aseptic technique
- Careful observation of the patient during transfusion
- Special precautions

PREPARATION OF THE PATIENT

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 should be explained in terms clearly understandable by the patient.

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 must 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.

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 a 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. When ordering blood for surgical procedures that only require intra-operative transfusion occasionally (fewer than 30% of occasions), a group and screen request is indicated. This involves the typing of a pre-operative specimen from the patient for ABO and Rh groups and a screening test for clinically significant antibodies. Blood is then only cross matched if clinically significant antibodies are detected or there is unexpected blood loss at surgery.

THE BLOOD COMPONENT

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 a cloudy yellow/straw colour and should not contain grossly visible aggregates. Thawed fresh frozen plasma (FFP) 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 component 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 another source. The blood unit is preferably verified by a medical practitioner and a registered nurse or by two registered nurses.

Although staffing and other requirements do not always make this practicable, 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 bedside.
- 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.

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 should 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.

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. The forearm veins are preferable 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.

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, blood pressure (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, respiratory rate and BP 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.

SPECIAL PRECAUTIONS

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 2 ml per minute. A relatively slow rate of 5 ml 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.

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 - 240 µm 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 (40 µm) 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.

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

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
- Calcium-free balanced salt solutions, e.g. Plasmalyte-L, Plasmalyte-B, Balsol, modified Ringer's lactate
- 4% Albumin
- Plasma protein fractions
- ABO-compatible plasma

FURTHER READING

- Blood Transfusion Safety. World Health Organisation.
The clinical use of blood handbook. **World Health Organisation. Malta. HO/BTS/99.3**
- World Health Organisation. Safe blood and blood products. **Manual on the management, maintenance and use of blood cold chain equipment. WHO**
- Australian & New Zealand Society of Blood Transfusion Inc. **Royal College of Nursing Australia. Guidelines for administration of blood components. 1st Ed. 2004**
- Pagliaro P, Rebutta P. Transfusion recipient identification. **Vox Sanguinis. 2006; 91:97-101**

3. RED CELL COMPONENTS

The transfusion of red cells has the ability to save lives and markedly improve survival rates and morbidity in patients, when prescribed in the correct clinical setting. Optimal use should involve administering enough RBCs to maximise clinical outcomes while at the same time avoiding unnecessary transfusions that increase costs and expose patients to potential infectious or non-infectious risks. A review of the most recent guidelines reveals substantial similarities. RBC transfusion is usually indicated if haemoglobin (Hb) <6g/dl and rarely indicated if Hb >10g/dl. For patients with Hb levels between 6-10 g/dl, other factors should be considered e.g. age, co-morbidities, intensive care, risk of ischaemia, rate and volume of blood loss. As a general guideline transfusion is indicated if Hb <7g/dl in post-operative patients, in critically ill patients with risk of end organ ischaemia or if symptoms of hypoxia are present. In surgical patients or with pre-existing cardiovascular disease, transfusion is recommended when the Hb is <8g/dl. The trigger for patients with acute coronary syndrome is equivocal as there is limited evidence available to recommend a transfusion to a Hb >8g/dl. A decision should be made on a clinical basis to transfuse to >8g/dl where indicated. 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 allogeneic blood, utilize cost-effective pharmaceutical preparations that prevent, minimize, or control blood loss (particularly in the surgical setting), and employ other blood conservation methods whenever appropriate.

INDICATIONS FOR RED CELL COMPONENTS

The primary indication for 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.

Acute blood loss

Acute blood loss of greater than 30% of blood volume (about 1 200-1 500 ml 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. Limited volumes of crystalloid solutions should be used initially in volume resuscitation.

General surgery

Consider transfusion if:

- The pre-operative Hb level is less than 8 g/dl and the surgery is associated with major blood loss (>500 ml).
- The intra- or post-operative Hb falls below 7 g/dl. A higher Hb 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 Hb 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 Hb concentration only, and the limitations of the haematocrit (Hct) level should be taken into account when assessing the need for RBC transfusion in hypovolaemic anaemic patients. In situations of massive transfusion, the number of RBC units transfused can be used as a surrogate for determining the transfusion requirements of FFP, platelet concentrate and cryoprecipitate. All hospitals should have a protocol in place that addresses massive blood transfusion (see Chapter 8).

Anaemia in Acute Coronary Syndromes (ACS)

In patients with ACS the latest review of the guidelines cannot recommend for or against a liberal or restrictive RBC transfusion threshold. Further research is needed to determine the threshold. Transfusion to a Hb level between 8 and 10 g/dl should be considered acceptable, but the effect of each unit transfused must be evaluated for the risk of heart failure due to fluid overload.

Anaemia

The aetiology of the 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 Hb level below 8 g/dl should be considered for a transfusion. In chronic nutritional anaemias, however, a Hb of 6 g/dl is often well tolerated without associated medical complications and should respond well to treatment of the deficiency without transfusion being required. The target (post-transfusion) Hb level will be determined by many factors, including the primary diagnosis. The target Hb will be higher in individuals who require chronic RBC transfusions (such as patients with thalassaemia). In general, the target Hb level will be higher in patients with a "medical" anaemia as opposed 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 Hb level is reached where the patient is asymptomatic.

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 Hb, weight, female gender, age, non-elective procedure, pre-operative creatinine levels, previous cardiac surgical procedure, and non-isolated procedure (e.g. coronary artery bypass graft (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, and guides the clinician in the ordering of additional tests.

Obstetric haemorrhage

During an obstetric haemorrhage, RBCs should be administered to maintain the patient free of signs and symptoms of inadequate tissue oxygen delivery. The Hb should be maintained between 6 and 10 g/dl during the resuscitation phase. Special attention must be given to maintaining adequate fibrinogen levels.

RED CELL COMPATIBILITY

Red cell transfusions must be ABO compatible. As far as possible, RBC 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 pre-formed 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.

STORAGE OF RED CELLS

Red cell products are preserved and stored at 1-6°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.

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 hypoparathyroidism may place patients at risk for 'citrate toxicity' during rapid transfusion of whole blood or FFP. 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 and decreased cardiac contractility owing to its ability to lower plasma ionized calcium through chelation. The flow rate of citrate determines the degree of toxicity. A rate corresponding to 0.04 mmol/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 much lesser extent, RBC concentrates. If possible the ionised calcium levels should be monitored and 10 ml 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. If calcium depletion is suspected, most modern blood gas analysers will give a very rapid measurement of ionised calcium. Any level lower than 0.7 mmol/L, should be treated. Calcium depletion alone is seldom a cause of impaired coagulation as the levels required to reduce coagulation are very low (<0.5 mmol/L).

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 Hb 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.

Preservative solutions

RBC concentrates are prepared by the removal of most of the plasma, and the removal of the buffy coat 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 300-350 ml (including the additive solution) and the haematocrit is between 0.55 and 0.70 l/l. One unit of RBC concentrate (at a dose of 4 ml/kg) can be expected to increase the Hb level of an average (70 kg) adult by approximately 1-2 g/dl. Stored red cells experience loss of deformability and, on day 42 of storage, about 75% of red cells are viable.

Hyperglycaemia 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 RBC concentrates stored in adenine additive solutions.

Electrolyte changes

At standard storage temperatures of 1-6°C, 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 5.5 mmols. 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.

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 RBC concentrates. The potential toxicity of transfused DEHP remains under investigation, but to date no studies have emerged indicating clinically significant effects.

LEUCOCYTE DEPLETED RED CELLS

See Chapter 6.

WASHED RED CELLS

Washed red cells are prepared by the removal of plasma and the buffy 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.

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 RBC 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 RBC 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 25 Gy. 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.

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 35-37°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.

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 RBC concentrates are more appropriate in most situations where O₂-carrying capacity needs boosting.

Indications:

- Exchange transfusion in neonates
- Massive haemorrhage

MASSIVE TRANSFUSION

See Chapter 8

IRRADIATED RED CELLS

See Chapter 7

BLOOD FOR EXCHANGE TRANSFUSION IN NEONATES

See Chapter 9

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.

FURTHER READING

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4. PLATELET TRANSFUSION

Platelet transfusions are indicated for the prevention of bleeding (prophylactic transfusions) or to stop active bleeding (therapeutic) as a result of reduced platelet numbers or abnormalities of platelet function.

PLATELET COMPONENTS

Pooled Buffy Coat Platelet Concentrates

These are derived from the buffy coat layers of a whole blood donation separated within 8 hours of donation. The buffy coats from 4-5 donations are pooled and re-suspended in either plasma or a platelet additive solution (PAS). Following a gentle spin the platelets separate from the other cells to yield a concentrated platelet suspension with a volume of 200-300 ml. The concentrate can then be filtered to produce a leucocyte depleted concentrate if indicated. Each unit contains a minimum of 2.4×10^{11} platelets.

Single Donor Apheresis Platelet Concentrates

Collected from a single donor by a variety of apheresis systems. In general, these systems can be programmed to collect much larger numbers of platelets than with pooled buffy coat preparations; this can then be split into 2 or 3 bags depending on the total yield. Also, all current apheresis systems automatically leucocyte deplete the concentrate.

Pooled platelet concentrates derived from whole blood donations and single donor apheresis concentrates have been shown to be therapeutically equivalent in terms of post transfusion increments and haemostatic efficacy, provided similar doses are given. Obviously there is far greater donor exposure with pooled concentrates; therefore patients requiring longer term support (e.g. haemopoietic stem cell transplantation and chemotherapy for haematological cancers) are preferably treated with single donor apheresis concentrates since the risk of HLA allo-immunisation is reduced.

