Blood Products

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The South African National Blood Transfusion Service (SANBS) issues over a million blood components per year. This brief overview of blood products will touch on screening, testing, processing, storage and clinical use of the major products.

Whole blood is collected from a donor into a bag prepared with sodium citrate, a stable, minimally toxic anticoagulant with pH buffering properties. It is chilled and transported to the blood processing facility where it is tested and processed into the various component products and thereafter stored under conditions specific to each product until required for clinical use.

Operating in a region with one of the highest HIV infection rates in the world has made accurate screening of donor units for infection a priority. Stringent donor selection procedures together with a policy of non-remuneration for donations and the use of volunteer donors only are the first steps in the process. Following collection blood is screened using advanced nucleic acid and serologic testing and the residual risk of transmitting HIV, HCV and HBV infection is remote.

After screening whole blood is centrifuged to separate the plasma, buffy coat (leucocytes and platelets) and red cells. The red cells are removed at this point to prepare red cell concentrate products. Removing the buffy coat and plasma removes 70-80% of the leucocytes from the red cell product, reducing the risk of non-haemolytic febrile transfusion reactions.

RED CELL PRODUCTS

Table 1: Packed Red Cells

What's in the bag	Sodium Citrate (anticoagulant)		
	111ml preservative solution containing:		
	Adenine	helps maintain ATP levels during storage	
	Glucose	provides a substrate for RBC energy pathways	
	Saline and *mannitol*	reduce the haemolysis of the banked red cells during the 42-day storage period	
Shelf life	@ 1-6°C up to 42 days		
Storage lesion		Day 1	Day 35
	pH	7.5	6.7
	K^{+*}	4.0 mmol/L	66 mmol/L
	Na^{+}	155 mmol/L	122 mmol/L
	Dextrose	24.5 mmol/L	5 mmol/L
	NH_3	100 mg	900 mg
	2,3 DPG*	13 mmol/L	<1 mmol/L
	Red cell survival	100 %	70 %
Compatibility testing	- ABO matching - Rh- patients should get Rh- blood as far as possible. - Antigen negative blood should always be transfused to patients with specific and clinically significant red cell antibodies.		
Dose	4ml/kg to raise Hb by 1g%		
	Packed cells (300±50ml)		R1217
	Packed cells (Leucocyte depleted) (260±50ml)		R2115.79
	Packed cells washed		R4028

*see notes below

*At standard storage temperatures of 1-6ºC, 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 9.5 mmols.

*Red cell **2,3 DPG** decreases with storage, levels drop significantly by 1 week, shifting the oxygen-dissociation curve to the left and decreasing tissue oxygen delivery. Full restoration of 2,3,DPG takes about 72 hours but there is 50% recovery within 7 hours of transfusion. In clinical situations of hypoxia and lactic acid production, and with decreasing pH, the oxygen dissociation curve is 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 HOWEVER 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.

Transfusion related metabolic or electrolyte derangements

-*Citrate toxicity**:*** Following transfusion the citrate from the unit is metabolized in the Krebs cycle of respiration in most cells in the body, particularly in the liver, muscle and renal cortex. In certain clinical conditions (liver disease, hypothermia and hypoparathyroidism; neonates with inadequate calcium stores and/or immature livers) patients be at increased risk for 'citrate toxicity' during rapid transfusion of red cells or FFP. In such cases citrate may precipitate arrhythmias and reduced cardiac contractility by binding plasma calcium thereby lowering plasma ionized calcium levels. With rapid transfusion or in clinical cases at risk of citrate toxicity, ionised calcium levels should be monitored and 10 ml of 10% calcium gluconate administered intravenously: 10 ml for every 2 units of whole blood given in under 10 minutes or 0.5ml/kg for paediatric patients with proven (or suspected) hypocalcaemia.

- *Hyperglycaemia* due to glucose containing solution (especially in cardiac surgery in infants, transfusions during liver transplant). Problem is greater with fresher cells.