INDICATIONS FOR PLATELET TRANSFUSIONS

Platelet transfusions are indicated for the prevention and treatment of bleeding in patients with thrombocytopenia or platelet function defects. The cause of the thrombocytopenia should be established before a decision is made to transfuse platelets since not all causes of thrombocytopenia are responsive to platelet transfusion and may even be contraindicated in some conditions.

Bone Marrow Failure

Therapeutic platelet transfusions are unequivocally indicated in patients with active, severe bleeding and thrombocytopenia, although this usually occurs when the platelet count is $<10 \times 10^9/l$.

Although prophylactic platelet transfusions are fairly standard practice for patients with bone marrow failure, there is a paucity of randomised studies comparing survival and incidence of haemorrhage in patients receiving prophylactic transfusions versus only therapeutic transfusions. Earlier studies suggested a threshold of $20 \times 10^9/l$, but more recent studies indicate that this trigger can be reduced.

Acute leukaemia

There are a number of studies that suggest that the threshold can be lowered to $10 \times 10^9/l$ provided there are no further risk factors such as sepsis, antibiotic medication or other haemostatic abnormalities. There are also some smaller studies indicating that a level of $5 \times 10^9/l$ may be safe in patients with no other risk factors. In patients with acute promyelocytic leukaemia it is probably prudent to set the threshold at $>20 \times 10^9/l$ given the prevalence of coagulopathy in this subgroup.

Haemopoietic stem cell transplantation

A threshold of $10 \times 10^9/l$ is generally accepted.

Chronic stable thrombocytopenia

Patients with chronic sustained failure of platelet production (e.g. myelodysplasia, aplastic anaemia) may not bleed abnormally despite platelet counts remaining consistently at $<10 \times 10^9/l$. Prophylactic platelet transfusions are best avoided owing to the risk of allo-immunisation and platelets should only be given therapeutically to treat overt bleeding episodes.

Prophylaxis for Surgery

The following are guidelines only since there is a lack of evidence to direct therapeutic decisions in this setting.

Bone marrow aspirate and biopsy: Platelet cover is not required even with severe thrombocytopenia provided local pressure is applied following the procedure.

Lumbar puncture, epidural anaesthesia, gastroscopy and biopsy, insertion of indwelling lines, transbronchial biopsy, liver biopsy, laparotomy or similar procedures: A threshold of $50 \times 10^9/l$ is recommended.

Surgery in critical sites (e.g. brain, eyes): Platelet count should be $>100 \times 10^9/l$.

Massive Transfusion

Maintain platelet count at $>50 \times 10^9/l$. In patients with multiple trauma or central nervous system injury the recommended threshold is $100 \times 10^9/l$.

Disseminated Intravascular Coagulation (DIC)

It is recommended that the platelet count be maintained at $30-50 \times 10^9/l$. In chronic DIC or where there is no bleeding, platelet transfusions are not recommended just to correct a low platelet count.

Cardiopulmonary Bypass (CPB)

Platelets should be readily available at all centres undertaking cardiac surgery. There is no evidence to support prophylactic platelet transfusion in patients undergoing CPB. Platelet transfusion should be reserved for those patients experiencing abnormal post-operative bleeding and in whom a surgical cause has been excluded. This usually follows thrombocytopenia ($<50 \times 10^9/l$) and/or a temporary platelet dysfunction sometimes seen in CPB.

It is important prior to CPB to review thoroughly all medications that may cause platelet dysfunction.

Liver Transplantation

Haemostasis is impaired for a variety of reasons in liver transplantation. Many centres use the thromboelastograph (TEG) to guide the need for platelet transfusion and other components.

Immune Thrombocytopenias

Autoimmune thrombocytopenia: In general, platelets are contraindicated. Platelet transfusions should be reserved for life-threatening haemorrhage together with other therapies such as intravenous immunoglobulin and methylprednisolone.

Neonatal alloimmune thrombocytopenia (NAIT): See Paediatric Blood Transfusion (Chapter 9).

Post transfusion purpura: See Haemovigilance, Risks and Adverse Effects of Blood Transfusion (Chapter 12).

CONTRAINDICATIONS TO PLATELET TRANSFUSIONS

Autoimmune thrombocytopenia

See above

Thrombotic Thrombocytopenic Purpura (TTP)

Heparin Induced Thrombocytopenia (HIT)

COMPATIBILITY

Group specific platelet transfusions are the components of choice. However, clinical demand and stock availability occasionally do not allow for this and ABO non-identical platelets have to be used. Some studies have indicated poorer platelet increments with ABO non-identical platelets although this is usually not clinically significant in terms of haemostatic efficacy. It is recommended that in this setting Group O platelets should be given to only group A, B and AB patients if the platelet concentrates have been screened for high titre anti-A and anti-B antibodies.

Since platelet concentrates may contain a small number of red cells Rh-D negative platelets should be given to premenopausal Rh-D negative women. If this is not possible, administration of anti-D immunoglobulin should be considered once the platelet count is corrected.

ADMINISTRATION AND DOSE

Platelets should ideally be transfused through a platelet administration set over a period of 15-30 minutes. They should not be transfused through giving sets that have been used for red cell concentrates or whole blood.

A pooled buffy coat platelet concentrate is equivalent to one adult dose and a single donor apheresis platelet concentrate is also given as a single adult dose.

Platelets for paediatric use are derived from a single apheresis donation by subdivision into small volume aliquots. The recommended dose for neonates and infants is 5-10 ml/kg.

Monitoring the response to platelet transfusions

If the platelets are given therapeutically for active bleeding, the clinical response is the best indication of effectiveness.

Response to prophylactic transfusions is best assessed by measuring the increase in the platelet count following the transfusion.

Practical “rule of thumb” approach: if the 1 hour post transfusion platelet count is $<5 \times 10^9/l$ or has failed to raise the count above the “trigger” count the platelet transfusion is unsatisfactory.

Corrected count increment (CCI):

$$\frac{\text{Platelet increment (x } 10^9/l) \times \text{body surface area (m}^2\text{)}}{\text{Platelet Dose (x } 10^{11}/l\text{)}}$$

A CCI of $<7.5 \times 10^9/l$ 18-24 hours after transfusion is regarded as unsatisfactory. Calculating the CCI in routine practice is not always feasible, since the platelet content is not routinely measured especially in pooled donor concentrates.

Platelet Refractoriness

This is usually defined as the repeated failure to obtain satisfactory responses as defined above. Non-immune causes include fever, infection, drugs, splenomegaly and DIC. The major immune cause is HLA allo-immunisation although leucocyte depletion significantly lowers the risk. Therefore, patients who are likely to require repeated platelet transfusions should receive leucocyte depleted concentrates and be exposed to as few donors as possible – this is best achieved by using single donor apheresis concentrates. HLA matched concentrates are a possible solution when allo-immunisation occurs; consultation with the transfusion service is necessary to arrange this.

Adverse effects

As with other blood components adverse reactions may occur. Febrile reactions are the most common. The risk of bacterial contamination is greater with platelet transfusions because of the requirement for room temperature storage.

Irradiation

Platelets may be irradiated with no loss of function (See Chapter 7).

FURTHER READING

- BCSH Guideline Guidelines for the Use of Platelet Transfusions **Brit J Haematol 2003;122:10-23**
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5. PLASMA COMPONENTS AND DERIVATIVES

OVERVIEW

Plasma products are diverse and comprise plasma components and plasma derivatives. Plasma components are those products produced by purely physical separation methods such as centrifugation. These products include fresh frozen plasma and cryoprecipitate. Products derived from large plasma pools (>12 donations) and subject to more complex physical and chemical processes such as alcohol-based fractionation are referred to as plasma derived medicinal products e.g. albumin. Below is an outline of the various plasma products, their accepted usage guidelines and dosage schedules. The information on plasma derivatives is provided for guidance and easy reference only. Detailed prescribing information is provided in the respective product approved package insert and other prescriber guidelines (e.g. SA Medicines Formulary).

GENERAL PRECAUTIONS FOR THE USE OF PLASMA PRODUCTS

All plasma products are potentially antigenic and therefore may elicit allergic and/or anaphylactic reactions. With each transfusion, the recipient should be observed with regular assessment of vital signs at least during the initial 15 minutes of any transfusion. The management of transfusion reactions is described in Chapter 12 of this guideline.

FFP is hyperosmolar due to the solutes listed in Table 2 below. 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.

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.

PLASMA COMPONENTS

Fresh Frozen Plasma (FFP)

Plasma for FFP is separated from anticoagulated whole blood within 18 hours of donation. Separation is by centrifugation of whole blood in a closed sterile system and rapidly freezing the plasma to below -18°C. The resultant FFP contains all the coagulation factors at normal physiological levels. The transfusion services in South Africa have introduced a donor plasma retest quarantine programme (also for cryoprecipitate and cryo-poor plasma) to minimise the risk of a window period infection. In areas where this programme is not in place, only plasma from regular donors is used for FFP production. No pathogen transmissions have been reported since the introduction of the programme. However, patients likely to receive large or repeated doses may benefit from pathogen inactivated plasma.

FFP composition:

The coagulation factors and solutes in FFP are shown in Tables 1 and 2 below

Table 1: Coagulation Factors and other proteins

Factor	Average Levels
Fibrinogen	500 mg 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	3 000-10 000 IU/ml

Table 2: Solutes

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

Volume and dosage guidelines:

The volume of an adult unit of FFP is 240-300 ml and the important constituents are listed in Tables 1 and 2. The initial dose recommendation is 10-15 ml/kg; further therapy is dependent on clinical response and laboratory monitoring.

Clinical indications

The evidence-based clinical indications are:

- Replacement of inherited single factor deficiencies where specific factor concentrate is not available
- Multiple coagulation factor deficiencies (DIC, massive blood transfusion, liver disease) with active bleeding and abnormal coagulation screening tests
- TTP – preferably cryo-poor plasma
- Reversal of warfarin overdose if a prothrombin complex concentrate is not available
- Vitamin K deficiency associated with active bleeding – e.g. haemorrhagic disease of the newborn
- Suxamethonium apnoea

Use of FFP is not justifiable and therefore not recommended in the following scenarios:

- Hypovolaemia
- Plasma exchange (except in TTP)
- As nutritional support in protein-losing states

Recently, the American Association of Blood Banks (AABB) published a meta-analysis and evidence-based guidelines for plasma transfusion. The guidelines suggest that plasma transfusion be used in two patient groups, those requiring massive transfusion and those with intracranial haemorrhage related to warfarin therapy. Plasma transfusion at high plasma:red cell ratios (1:1) in massive transfusion was associated with a reduction in the risk of death and multi-organ failure; although the quality of the evidence was low (see Chapter 8). There was insufficient data to recommend for or against transfusion of plasma in patients undergoing surgery in the absence of massive transfusion or in the absence of intracranial haemorrhage. In addition, many institutes are using plasma that has been thawed and stored in a liquid state at 1-6°C for 5 days post thawing. Ideally, a diagnosis of coagulopathy should be rapidly established (preferably using point-of-care tests such as TEG or ROTEM) before FFP is given. Such tests can provide results within less than 15 minutes.

Cryoprecipitate

This is the cold insoluble fraction of FFP and is obtained by thawing FFP at 0-4°C. It is stored at or below -18°C for up to 1 year. It is available in volumes up to 15 ml. Cryoprecipitate contains Factor VIII/vWF (approximately 100 IU per unit), fibrinogen (150-200 mg per unit) as well as fibronectin and Factor XIII.

Indications and dosing

Cryoprecipitate is indicated primarily for treating congenital or acquired hypofibrinogenaemia (defined as fibrinogen below the lower limit of the reference range for the laboratory) or dysfibrinogenaemia. The dose is 1 Unit Cryoprecipitate/10 kg body weight or 8-12 Units per adult dose. It is given through a standard blood administration set. It may also be used for treating hereditary Factor XIII deficiency. It has been recommended for both obstetric haemorrhage and massive transfusion where there is a demonstrable fibrinogen deficit ($<1.5\text{g/L}$).

Cryosupernatant (cryo-poor FFP)

This is the component available following extraction of cryoprecipitate from FFP. It is stored in limited quantities. Cryosupernatant is indicated for use in therapeutic plasma exchange in the management of TTP.

PLASMA DERIVED MEDICINAL PRODUCTS

In terms of the legislation of medicines in South Africa, plasma derived products manufactured from a pool of more than 12 donations are classified as medicines. All registered medicines are supplied with a package insert approved by the Medicines Regulatory Authority. This insert contains detailed information regarding the product.

Solvent detergent treated FFP – NBI Bioplasma FDP 28/30.3/405

Produced from pooled fresh human plasma. It undergoes a pathogen inactivation procedure using a solvent detergent treatment process which inactivates lipoprotein-coated viruses including HIV, HBV and HCV. 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 can be used when coagulation factors are required. This product is available either as a 50 ml or 200 ml pack size with Water for Injection and reconstitution set included. It is stored at room temperature (below 25°C). This product contains no antimicrobial agents or preservatives.

Coagulation Factor Concentrates

Haemsolvate Factor VIII

- S4 Haemsolvate Factor VIII 300IU Human factor VIII concentrate 31/30.3/392
- S4 Haemsolvate Factor VIII 500 IU Human Factor VIII concentrate Y/30.3/292

This is an intermediate purity Factor VIII concentrate produced by NBI and prepared from pooled fresh human plasma. 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, HBV and HCV. See Table 3 for further details and also refer to the package insert.

Haemsolvex Factor IX

- S4 Haemsolvex Factor IX (Powder for injection) Human Factor IX Complex W/30.3/191

This is a prothrombin complex concentrate containing prothrombin (factor II), 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, HBV and HCV. Refer to Table 3 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, HBV and HCV.

Table 3: Coagulation Factor Concentrates

Products	Content	Units	Volume
VIAHF 250 (WPBTS)(Paediatric)	Factor VIII/vWF	250 IU FVIII	50 ml after reconstitution with water for injection
VIAHF 500 (WPBTS)(Adult)	Factor VIII/vWF	400-600 IU FVIII	As above
Haemsolvate Factor VIII 300 IU (NBI)	Factor VIII/vWF	300 IU FVIII/vWF	10 ml after reconstitution with water for injection
Haemsolvate Factor VIII 500 IU (NBI) Two pack sizes: 500 IU and 2x 500 IU	Factor VIII/vWF	500 IU FVIII/vWF	As above
Haemsolvex Factor IX	Factor IX, Factor II, Factor VII, Factor X	500 IU FIX	As above

Dosage schedules and treatment guidelines

For details refer to your local haemophilia centre and SA Treatment Guidelines. 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 for management.

Haemophilia A

Factor VIII has an average half-life of 12 hours. Treatment should therefore be given every 8-12 hours according to the clinical indication. 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). 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.

10-30% of haemophilia A patients develop antibodies (inhibitors) to Factor VIII and may not respond to therapy. For patients with low titre inhibitors (<5 Bethesda units) a higher dose of factor concentrate is required. For patients with high titre inhibitors (>5 Bethesda units), a bypassing agent such as FEIBA or rVIIa should be used.

von Willebrand's Disease (vWD)

Haemolyse 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.

Recommendations vary and the best methods of monitoring the response are clinical assessment and measurement of Factor VIII levels. Initial dosage recommendation is 50 IU Factor VIII concentrate per kg body weight. Laboratory monitoring should be every 24 hours with regular interim clinical observation.

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 (1 may suffice instead of 1.2 for quick rule of thumb calculations).

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.

Plasma expanders

Albumin

- S4 Albusol 4% Human plasma albumin 4% T/30.3/738
- S4 Albusol 20% Human plasma albumin 20% T/30.3/739
- WPBTS Albumin 20% S4 50 ml T/706 (Act 101 of 1965)
100 ml T/707 (Act 101 of 1965)

Protein Solution

- WPBTS Stabilised Human Serum (SHS)
S4 50 ml T/30.3/704
S4 250 ml T/30.3/705

All the above are prepared from pooled human plasma from volunteer, non-remunerated donors. Each donation has been individually tested by serologic and nucleic acid amplification technology for HIV, HBV and HCV 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 to inactivate HIV, HBV and HCV. 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 as 200 ml pack size (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 as 50 ml (10 g/50 ml) and 100 ml (20 g/100 ml) pack sizes. 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 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.

WPBTS 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. Hypo-osmolar solutions may pose a risk to patients with head injuries.
- 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.
- 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)
- Since there is 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 hypoproteinaemia caused by loss of plasma proteins 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.

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 HIV, HBV and HCV using both serological and nucleic acid amplification technology.

Polygam:

S4 Polygam 1 g lyophilized powder for IV injection Polyvalent human normal immunoglobulin Z/30.2/367

S4 Polygam 3 g lyophilized powder for IV injection Polyvalent human normal immunoglobulin Z/30.2/368

S4 Polygam 6 g lyophilized powder for IV injection Polyvalent human normal immunoglobulin Z/302/369

S4 Polygam 12 g lyophilized powder for IV injection Polyvalent human normal immunoglobulin 29/30.2/511

This is a polyvalent human normal immunoglobulin for intravenous use containing mainly IgG with a broad spectrum of antibodies against infectious agents. It is prepared by cold ethanol fractionation and pH 4.0 pepsin treatment to further reduce the risk of viral transmission. 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/400 ml 3% solution). Each pack consists of a clear glass bottle containing lyophilised powder, bag(s) of 0.9% m/v sodium chloride and a reconstituent set.

Clinical Indications

- 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:
 - Immune thrombocytopenia 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.