- *Hyperkalaemia*

Washed Red Cells

These are prepared on demand from banked packed cells. Cells are suspended in isotonic saline, centrifuged, saline removed and then re-suspended in isotonic saline for transfusion. They should be administered within 24 hrs because of the increased likelihood of bacterial contamination in preparation and the lack of nutrient admixture. Washed cells are indicated in the following circumstances:

1. severe, recurrent allergic transfusion reactions
2. known IgA deficiency in patients who have formed anti-IgA antibodies
3. Stored red cells which have been gamma irradiated (washes off the potassium which collects following irradiation, best managed by transfusing as soon as possible after irradiation)
4. paroxysmal nocturnal haemoglobinuria
5. Neonates with T-activated red cells (red cell T-crypt antigens have been exposed by bacterial infection particularly associated with necrotizing enterocolitis)

Evidence is mounting that the last two indications may no longer be relevant. In the case of neonates with T-cell activation, increasing use of packed cells (which have minimal plasma) as opposed to whole blood means it is probably unnecessary to provide washed red cells as a routine.

Frozen Red Cells

These are used in the case of unusual phenotypes (for patients with rare red cell phenotypes or multiple red cell antibodies) or in the case of autologous donation when donations are made over an extended period (beyond the shelf life of the liquid preserved red cells). This modification is prepared by adding glycerol, a cryoprotective agent, to red cells before freezing. Frozen red cells may be stored for up to 10 years and for longer intervals if there is a particular need for specific units. The thawed unit should be deglycerolized prior to transfusion. This is done by washing the cells with sodium chloride. The washed red cells are then re-suspended in additive solution and have a 24 hour shelf life.

This facility is not offered at the WPBTS or SANBS.

Whole Blood

When blood is harvested it is separated into component therapy soon after arrival in the processing plant. If it is kept as whole blood there is rapid degradation of the platelets and the clotting factors rendering them ineffectual within hours to days of donation. Whole blood is stored as for packed cells and has a shelf life of approximately 28 days. Whole blood may be considered in cases of exchange transfusion or massive haemorrhage but in the latter case, where coagulation may be a concern, component therapy may still be preferable.

PLATELETS

Table 2: Platelets

Preparation	- Derived from the buffy coat layer, separated within 8 hours of donation. - May be irradiated with no loss of function.	
	Pooled: 4-5 donations are pooled, re-suspended in plasma or platelet additive solution (PAS): 200-300ml containing ≥2.4x10^{11} plt	
	Single donor apheresis concentrate: from a single donor, up to 3 bags collected per donation. Automatically leuco-depleted.	
Storage	Stored at 20 - 24º on a platelet agitator	
Shelf Life	5 days	
Compatibility Testing	Ideally ABO compatible. In cases of severe shortages, can use non-identical (ideally group O), this may result in reduced platelet increase. RhD –ve should be given to premenopausal RhD -ve women.	
Indications	Thrombocytopaenia associated with actual or potential bleeding	
Dose	10ml/kg should raise the platelet count by 50x10^{9}	
Cost	Pooled platelet	R8507
	Leucodepleted	R10355
	Single donor mega unit	R11418
	Infant platelet (50ml)	R2004.39

Platelet Refractoriness

Repeated failure to obtain satisfactory elevation of platelet count despite multiple transfusions. HLA allo-immunisation is the main immune related cause, (leukocyte depletion lowers the risk). Non-immune causes include fever, infection, drugs, splenomegaly and DIC. Patients who are likely to require repeated platelet transfusions (e.g. ITP) 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.

Adverse Effects with Platelets

Febrile reactions. Risk of bacterial contamination is greater because platelets stored at room temperature.

PLASMA PRODUCTS

Plasma components are derived by physical separation methods (e.g. centrifugation) and include FFP and cryoprecipitate whereas plasma derivatives are derived from large pools of plasma by more complex physical and chemical processes (e.g. alcohol based fractionation). Products derived from a pool of 12+ donations are classified as medicines and need to be registered. All plasma products are potentially antigenic.

Fresh Frozen Plasma (FFP)

Table 3: FFP

Preparation	Separated by centrifugation within 18 hrs of collection	
What's in the bag*	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
Storage	- -18^{0}C (thus expect normal physiological levels of coagulation factors) -Thaw at 30-37^{0}C then transfuse within 4 hours (labile factors deteriorate within hours)	
Crossmatch	-ABO matched or blood with low anti-A or anti-B titres -O FFP should only be given to O-group patients -RhD sensitisation is unlikely	
Indications	-factor deficiencies where specific factor concentrate is not available -Multiple factor deficiencies with active bleeding (DIC, liver disease) and coagulopathy confirmed with point-of-care testing -Warfarin toxicity -Vitamin K deficiency with active bleeding -Suxamethonium apnoea	
Dose	10 – 15ml/kg,	
Cost	FFP (280±70ml)	R1193
	Leucocyte reduced FFP ((280±70ml)	R2404

* FFP is hyperosmolar, hypernatraemic and hypokalaemic and may precipitate pulmonary oedema and electrolyte imbalances if large volumes are transfused.