Table 4: Guidelines for intravenous dosage regimens for Polygam

Replacement Therapy in Immunodeficiency		
Indication:	Dose:	Frequent of Infusions:
Primary immunodeficiency:	Starting dose: 0,4 – 0,8 g/kg	every 2 – 4 weeks to obtain IgG trough levels of at least
	thereafter: 0,2 – 0,8 g/kg	4 – 6 g/l
Secondary immunodeficiency:	0,2 – 0,4 g/kg	every 3 – 4 weeks to obtain IgG trough levels of at least
Children with AIDS:	0,2 – 0,4 g/kg	4 – 6 g/l
		every 3 – 4 weeks
Immunomodulation:		
Indication:	Dose:	Frequency of Infusions:
Immune Thrombocytopenia	0,8 – 1 g/kg	on day 1, may be repeated once within 3 days
	or 0,4 g/kg/day	or for 2 – 5 days. May be repeated if relapse occurs
Kawasaki Disease:	2 g/kg	as a single dose in conjunction with aspirin
	or 1,6 – 2 g/kg	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

Immunoglobulins for intramuscular injection

They 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 5: Further details for Intramuscular Immunoglobulin preparations

Product	Composition	Indication	Dose
Hebagam® IM (Human hepatitis B immunoglobulin solution for IM injection). S4 T/30.2/740	100 IU/ml 2 ml ampoule.	Immunoprophylaxis for Hepatitis B: 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® 2 ml/5 ml (human normal immunoglobulin for IM injection). S4 T/30.2/740 S4 T/30.2/741	16% gammaglobulin 2 ml and 5 ml ampoules.	Hepatitis A Prophylaxis Pre-exposure prophylaxis: Travellers to endemic areas. Visit <3 months. Visit >3 months. (continued exposure) Post-exposure prophylaxis: Within one week of household contact. Measles prophylaxis Within one week of contact. Susceptible immunocompromised children. Congenital Immunoglobulin deficiencies. Transient hypogammaglobulinaemia.	0.02 ml/kg. 0.06 ml/kg every 4 – 6 months. 0.02 ml/kg – 0.04 ml/kg. 0.2 ml/kg – 0.25 ml/kg (maximum 15 ml). 0.5 ml/kg (maximum 15 ml). 0.2 ml/kg – 0.5 ml/kg Repeat every 4 – 8 weeks. 0.2 ml/kg – 0.5 ml/kg repeat when necessary.



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Take the case of our infusion bags. With a simple switch of vision, instead of looking far afield to find solutions, we decided to refocus our attention. Consequently, we are now proud to be able to provide our customers with a steady, reliable, cost effective supply of locally sourced bags.

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More care for more people.

Table 5: Further details for Intramuscular Immunoglobulin preparations (continued)

Product	Composition	Indication	Dose
Rabigam® IM (Human rabies immunoglobulin solution for IM injection). S4 T/30.3/748	150 IU/ml 2 ml 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 up to 7 th day after the first dose of vaccine was given.	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 dose of Rabigam IM into the depth of and around the wound if anatomically possible. Administer any remainder of the dose by deep intramuscular 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). S4 T/30.2/750	500 IU (100 µg) per 2 ml ampoule.	Antenatal prophylaxis. Prophylaxis following potentially sensitising events, including abortions. Postnatal prophylaxis. Transfusion of Rh ₀ incompatible blood. Transfusion of Rh ₀ positive platelets in Rh ₀ negative women of child bearing age.	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. The dose is calculated to clear the estimated quantity of red cells given – 125 IU (25 µg) for each ml of red cells. 250 IU (50 µg) for each dose of platelets. If more than 2 adult platelet doses are given 500 IU (100 µg).

Table 5: Further details for Intramuscular Immunoglobulin preparations (continued)

Product	Composition	Indication	Dose
Tetagam IM 250 IU (Human tetanus immunoglobulin solution for IM injection). S4 T/30.2/749	125 IU/ml 2 ml ampoule.	Prophylaxis: High risk injuries to non-immune and immune patients.	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). 3 000 IU – 6 000 IU as a single dose by infiltration into the wound site as well as IM.
Vazigam® IM (Human varicella-zoster immunoglobulin solution for IM injection). S4 T/30.2/749	100 IU/ml 2 ml ampoule.	<p>Treatment: Clinical tetanus.</p> <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 1 000 g 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. Pregnant women with negative varicella-zoster immune status, especially up to 3rd trimester. Bone marrow transplant recipients despite a history of chickenpox, who have had exposure to the varicella-zoster virus. <p>Immunocompromised patients, who have had exposure to the varicella-zoster virus, including:</p> <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. 	<p>2 ml for patients up to 5 years.</p> <p>4 ml for those aged 6 to 10 years.</p> <p>5 ml for those aged 11 to 14 years.</p> <p>6 ml for those aged 15 years and older.</p>

Further Reading

- BCSH Taskforce Guidelines for the use of fresh frozen plasma, cryoprecipitate and cryo-supernatant **Brit J Haematol 2004;126:11-28**
- Roback J, Caldwell S, Carson J et al Evidence based practice guidelines for plasma transfusion **Transfusion 2010;50:1227-1239**
- Murad MH, Stubbs JR, Gandhi J et al The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis **Transfusion 2010;50:1370-1383**
- Yazer MH, Cortese-Hasset, Triulzi DJ Coagulation factor levels in plasma frozen within 24 hours of phlebotomy over 5 days of storage at 1 to 6°C **Transfusion 2008;48:2525-2530**
- Barron ME, Wilkes MM, Navrickis RJ A systematic review of the safety of colloids **Arch Surg 2004;139:552-563**
- James MA Volume expanders: crystalloids vs plasma colloids vs synthetic colloids **ISBT Science Series 2006;1:52-58**
- Finfer S, Norton R, Bellomo R et al The SAFE study: saline vs albumin for fluid resuscitation in the critically ill **Vox Sanguinis 2004;87(suppl):5123-5**
- Ahmed S, Harrity C, Johnson S et al The efficacy of fibrinogen concentrate compared with cryoprecipitate in major obstetric haemorrhage – an observational study **Transf Med 2012;22:344-49**
- Sorensen B, Bevan D A critical evaluation of cryoprecipitate for replacement of fibrinogen **Brit J Haematol 2010;149:834-843**
- Mahlangu J, Gillham A Treatment Guidelines for Haemophilia in South Africa **S Afr Med J;98(2):127-138**

6. TRANSFUSION RELATED IMMUNOMODULATION AND LEUCOCYTE DEPLETION OF BLOOD COMPONENTS

Transfusion related immunomodulation (TRIM) refers to the well-documented laboratory evidence of immune alterations following allogeneic blood transfusions, such as clonal deletion or anergy, induction of suppressor cells, production of anti-idiotypic antibodies, suppression of NK cell activity, among others.

There are also clinical effects that may be the result of TRIM such as:

- Enhanced survival of renal allografts
- Increased risk of post-operative bacterial infections and recurrence of resected cancers
- Increased short-term mortality from all causes in transfused versus non-transfused patients
- Activation of pre-existing CMV or HIV infection in transfused versus non-transfused patients

TRIM is probably mediated by

- Allogeneic mononuclear cells that remain viable for at least 2 weeks in stored RBC concentrates
- Pro-inflammatory soluble mediators released from white cells and which accumulate in the supernatant of red cell concentrates during storage
- Soluble class I HLA molecules in allogeneic plasma

Filters capable of removing leucocytes (which appear to be the prime mediators of the pro-inflammatory and TRIM effects) by several orders of magnitude are readily available and effectively reduce the number of white cells in a red cell concentrate to $<1 \times 10^6$. A less efficient, but less costly process for removing white cells from blood components is to remove the buffy coat layer from red cell concentrates and also to prepare random donor platelet concentrates from the buffy coats. The resulting red cell and platelet concentrates contain leucocytes intermediate in number between filtered components and those where the buffy coat is retained.

A number of well-resourced countries have adopted a policy of universal pre-storage leucocyte depletion using the filters described above while others have recommended a policy of selective leucocyte depletion of blood components. The costs associated with universal leucocyte depletion are significant amounting to approximately 24% of the total annual turnover of the blood services. Given the competing health priorities in a middle income developing country such as South Africa, there should be convincing evidence that universal leucocyte depletion of blood products is clinically beneficial and cost-effective.

Having reviewed the literature we conclude the following:

- There is good evidence to support the avoidance of febrile non-haemolytic transfusion reactions (FNHTRs) by using leucocyte depleted components.
- Administering leucocyte depleted platelet concentrates reduces the incidence of refractoriness to platelet transfusions.
- Administering leucocyte depleted components significantly reduces the risk of transfusion transmitted CMV infection in susceptible recipients (e.g. neonates).
- The evidence for reduction of the incidence of post-operative bacterial infection and recurrent cancer following resection is not consistent.
- Evidence to support an increase in short-term mortality using non leucocyte reduced components is inconsistent; however, subgroup analyses do suggest a benefit for cardiac surgery and critically ill patients.
- An association with reactivation of viral infections (HIV and CMV) and survival has not been demonstrated.
- Sensitisation to transplant antigens can be lessened by administering leucocyte depleted products where HLA-alloimmunisation is important.
- Using leucocyte depleted products may reduce potential prions in blood components, but there is as yet no evidence that this will avoid transmission of variant Creutzfeldt Jakob Disease (vCJD) by transfusion.

The blood services have therefore adopted the following policy with respect to leucocyte depletion of blood components

- 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 must incorporate a leucocyte depletion process (standard practice with current apheresis technology)
- The following patients should receive leucocyte depleted components:
 - o Patients on chronic transfusion regimens
 - o Those at risk for CMV infection
 - o Infants <1 year old
 - o Critically ill, cardiac surgery and trauma patients (particularly those requiring massive transfusion)
- Pre-storage (<48 hours after donation) leucocyte depletion in blood processing laboratories is recommended. If this is unobtainable the freshest components available may be filtered in the blood bank for immediate use (24 hour expiry). Bedside leucocyte depletion filters are not recommended unless neither of the former 2 options is available.