Cryoprecipitate

Table 4: Cryoprecipitate

Preparation	Extracted when FFP is thawed to 0 – 4 ^{0}C	
Storage	-18^{0}C for up to 1 year	
Active factors	- Factor VIII/vWF - Fibrinogen - Fibronectin - Factor XIII	
Cross matching	Not required	
Indications	- Congenital or acquired hypofibrinogenaemia (e.g. massive haemorrhage with fibrinogen <1.5g/L) - Factor XIII deficiency	
Dose	1 unit/ 5 - 10kg	
Cost	Cryo 100iU (10±1 ml)	R709

Cryosupernatant a.k.a. cryo-poor FFP is the component available following extraction of cryoprecipitate from FFP. The only indication is for use in therapeutic plasma exchange in the management of TTP.

PLASMA DERIVATIVES

Freeze-Dried Plasma (Bioplasma® National Bioproducts Institute) is produced from pooled virally inactivated fresh plasma using cold ethanol fractionation to separate the plasma into intermediate protein fractions. The various fractions undergo purification by precipitation, centrifugation and filtration. Formulations and sterile filling processes are employed to produce sterile final products. It should be stored at room temperature and has a shelf life of several years making it useful for pre-hospital conditions. It is reconstituted with sterile water and should be infused immediately through a blood giving set in a line with no residual calcium containing fluid. Rapid infusions may precipitate citrate toxicity.

100ml of FDP contains 4 – 6g plasma proteins with a normal distribution of human plasma components including albumin, immunoglobulins, coagulation and complement factors and their inhibitors. Coagulation factor activity is reduced by approximately 15% compared to FFP in animal models.

Albumin is available in 4% and 20% solutions. Prepared from pooled plasma using ethanol fractionation, sterilised by filtration and pasteurised by heat for 10 hours at 60°C to inactivate any HIV, HBV and HCV that may not have been detected in the initial screening of the donations. 20% solutions are indicated for hypoproteinaemia where as 4% solutions are used in certain contexts for plasma volume expansion. Care should be exercised where large volumes are administered as hyponatraemia may ensue:

Table 5: Albumin solutions available in SA

PRODUCT	VOLUME	ALBUMIN CONTENT	STABILISERS	[Na^+]	[K+]	[Citrate]	pH
Albusol 4%	200ml	8g/200ml	Sodium carpylate, 3 % dextrose	130	2	<4	7.0
Albusol 20%	50 or 100ml	20g/100ml	acetyl tryptophanate, sodium caprylate	<100	<10	<20	7.0
WPBTS 20% albumin	50 or 100ml	20g/100ml	Sodium carpylate	<130	<19		7.0

COAGULATION FACTOR CONCENTRATES

Table 6: Coagulation factor concentrates available in SA

PRODUCTS	CONTENT	UNITS	INDICATION
VIAHF 250 (*WPBTS*)(Paediatric)	Factor VIII/vWF	250 IU FVIII	Haemophilia A Von Willebrand disease
VIAHF 500 (*WPBTS)*(Adult)	Factor VIII/vWF	400-600 IU FVIII	Haemophilia A Von Willebrand disease
Haemosolvate Factor VIII 300 IU (*NBI*)	Factor VIII/vWF	300 IU FVIII/vWF	Haemophilia A Von Willebrand disease
Haemosolvate Factor VIII 500 IU (*NBI*) Two pack sizes: 500 IU and 2x 500 IU	Factor VIII/vWF	500 IU FVIII/vWF	Haemophilia A Von Willebrand disease
Haemosolvex Factor IX	Factor IX, Factor II, Factor VII, Factor X	500 IU FIX	Haemophilia B

LEUCOCYTE DEPLETION (LD):

Leucocytes distinguish self from foreign cells on the basis of Human Leucocyte Antigen (HLA) protein on the cell membrane. There is an enormous diversity of HLA proteins expressed on individual leucocytes and the chance of two unrelated individuals with identical HLA molecules on all loci is very low. With allogenic blood transfusion there will be tremendous exposure to these antigens and this is responsible for many of the non-haemolytic transfusion reactions seen. The leucocyte content of a unit of fresh whole blood is approximately 10^9 WBC/unit; this is reduced to 10^8 WBC/unit with the removal of the buffy coat layer. Leucocyte reduction using either filtration or apheresis will reduce the leucocyte content to 1 – 5x10^6 WBC/unit.