It is emphasised that the above are guidelines in a subject where there is some controversy. For further background to this the last 2 references listed below are particularly relevant. If individual clinicians wish to use leucocyte depleted products outside the guidelines, they should order accordingly and the blood banks will issue provided they have stocks. By continually monitoring the usage and gearing up accordingly the services should be in a position to meet such demands.

FURTHER READING

- Blajchman MA, Vamvakas EC Transfusion related immunomodulation, in Murphy MF, Pamphilon DH (Eds) **Practical Transfusion Medicine 3rd Edition, Wiley-Blackwell 2009, 98-106**
- Bird AR, Crookes R Leucocyte depletion of blood components: guidelines of the blood transfusion services of South Africa **S Afr Med J 2006;96:395-6**
- Blumberg N Deleterious clinical effects of transfusion immunomodulation: proven beyond a reasonable doubt **Transfusion 2005; 45(Suppl): 33S-9S**
- Vamvakas EC & Blumberg N Deleterious effects of transfusion immunomodulation: proven beyond a reasonable doubt **Transfusion 2006;46:492-495**

7. GAMMA IRRADIATION OF BLOOD COMPONENTS

Transfusion associated graft versus host disease (TA-GvHD) is an extremely rare but often fatal complication which may follow the transfusion of lymphocyte containing blood components. Under certain conditions (e.g. immunosuppression, donor and patient share HLA haplotype) the infused lymphocytes engraft and proliferate in the recipient. Cellular interaction between donor T lymphocytes and recipient cells leads to cellular damage (particularly the skin, thymus, gastro-intestinal tract, liver and spleen) very similar to GvHD seen after allogeneic stem cell transplantation. An additional specific feature of TA-GvHD is severe bone marrow hypoplasia.

Gamma irradiation is currently the only recommended method for prevention of TA-GvHD, although there is some preliminary evidence to suggest that leucocyte depleted components may remove the risk of TA-GvHD. TA-GvHD has been reported following transfusion of whole blood, red cell concentrates, platelets and granulocytes. It has not been reported following transfusion of cryoprecipitate, fresh frozen plasma or fractionated products.

The minimum dose achieved in the irradiation volume is 25 Gy with no part receiving more than 50 Gy.

Red cell concentrates can be irradiated up to 14 days after collection and stored for a further 14 days without significant loss of viability. Gamma irradiation of red cells leads to an accelerated leakage of potassium and an increase in extracellular levels of potassium. So-called "top up" transfusions at standard flow rates do not lead to a risk of hyperkalaemia, even with premature neonates. Hyperkalaemia may be a potential complication in rapid large volume transfusions such as intrauterine transfusion or neonatal exchange transfusion. Provided the unit is less than 5 days old this complication is unlikely. If fresh blood is not available washing of the red cells will prevent hyperkalaemia in the recipient.

CLINICAL INDICATIONS FOR IRRADIATED BLOOD COMPONENTS

- Blood components donated by blood relatives
- Intrauterine transfusion (IUT)
- Exchange transfusion (ET) following IUT
- Recommended for all ETs, provided this does not unduly delay the ET
- Platelets transfused in utero for alloimmune thrombocytopenia. Red cells and platelets transfused up to 6 months after the expected date of delivery should also be irradiated
- Lymphocyte immunodeficiency syndromes
- All recipients of allogeneic haematopoietic stem cell transplantation (HSCT) – from time of initiation of conditioning regimen. This should continue while the patient is on GvHD prophylaxis or lymphocytes are $>1 \times 10^9/l$
- Patients undergoing autologous stem cell harvesting – until there is evidence of haematopoietic engraftment and lymphoid reconstitution
- Hodgkin lymphoma
- Treatment with purine analogues (fludarabine, cladribine, deoxycytosine)
- Antithymocyte globulin (ATG) for severe aplastic anaemia

FURTHER READING

- Guidelines on the use of irradiated blood components British Committee for Standards in Haematology (Transfusion Task Force) **Brit J Haematol 2010;152:35-51**

8. MANAGEMENT OF MASSIVE BLOOD LOSS

DEFINITION

This has arbitrarily been defined as the loss of one blood volume equivalent within a 24 hour period. More practical definitions in the acute setting would be 50% blood volume loss within 3 hours or blood loss at >150 ml/min.

VOLUME RESUSCITATION

The first therapeutic goal is maintenance of tissue perfusion and oxygenation in order to prevent hypovolaemic shock and consequent multi-organ failure. Initial restoration of circulating blood volume is usually achieved by the rapid infusion of crystalloid through a large bore cannula. Do not over resuscitate: permissive hypotension is the restriction of intravenous fluid to maintain a systolic BP of around 90 mmHg, with the goal of minimising blood loss; only suitable for non-head injured patients. The initial goals of resuscitation are achieving a urine output of >0.5ml/kg/hr, a haemoglobin level of 8-10 g/dl and a serum lactate level below 2.5 mmol/l.

The rationale of fluid resuscitation in patients with massive ongoing blood loss is based on the principles of damage control resuscitation. Urgent transfusion is required, not only for volume replacement, but also to replace clotting factors. Severe injuries predispose to clotting deficiencies (shown to be present within minutes of injury, before any therapeutic intervention has commenced), as well as hypothermia, acidosis and the haemodilutional effects of crystalloids.

TRANSFUSION OF BLOOD AND BLOOD PRODUCTS

Under ideal circumstances, the transfusion of warm fresh whole blood would be the logical treatment for massive or ongoing blood loss. This is rarely possible and, as red cell concentrates contain no platelets or clotting factors, all components of blood need to be replaced. To prevent coagulopathy without wastage, a protocol needs to be in place to govern the provision and use of blood and blood products. This "massive transfusion protocol" should be an evidence-based policy guideline and practical plan of action, unique to every institution and the blood transfusion service involved.

As soon as it is evident that there is significant ongoing blood loss likely to require >10 units red cell concentrates, the massive transfusion protocol should be activated. This implies that emergency blood (Group O) is commenced immediately, while the local blood bank is requested to urgently provide batches of cross matched leucocyte depleted RBC concentrates, thawed plasma and platelets. While there is some evidence to administer these in ratio of 1:1:1 in battle casualties, irrespective of coagulation screening tests, the evidence to support this in civilian populations is not good. Every effort should be made to prevent hypothermia and acidosis. Do not over resuscitate and aim for a Hb of 8-10 g/dl, although the latter may be an unreliable index when there is active bleeding.

Arrest Bleeding

It is self-evident that treatment of any traumatic, surgical or obstetric source of bleeding should be rapidly managed, either through surgical intervention, angio-embolization or other appropriate measures. Hypotensive resuscitation should be practised until arrest of bleeding is imminent.

Leucocyte Depleted Blood

Although the majority of well-resourced countries now provide leucocyte depleted blood components to all patients, in South Africa selective use of leucocyte depleted components is recommended (see Chapter 6). Current local guidelines support leucocyte depleted products in critically ill patients and patients requiring massive transfusion fall into this category. However, if leucocyte depleted products are not immediately available, blood components should not be withheld pending their availability.

Red cell concentrates

Transfusion of red cells is generally indicated when there is a 30-40% loss of blood volume, or earlier if ongoing or massive bleeding is suspected. While Hb and Hct levels should be regularly checked, it is acknowledged that they are not necessarily good markers of acute blood loss. While it is a common recommendation to use red cell concentrates <14 days old in this setting since some early observational studies have suggested that mortality rates and organ dysfunction are commoner in patients transfused with older concentrates. There is, however, a paucity of randomised prospective studies to confirm this. If for any reason whole blood is infused, older stored red cells may contribute to hyperkalaemia, particularly in patients with underlying renal or hepatic disease.

Early communication with the blood bank is important particularly in an extreme situation where uncrossmatched Group O blood may have to be issued. Trauma and emergency units should have emergency fridges supplied and monitored by the blood services in which Group O Rh positive and negative red cells are stored. Since blood group determination can be quickly performed, it is important to send samples to the blood bank so they are able to issue ABO specific red cells and protect stocks of Group O blood. It is acceptable to issue Group O Rh positive red cells to males and to post-menopausal women.

The risk of clerical errors is high in this clinical setting, particularly where there is more than one patient in the trauma centre or ICU requiring large volumes of blood components and care in identification of patients and labelling of specimens is critical.

Platelets

Massive ongoing bleeding requires transfusion of platelets, plasma and red cells, usually in a ratio of 1:1:1, so as to reconstitute whole blood. Whether as a result of haemodilution or developing DIC, platelet transfusion is recommended by most guidelines when the count falls to $<50 \times 10^9/l$ in a patient without active bleeding. A maintenance level of $100 \times 10^9/l$ is recommended for high velocity injuries or central nervous system trauma.

Fresh frozen plasma (FFP) and cryoprecipitate

With a dilutional coagulopathy the fibrinogen level is often the first to fall. If it drops below 1.0 g/l, cryoprecipitate is indicated – 10 units of cryoprecipitate contain on average 2.0 g of fibrinogen and should raise the level by approximately 1.0 g/l.

The generally recommended indication for FFP is an INR or APTT ratio of >1.5 , but it should be noted that the evidence base for this is thin. The usually recommended dose is 10-15 ml/kg body weight, however, in actively bleeding patients, doses in excess of 30 ml/kg may be required. Algorithms using point-of-care testing have now been validated and appear to be superior to INR or APTT.

USE OF PHARMACEUTICAL AGENTS TO REDUCE BLOOD LOSS

Antifibrinolytic drugs

A recent large randomised placebo-controlled trial of tranexamic acid in trauma patients with significant haemorrhage (CRASH-2) demonstrated significantly reduced all-cause mortality and death due to bleeding in the treatment arm. The authors concluded that consideration should therefore be given to routinely treating such patients with tranexamic acid, 10 mg/kg IV immediately and another dose over 6 hours, provided the first dose can be administered within the first 3 hours after injury.

Recombinant Factor VIIa (rVIIa)

This is currently licensed for the treatment of haemophiliacs who have developed inhibitors. It has also been quite extensively used “off label” as a universal haemostatic agent, particularly in different types of massive blood loss. Until there is sound evidence from controlled trials, it is probably best reserved for situations where there is continuing massive blood loss, surgical control of bleeding is not possible and coagulopathies have been appropriately managed with FFP, cryoprecipitate and platelets. Since it is prohibitively expensive, a local protocol should be in place to obtain approval for its use.

AUTOTRANSFUSION (See Chapter 10)

Autotransfusion of the patient's shed blood obviously guarantees compatibility and removes the risk of allogeneic transfusion transmitted disease, although the current risk of the latter in South Africa is extremely low.

It is safe to use in stab wounds, gunshot wounds and blunt trauma. It should not be considered in left lower chest penetrating injuries, potential bowel contamination, established coagulopathies and haemothoraces >8 hours old.

COAGULOPATHY

Coagulopathy after traumatic injury is the result of multiple independent, but interacting mechanisms. Early coagulopathy is initiated by thrombin from tissue injury and then driven by shock. Initiation of coagulation occurs with activation of anticoagulant and fibrinolytic pathways. In trauma patients severe tissue destruction, hypoxia, acidosis, shock, dilution and hypothermia all may act as contributory factors for the development of the Acute Coagulopathy of Trauma. Acidosis specifically interferes with the assembly of coagulation factor complexes and hypothermia prevents the activation of platelets. There is significant interplay between all mechanisms.

Dilutional coagulopathy is not uncommon with crystalloid and synthetic colloid fluid resuscitation. In obstetric practice DIC is often seen in abruptio placentae with massive blood loss.

The first clinical sign is often microvascular oozing, followed later by end organ damage as a result of microthrombi. Regular laboratory monitoring, if available, should alert the clinician to developing DIC before clinical signs appear – low fibrinogen levels, raised INR and APTT, detection of fibrin degradation products such as D-dimers and thrombocytopenia are typical in DIC. Treatment of the coagulopathy of DIC is similar to that of dilutional coagulopathy as outlined above, with replacement by appropriate blood components. TEG or ROTEM devices are particularly good at detecting thrombolysis.

The mechanisms by which tissue trauma, shock, and inflammation initiate coagulopathy remain unclear. Acute Coagulopathy of Trauma should be considered distinct from disseminated intravascular coagulation. Rapid diagnosis and directed interventions are essential.

METABOLIC COMPLICATIONS OF MASSIVE TRANSFUSION

The commonest is hypocalcaemia as a result of citrate toxicity. This is particularly seen following large volume plasma infusions and is the result of impaired citrate metabolism especially in the presence of abnormal liver metabolism. Ionised calcium is the best measure of monitoring this complication – ionised calcium reduces myocardial contractility and causes vasodilatation which further increases bleeding and shock. It should be treated by intravenous infusion of calcium chloride at a dosage of 10 ml.

Hyperkalaemia may occur particularly if stored whole blood has been used and if >6 mmol/l requires active intervention.

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9. PAEDIATRIC BLOOD TRANSFUSION

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.

INTRAUTERINE TRANSFUSION (IUT)

This should be done only 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.

NEONATAL TRANSFUSION

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 an Hct of 0.5 - 0.6 l/l. Some centres, particularly in the USA, reconstitute RBC concentrates with fresh frozen plasma but it increases donor exposure and is not recommended unless whole blood is unavailable. The unit should be group O (or ABO

compatible with maternal and neonatal plasma), Rh-D negative, crossmatch compatible with maternal and neonatal plasma, <5 days old, irradiated (must be transfused within 24 hours of irradiation) and leucocyte-depleted. An exchange of double the infant's circulating blood volume is recommended: for pre-term infants 180-200 ml/kg, and for term infants 160-180 ml/kg should be transfused. For bigger infants where the calculated volume needed exceeds the amount in 1 unit of whole blood, then only one unit should be ordered initially. Serum bilirubin results post exchange transfusion will determine whether further blood is required. 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 ionised calcium is advisable.

Small Volume Red Cell Transfusion

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 subsequent transfusion.

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

- | | |
|---------------------------------------------|-------------------------|
| • Anaemia in the first 24 hours | Hb < 12g/dl |
| • Neonate receiving mechanical ventilation | Hb < 12g/dl |
| • Acute blood loss | > 10% blood volume lost |
| • Oxygen dependent (not ventilated) | Hb < 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 impaired oxygen release. Leucocyte depleted products are also recommended for infants (see Chapter 6).

Neonatal units should arrange with their 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 minimises the infectious risk and red cell antigen exposure.

RED CELL TRANSFUSION IN OLDER CHILDREN (>1 YEAR)

Older children tolerate low Hb levels relatively well, unless there is accompanying respiratory or cardiac compromise. A Hb threshold of 7 g/dl is suggested, unless there is underlying severe cardiopulmonary disease, when the recommended threshold is 10-12 g/dl. As in adults, there is a tendency to more restrictive strategies, since recent studies have shown no significant increase in morbidity as a result. The recommended

top-up transfusion dose for children is 10-20 ml/kg via a standard blood administration set or syringe with equivalent filtration. An initial dose of 15 ml/kg is ideal but as much as 20 ml/kg may be transfused in a haemodynamically stable patient if further transfusions are required. A 40 kg child receiving one standard red cell concentrate (\pm 300 ml) is receiving <10 ml/kg and therefore older children may require more than one unit, even with a restrictive strategy. Another approach is to use a formula:

$\text{Hb(target)} - \text{Hb(actual)} \times \text{weight} \times \text{transfusion factor}$ (4 for RBC concentrates and 6 for whole blood). In normovolaemic patients furosemide (1 mg/kg) may be prescribed to prevent volume overload.

All infant and paediatric small volume RBC concentrates are leucocyte depleted, but in older children where adult RBC concentrates are used, a specific request must be made to for a leucocyte depleted product. The guidelines are given in Chapter 6, but bear repeating:

- Patients who have previously experienced febrile non-haemolytic febrile reactions
- Patients receiving multiple or lifelong transfusions
- Patients likely to receive organ or haemopoietic stem cell transplants
- Patients at high risk for CMV infection
- Critically ill patients and those who undergo cardiac surgery

If anaemia is accompanied by thrombocytopenia at a level requiring a platelet transfusion, fluid overload may result if platelets are rapidly transfused first.

The blood bank can usually issue group specific RBC concentrates within 20 minutes of receiving the cross match request or immediately if the patient's blood group has previously been documented. In the event of a dire emergency uncross-matched Group O blood can be given from the emergency fridge. Since Rh-D negative blood is usually in short supply, this should generally be reserved for females. Males can usually quite safely be given Group O Rh-D positive blood in emergency situations.

SPECIFIC COMPONENTS FOR NEONATES AND INFANTS

The use of an adult RBC concentrate, FFP or platelet concentrate for infants and small children would result in significant wastage given the volumes required. The blood services therefore prepare special products for paediatric use as follows:

- RBC concentrates: 25-150 ml
- FFP 100-160 ml
- Platelets: 50-60 ml; usually obtained from a single adult apheresis platelet unit which is split into a number of neonate/infant units.

PLATELET TRANSFUSION

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

- Consider in all neonates at $<30 \times 10^9/l$
- Consider if increased bleeding risk $<50 \times 10^9/l$
 - o $<1\ 000\text{ g}$ and $<1\text{ week old}$
 - o Clinically unstable (e.g. labile BP)
 - o Previous major bleeding (e.g. grade 3-4 intraventricular haemorrhage)
 - o Current minor bleeding
 - o Coagulopathy
 - o Planned surgery or exchange transfusion
- Major bleeding $<100 \times 10^9/l$

ABO group specific platelets are recommended. In neonatal alloimmune thrombocytopenia (NAITP), HPA-compatible platelets are required. In an emergency or when HPA typed platelets are unavailable, the use of maternal platelets is an option when the count is $<30 \times 10^9/l$. Notwithstanding the threshold guidelines, the general principle should always be to treat the patient and not the platelet count. As far as possible platelet transfusions should be avoided for patients with immune thrombocytopenia unless there is life threatening haemorrhage or bleeding in critical areas while initiating therapies such as steroids and intravenous immunoglobulins. Platelets should not be given to patients with aplastic anaemia who are not bleeding for fear of generating platelet antibodies and rendering the patient refractory.

Dosage

Platelets for neonates are usually prepared from single donor apheresis procedures. In older children single donor apheresis units are generally reserved for those with severe pyrexial reactions, refractoriness and those being considered for stem cell transplantation. A dose of $15\text{-}20\text{ ml/kg}$ is recommended and should be transfused using a platelet administration set. The platelets should be infused as rapidly as possible. If blood volume overload is a concern, furosemide (1 mg/kg) can be administered.