There is good evidence that transfusion of LD blood products results in reduction in febrile non-haemolytic transfusion reactions (FNHTR), reduces platelet refractoriness in patients receiving multiple platelet transfusions and reduces CMV transmission in susceptible patients (neonates, transplant). The evidence for reducing the risk of bacterial infection or cancer recurrence post resection is inconsistent, as is that for reducing short term mortality post transfusion except possibly in cardiac surgery and critically ill patients. There is no evidence for a reduction in the risk of reactivation of viral infections such as HIV and no change in survival for these patients.

LD should ideally happen pre-storage as leucocytes may fragment during storage and these fragments pass though the filters used for LD, in addition inflammatory cytokines which contribute to the FNHTR accumulate in stored blood and these will not be reduced by post-storage depletion. If the SANBS/WPBTS were to universally LD all products pre-storage their costs would increase by approximately 25% making the organisations unviable and leading to probable collapse of the South African service. The policy of the SANBTS (as per Clinical Guidelines 2014) is:

- 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)
- It is recommended that the following patients receive leucocyte depleted components:
- Patients on chronic transfusion regimens
  - Those at risk for CMV infection (all transplant patients)
  - Infants <1 year old
  - 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.

IRRADIATED BLOOD

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. As with Graft vs Host Disease seen with stem cell transplant, cellular damage to the host skin, thymus, gastro-intestinal tract, liver and spleen result, in addition bone marrow hypoplasia is a feature that is specific to TA-GvHD. TA-GvHD has been reported following transfusion of whole blood, packed red cells, platelets and granulocytes but not FFP, cryoprecipitate or fractionated products.

While there is preliminary evidence that leucocyte depletion may reduce TA-GvHD the only means to prevent this complication is by gamma-irradiation of the product before transfusion. 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. 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. In the absence of fresh blood washing of cells will reduce the potassium content pre-transfusion.

Irradiated blood is recommended for:

- 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 (incl. thymic hypoplasia)
- All recipients of allogeneic haemopoietic 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 x 109/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, deoxycoformycin)
- Anti-thymocyte globulin (ATG) for severe aplastic anaemia

COMPATIBILITY TESTING

When group & screen is ordered testing for ABO and Rhesus groups and a screening test for clinically significant antibodies (Kell, Duffy, Kidd etc) is done. Blood is only cross matched at this stage if clinically significant antibodies are detected.

In infants <4 months of age antibodies derive from maternal blood and so a sample of maternal blood can be used for cross-matching. The development of antibodies to red cell antigens is very uncommon in the first 4 months of life and certain blood transfusion services recognize this and are happy to waive the requirement of repeated blood sampling for ongoing transfusions for infants in this age group.

Blood group	Antigens	Antibodies	Can give blood to	Can receive blood from
AB	A and B	None	AB	AB, A, B, O
A	A	B	A and AB	A and O
B	B	A	B and AB	B and O
O	None	A and B	AB, A, B, O	O

Table 7: Major donor recipient blood grouping

Cross-matching of blood determines whether the recipient has pre-formed antibodies against any antigens on the donor's cells and whether a donor's blood is compatible with that of an intended recipient. A complete cross-matching process takes about an hour. If blood is needed in an emergency ABO and Rh type-specific blood can be requested. The blood bank will continue the cross matching process in this case while the transfusion is in progress but the clinician accepts the risk of administering incompletely cross-matched product.

Universal donor blood (O- or O+ for males) may be kept in appropriate conditions in institutions where blood may be required in less time that it takes to procure from a blood bank.

ADMINISTRATION FACTORS

Red blood cells, whole blood, cryoprecipitate, FFP and WPBTS VIAHF (Factor VIII concentrate) are administered through a standard blood recipient set (170 - 240 µm mesh filters) to prevent the transfusion of clots or coagulation debris. The use of micro aggregate (40 µm) filters is not recommended.

A platelet giving set should be used for platelet transfusion. Use of a standard blood administration set will result in greater loss of the available platelets due to a larger surface area for adhesion.

Blood transfusions must be completed within 6 hours of entry of the pack. Platelets should be given over 20 – 30 minutes.

Rapid transfusion of cold product may result in hyperthermia however care should be taken with rewarming as overheating of the blood can cause extensive haemolysis.