FRESH FROZEN PLASMA (FFP)

Indications for FFP in paediatric patients include:

- Neonates with a significant risk of bleeding (INR or APTT >1.5)
- Haemorrhagic disease of the newborn (while waiting for response to Vitamin K)
- Congenital coagulation deficiencies where a specific factor concentrate is not available or the deficient factor has not been identified

FFP is not recommended to treat sepsis, as a volume replacement fluid or to treat erythrocytosis/polycythaemia. No benefit has been shown for routine prophylactic use to treat PVH in pre-term infants.

ABO group specific plasma (or preferably AB plasma if available) is recommended. Group O FFP should not be given to neonates who are not group O unless the anti-A and -B titres have been screened for. A dose of 10-20 ml/kg is recommended administered via a standard blood administration set (170-200 µm filter) or via a syringe with equivalent filtration. As FFP is hyperosmolar, fluid overload is a risk in normovolaemic patients and close monitoring is advisable.

CRYOPRECIPITATE

Indicated for acquired (DIC most commonly) or congenital hypofibrinogenaemia. The threshold for transfusion is <1.5g/l depending on clinical circumstances (e.g. active bleeding, invasive procedure). Recommended dose is 5 ml/kg rapidly infused. It is dispensed as individual units each containing 10-15 ml and approximately 200 mg of fibrinogen.

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 (T-activation).

T-activation can easily be detected by screening the affected red cells with a lectin (*arachis hypogea*). Adult plasma commonly contains anti-T, a potentially haemolytic IgM antibody. Although there have been published case reports of haemolysis following transfusion in neonates with NEC, detection of T-activation in these infants is not necessarily predictive for clinically significant haemolysis and there is a wide variation internationally in the policies adopted. It is, however, probably reasonable to provide components from donors who have low titre anti-T. Red cell concentrates contain minute volumes of plasma and the routine use of washed red cells in these patients is unnecessary.

ERYTHROPOIETIN

Healthy neonates commonly develop a “physiological anaemia” in the first few weeks after birth, with haemoglobin levels dropping to approximately 9 g/dl. Pre-term neonates and ill neonates may drop to even lower levels of 7-8 g/dl as a result of relatively ineffective production of erythropoietin plus loss of blood from frequent sampling for laboratory tests.

Although erythropoietin stimulates erythropoiesis in pre-term infants, elimination of or marked reduction in the need for red cell transfusions has not been demonstrated in clinical trials. Routine use of erythropoietin in neonates is not recommended.

IRRADIATION

The indications for irradiation are outlined in Chapter 7. Note that while irradiation is recommended prior to exchange transfusion, it should not be unduly delayed pending availability of an irradiated unit.

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10. ALTERNATIVES TO ALLOGENEIC BLOOD TRANSFUSION

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 haemostatic 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 auto-recovery 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.

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 450-500 ml of blood and the longer term reduction in haemoglobin levels. They must weigh >50 kg, 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.

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. It should be noted that NAT (nucleic acid testing) has minimized the risk of viral transmission and as such designated transfusion is no longer recommended by the blood transfusion services in South Africa. The service does however remain available on request.

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 TA-GvHD (See Chapter 7). Therefore all blood from family donors must be gamma-irradiated prior to transfusion.

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 an 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.

BLOOD RECOVERY (AUTOTRANSFUSION)

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.

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.

PHARMACOLOGICAL INTERVENTIONS

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

Examples are:

Collagen haemostat pad, 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 used to increase Factor VIII in mild haemophilia A and type 1 von Willebrand's disease. Trials of DDAVP to reduce blood loss in cardiac surgery have yielded mixed results.

Aminocaproic acid and Tranexamic acid (Anti-fibrinolytic agents)

Trials have been published demonstrating efficacy in reducing blood loss post cardiac surgery, in gynaecological bleeding and with massive transfusion.

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 (HBOCs)

Despite 2-3 decades of development, the number of products that have reached clinical trials status is limited. Hemopure, a polymerized bovine hemoglobin, (not currently available in South Africa), is utilized for the treatment of surgical anaemia in adults for the purpose of delaying or reducing the need for allogeneic red cells. It has been used successfully in a number of patients in an uncontrolled surveillance programme.

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 O₂-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) and is therefore useful as an O₂-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. High cost and availability are major considerations.

Erythropoietin

Erythropoietin is the recommended treatment for anaemia of renal disease, proved effective in anaemia induced by anti-retroviral agents and has been widely used for chemotherapy-induced anaemia. 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

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.

MANAGEMENT OF PATIENTS WHO REFUSE TRANSFUSION OF BLOOD COMPONENTS (e.g. JEHOVAH'S WITNESS PATIENTS)

Jehovah's Witness patients will refuse standard blood components such as RBC concentrates, FFP and platelets, including PAD. Fractionated products are matters for personal decision by each individual.

Since the 1990's Jehovah's Witnesses have set up more than 1 700 Hospital Liaison Committees in major centres around the world, including 24 in South Africa. It is recommended that they be contacted when an individual JW patient is undergoing treatment or surgery that has a high likelihood of requiring transfusion support so that strategies that minimise the chances of requiring blood products can be developed for the individual patient.

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11. HIV/AIDS AND BLOOD TRANSFUSION

The emergence of the HIV epidemic in the early 1980's has had a profound impact on the blood transfusion service, prompting targeted donor education, improved donor selection criteria and the implementation of progressively more robust testing. With the unfolding of the epidemic, it became evident that clinically significant cytopenias (anaemia, thrombocytopenia and neutropenia) are common in persons with HIV. Whereas the underlying causes of the cytopenias might differ from HIV-negative individuals, the role of blood transfusion in the management of these haematological conditions does not differ substantially between HIV-negative and HIV-positive patients.

Management should be focused on the identification and treatment of the underlying causes of the cytopenias and non-transfusion options such as haematinics should remain first line therapy. The decision to transfuse should be based on the individual patient's clinical status and co-morbidity rather than on laboratory indices only. In general, indications for transfusion in HIV-positive patients are the same as for HIV-negative patients. Blood should only be transfused when clinically indicated and where the benefits clearly outweigh the recognised risks. Critically ill HIV positive patients with longstanding severe chronic anaemia are at particular risk of fluid overload and pulmonary oedema. Slow transfusion of one unit of blood with reassessment of the need for further transfusion assists in limiting transfusion to the minimum effective volume of blood required to stabilise the patient. Routine transfusion to predefined Hb or platelet levels should be avoided.

SPECIAL CONSIDERATIONS IN HIV

Leucocyte Depleted Blood:

The routine use of leucocyte depleted blood in HIV-positive patients is not recommended. Despite being immunosuppressed, there is no substantive data supporting improved outcomes in HIV-positive patients who routinely receive leucocyte depleted blood components. The indications for the transfusion of leucocyte depleted blood products are the same for HIV-positive and HIV-negative patients. (See Chapter 6.)

Irradiated Blood Products:

HIV-positive patients do not routinely require blood products to be irradiated. It has been proposed that CD4 depletion in HIV-positive patients decreases the number of donor cells required to induce TA-GvHD, but to date there has been only one reported case of TA-GvHD in HIV-positive patients, despite the widespread use of blood transfusion in patients with profound immune suppression. The indication for irradiated blood products remain the same in HIV-positive patients as for HIV-negative patients. (See Chapter 7.)

Direct Antiglobulin Test (DAT) positive patients:

The DAT is positive in up to 20-40% of HIV-positive patients. Of these, few demonstrate signs of clinically significant haemolysis. However, the presence of a positive DAT, with or without overt haemolysis, complicates compatibility testing and the rapid access of blood for transfusion. Red cell auto-antibodies can mask clinically significant allo-antibodies that may have developed following prior antigen exposure e.g. pregnancy or transfusion. In non-urgent cases, full serological investigation is required to determine the specificity of the auto-antibody and to exclude co-existing allo-antibodies. In the absence of clinically significant allo-antibodies, it is acceptable to issue red cells to patients with a positive DAT where the indirect antiglobulin test phase of the crossmatch is also positive. A haemolytic transfusion reaction in these patients is unlikely, however, slow transfusion and careful monitoring is recommended.

Confidentiality and disclosure of HIV status to blood transfusion services:

The communication of any information pertaining to a patient's HIV status is subject to the confidentiality provisions of Section 14 of the National Health Act which makes it clear that '[all] information concerning a user, including information relating to his or her health status ... is confidential'. However, this right to confidentiality is further subject to the provisions of Section 15, which deals with access to health records. Section 15(1) ensures that the guarantee of confidentiality should not stand in the way of running an efficient and effective health service, which would include the appropriate handling of blood and blood products. As HIV infection is associated with higher rates of DAT positive patients, disclosure of a patient's HIV status will assist in limiting unnecessary delays in the issuing of compatible blood.

Please refer to the Southern African HIV Clinicians Society's *Review of the use of blood and blood products in HIV infected patients* for additional information and guidance on the use of blood and blood products in HIV-positive patients.

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12. HAEMOVIGILANCE, RISKS AND ADVERSE REACTIONS ASSOCIATED WITH TRANSFUSION

It is imperative that all information recorded on the blood specimen tube and the blood request form is completed fully, legibly and accurately for every blood request. Identification errors should be avoided at all costs since transfusing incompatible blood components may have fatal consequences.

When transfusing blood or a blood product, the attending clinician is responsible for evaluating the risk/benefit ratio to the patient. All blood products carry a risk of adverse effects, ranging from sensitization to donor cells or proteins, to transmission of disease, including HIV infection. The transfusion services endeavour to minimise major risks in the following manner:

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.

Donation Testing

All donated units are individually screened for laboratory evidence of Syphilis, HBV and HCV, 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 (NAT) 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; since the introduction of this technology in 2005 there have been no documented reports of HIV or HCV transmission by transfusion and two confirmed HBV transmissions.

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 counselling and testing the recipient and for managing and treating the patient, or for referring the patient to a specialist, where appropriate.

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

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 15-30 minutes thereafter. Transfusions should be stopped immediately should there be any signs of an untoward reaction.

Definition

A transfusion reaction is 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 swift action. 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:
 - o Further transfusion therapy if required.
 - o Suitable therapy to combat the effects of the reaction.

Monitoring

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

- Pulse.
- BP.
- Temperature.
- Respiration rate.
- General visual observations.
- General urinary observations.
- 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	Fever/sweating
Tachycardia/bradycardia	Dyspnoea/bronchospasm
Hypertension/hypotension	Urticaria/pruritus
Chest/flank pain	Nausea/vomiting
Haemoglobinuria	Oliguria/anuria
Agitation	Jaundice

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, clearly labelled – a minimum requirement will include:
 - o Clotted blood sample.
 - o EDTA tube.
 - o Perform a dipstix on post transfusion urine sample for haemoglobinuria.
- Return the suspect unit/s, empty blood bags 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.

Mortality/death associated with transfusion

According to Section 68 of the National Health Act 61 of 2003, in case a patient demises while receiving or following a transfusion, the following steps must take place:

The blood bank must be notified of the case as a mortality following a transfusion.

Post transfusion samples must be taken immediately and sent to the blood bank.

A post-mortem must be conducted to establish the cause of death.

The treating doctor's report and post-mortem results must be sent to the blood bank or directly to the Haemovigilance office.

Once the blood transfusion service has completed the investigation, a report will be sent to the treating doctor and/or hospital manager and the deputy director-general of the department of health.

The case will be classified according to the outcome of the investigations and post-mortem results.

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 (Table 6) are the most serious or the most frequently observed and are described fully.

Table 6 Adverse 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 reactions can result from incorrectly heated/stored red cell products.</p> <p>NOTE:</p> <p>In the case of an acute haemolytic 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/anaemia Haemoglobinuria.</p>	<p>Stop the transfusion, change the transfusion set and filter. Maintain venous access with crystalloid/colloid solutions.</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.</p> <p>Monitor vital signs, including in some instances the pulmonary arterial pressure or CVP.</p> <p>Measure urinary output, observe for abnormal bleeding, especially if the patient is in post-operative stage.</p> <p>Maintain intravascular volume and urinary output with crystalloid/colloid solutions.</p> <p>Prevent/treat renal failure with furosemide i.v. 120 mg (and mannitol 1 gram). Vasopressors (e.g. dopamine) may be required.</p> <p>Monitor patient closely.</p> <p>Consult Renal physician with a view to starting haemodialysis to reduce plasma haemoglobin and prevent acute renal failure.</p> <p>Consult Haematology/Renal Dept for further assessment of coagulation profile and renal functions.</p>

Table 6 Adverse Reactions (continued)

BACTERIAL CONTAMINATION	SIGNS/SYMPTOMS	MANAGEMENT
Caused by any contaminated blood product (most frequently associated with platelet concentrates).	Usually rapid onset, about one hour post transfusion. Chills, fever, abdominal cramps, vomiting or diarrhoea, renal failure, flushed dry skin, hypotension and shock.	<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 bank 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
Severe, usually due to antibodies to IgA immunoglobulin, less frequently severe reactions to other plasma proteins.	Sudden onset. Symptoms include dyspnoea, hypotension/shock, facial and/or glottal oedema plus explosive GI symptoms. May lead to cardiac arrest/death.	<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.</p> <p>Monitor vital signs.</p> <p>Prevention:</p> <p>Patients may be IgA deficient and require assessment of immunoglobulin profile. Further therapy must be with washed red cells that are plasma free.</p>

Table 6 Adverse Reactions (continued)

TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)	SIGNS/SYMPTOMS	MANAGEMENT
Severe, usually caused by leucoagglutinins in the plasma of the donor. Generally under-recognised and under-reported.	No lung injury prior to the transfusion. 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.
TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD (TACO)	SIGNS/SYMPTOMS	MANAGEMENT
This is usually due to rapid or massive transfusion of blood in patients with diminished cardiac reserve or chronic anaemia.	Dyspnoea, orthopnoea, cyanosis, tachycardia, increased blood pressure and pulmonary oedema and may develop within 1 – 6 hours of transfusion.	Stop transfusion immediately and follow other steps for managing suspected transfusion reactions. Place the patient in an upright position and treat symptoms with oxygen, diuretics and other cardiac failure therapy. Transfusion-associated Circulatory Overload is easily prevented by closely monitoring patients receiving transfusions and transfusing smaller volumes of blood at a slower rate.
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 if mild.	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.

Table 6 Adverse Reactions (continued)

TRANSFUSION-ASSOCIATED GRAFT vs HOST DISEASE (TA-GvHD)	SIGNS/SYMPTOMS	MANAGEMENT
<p>This extremely rare condition results from the transfusion of lymphocytes that share an HLA haplotype with the recipient. Characteristically the donor lymphocytes are homozygous for a particular HLA haplotype whereas 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. Leucocyte depletion is not considered to be adequate to prevent TA-GvHD.</p>	<p>The reaction is often florid and occurs 10 – 14 days after the transfusion. The patient presents with severe jaundice, a maculopapular rash, pancytopenia and diarrhoea.</p>	<p>This condition carries an extremely high mortality rate. Therapy is directed at eliminating the clone of engrafted lymphocytes by chemotherapy. This should be done by a specialist oncology unit.</p>
POST TRANSFUSION PURPURA	SIGNS/SYMPTOMS	MANAGEMENT
<p>This rare condition results from recipient alloantibodies directed against 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 marked thrombocytopenia occurring some 9 – 10 days after transfusion. The recipient's own platelets appear also to be destroyed in this reaction by unknown mechanisms.</p> <p>Patients may present with haemorrhage, mucosal bleeding and/or purpura on pressure areas.</p>	<p>This potentially lethal reaction is treated ideally with intravenous Gammaglobulin (2 g/kg over 2 – 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>

Table 6 Adverse Reactions (continued)

FEBRILE NON HAEMOLYTIC TRANSFUSION REACTIONS	SIGNS/SYMPTOMS	MANAGEMENT
Cause: Usually recipient leucocyte or platelet antibodies to transfused donor cells.	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. Isolated fever > 38 degrees Celsius or, a rise of 1 degree Celsius from the pre-transfusion value.	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. Further management: if repeated on further transfusion, then transfuse with leucocyte depleted blood. If latter not available, then give antipyretics 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 muco-cutaneous symptoms only.	Stop the transfusion. Keep IV open. Notify 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 haemolytic transfusion reaction.

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.

HAEMOVIGILANCE PROGRAMME

The South African Haemovigilance Programme was established in 2000 as a voluntary, non-punitive initiative aimed at improving the quality and safety of all processes/procedures related to blood transfusion as well as the prevention of transfusion-related reactions. The aim of the programme is also to gather information and reports on adverse events associated with the transfusion of blood products in a structured manner and to analyse and distribute the results. This will then enable 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 of adverse transfusion reactions/effects by hospital staff is thus mandatory for the success of the programme. The blood banks routinely supply forms for reporting such events and this is fed back to a haemovigilance officer at SANBS/WPBTS who collates and analyses the national data. It is imperative that all suspected adverse events relating to the transfusion of blood components should be reported to the nearest blood bank as soon as possible. International trends have dictated the inclusion of adverse donor reactions in an effort to improve on donor healthcare by tracking all adverse events associated with blood donation from the collection to the end delivery outcome.

FURTHER READING

- SANBS/WPBTS **Haemovigilance Report 2012** Electronic copy available on www.sanbs.org.za and www.wpblood.org.za

ABBREVIATIONS

AABB	–	American Association of Blood Banks
ACS	–	acute coronary syndrome
ANH	–	acute normovolaemic haemodilution
APTT	–	activated partial thromboplastin time
BP	–	blood pressure
CABG	–	coronary artery bypass graft
CCI	–	corrected count increment
CMV	–	cytomegalovirus
CPB	–	cardiopulmonary bypass
CVP	–	central venous pressure
DAT	–	direct antiglobulin test
DEHP	–	di (2-ethylhexyl) phthalate
DIC	–	disseminated intravascular coagulation
ET	–	exchange transfusion
FFP	–	fresh frozen plasma
FNHTR	–	febrile non haemolytic transfusion reaction
HBV	–	hepatitis B virus
Hb	–	haemoglobin
Hct	–	haematocrit
HCV	–	hepatitis C virus
HIT	–	heparin induced thrombocytopenia
HIV	–	human immunodeficiency virus
HSCT	–	haemopoietic stem cell transplantation
INR	–	international normalised ratio
IUT	–	intrauterine transfusion
PAS	–	platelet additive solution
RBC	–	red blood cell
TA-GvHD	–	transfusion associated graft versus host disease
TRALI	–	transfusion related acute lung injury
TRIM	–	transfusion related immunomodulation
TTP	–	thrombotic thrombocytopenic purpura
vWD	–	von Willebrand's Disease

Notes



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