

10 Plasma derived products

There are wide ranges of plasma products available with specific indications for their use. All plasma products utilise liquid or frozen plasma as their starting material. This may then be subjected to simple physical or more complex chemico-physical processing to produce specific products; the latter are termed plasma derivatives.

The various products, usage guidelines, and recommended dosage schedules are outlined below. Clinicians should be aware that all these products are antigenic and are potentially capable of causing allergic or anaphylactic reactions. The patient should be observed as for cellular products during the initial 15 minutes of any transfusion.

1 FRESH FROZEN PLASMA

Fresh frozen plasma is separated from anticoagulated whole blood within 18 hours of donation. This is done by separating the plasma in a closed sterile system and freezing it to below -18°C . It contains all the clotting factors in normal physiological levels. Fresh frozen single donor plasma carries the same risk of latent viral infection as a unit of red cell concentrate. However, a lyophilised fresh plasma product (Bioplasma FDP), aliquoted from large pools of plasma and treated with a solvent-detergent preparation to inactivate undetected lipoprotein coated viruses is available from National Bioproducts Institute in 50 ml and 200 ml volumes when reconstituted. Other areas, at the time of writing, are introducing retested quarantined FFP as an alternative method of avoiding window period infections. Indications and dosages for both products are similar.

FFP must be thawed before use according to the instructions detailed on the package, or by the hospital blood bank before issue. In the case of FDP reconstitute according to the guidelines provided by the manufacturer.

Table 5: Fresh frozen plasma

PRODUCT	VOLUME	CONTENT	DOSAGE
Fresh frozen plasma	± 280 ml	Physiological levels of all coagulation factors	15 - 20 ml/kg as an initial dose. Further therapy is dependant on response and laboratory monitoring

Table 6: Average levels of coagulation factor in a unit of FFP

FACTOR	AVERAGE LEVELS PER UNIT OF FFP
Fibrinogen	200 mg
Factor II	1,03 u/ml
Factor V	0,64 u/ml
Factor VII	1,21 u/ml
Factor VIII	0,85 u/ml
Factor IX	0,91 u/ml
Factor X	1,25 u/ml
Factor XI	0,79 u/ml
Antithrombin III	104%
Plasma pseudo-Cholinesterase	3000-10 000 iu/l

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

Table 7: Solutes in FFP

SOLUTE	AVERAGE LEVELS PER UNIT OF FFP
Glucose	24,8 mmol/l
Potassium	3,0 mmol/l
Sodium	165 mmol/l
Chloride	79 mmol/l
Osmolarity	322 mmol/l
pH	7,9

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

Table 8: Clinical indications for FFP

DEFINITE INDICATIONS	CONDITIONAL USES (if active bleeding and evidence of disturbed coagulation)	NO JUSTIFICATION FOR USE OF FFP
<ul style="list-style-type: none">• Replacement of single factor deficiencies (If single factor concentrates not available).• Immediate reversal of Warfarin effect.• Vitamin K deficiency associated with active bleeding.• Acute DIC.• Thrombotic thrombocytopenic purpura (TTP) (Preferably cryo poor plasma)• Inherited deficiencies of coagulation.• Scoline apnoea	<ul style="list-style-type: none">• Massive transfusions.• Liver disease.• Cardiopulmonary by-pass surgery.	<ul style="list-style-type: none">• Hypovolaemia.• Plasma exchange procedure (except TTP).• Nutritional support and protein losing states.

NOTES:

Units of FFP must be administered through a blood giving set after thawing at 30-37 °C. Compatibility testing is not required but units should be ABO compatible with the patient's red cells, especially if large volumes are to be transfused. If the ABO group of the patient is not available then group AB fresh frozen plasma should be used as it contains no A or B isoagglutinins.

Transfuse as rapidly as possible, at 15-20 minutes per unit in the average adult in order to obtain a good clinical effect. The labile coagulation factors deteriorate within a few hours of thawing or reconstitution.

2 SPECIFIC COAGULATION FACTOR PRODUCTS

All these products are produced from fresh frozen plasma and are used in a variety of bleeding disorders when one or other of the coagulation factors is deficient.

Table 9: Coagulation concentrates

PRODUCT	CONTENT	UNITS	VOLUME
Cryoprecipitate (cold soluble fraction of FFP)	Factor VIII/vWF	±100 iu	6-8 ml
	Fibrinogen	150-250 mg	
	Fibronectin	150-250 mg	
	FXIII		
VIRALLY INACTIVATED CONCENTRATES			
VIAHF 250(WPBTS) (Paediatric)	Factor VIII/vWF	250 iu	50 ml after reconstitution with sterile water
VIAHF 500 (Adult)(WPBTS)	Factor VIII/vWF	400-600 iu	As above
Haemosolvate Factor VIII (NBI)	Factor VIII/vWF	300 iu	10 ml after reconstitution with sterile water for injection
		500 iu	
		1000 iu	
Haemosolvex Factor IX (NBI)	Factor IX (also contains II, VII and X)	500 iu	10 ml after reconstitution with sterile water for injection

Table 10: Clinical indications for coagulation concentrates

PRODUCT	CONDITION
Cryoprecipitate	Hypofibrinogenaemia - Acquired and congenital. Factor XIII deficiency
VIAHF / Haemosolvate, Factor VIII	Haemophilia A von Willebrands Disease
Haemosolvex	Haemophilia B (Christmas Disease)
Factor IX	Congenital/Acquired deficiency of II, VII, X, IX

NOTE:

Check package insert for reconstitution procedures and storage.
Infuse through a blood filter if using WPBTS VIAHF. The filter can be flushed after transfusion with sterile saline to ensure the entire product reaches the patient.

a) Dosage Schedule

The levels of Factor VIII or other relevant factor should be monitored throughout therapy. This facility may not be available in areas away from major treatment centres and dosage schedules may have to be empirically applied therefore as suggested below. *However, elective major surgery in haemophiliacs and treatment of major haemorrhage should be undertaken only at centres where access to proper monitoring is available. Contact your local haematologist or haemophilia treatment centre for help.*

Factor VIII has a half-life of 8-12 hours so treatment should be given every 8-12 hours for at least the first 24 hours and then every 12 hours. After major surgery the transfusions may be required on a scheduled basis for at least 10 days. Following transfusion of Factor VIII there is a more prolonged rise in Factor VIII in patients with vWD; therefore transfusions of concentrate for vWD are usually required only every 24 hours.

3 HAEMOPHILIA A

When haematological monitoring is available the number of Factor VIII units required may be calculated from the following formula:

$$\text{Factor VIII dose} = \frac{\text{Patient's mass (kg)} \times \text{Desired increase in Factor VIII}}{2}$$

Table 11: Haemophilia A Target factor levels

DEGREE OF BLEEDING	DESIRED FACTOR LEVEL
Minor bleeding (ecchymoses, cuts)	Levels should be raised initially to 50% and maintained at 25% for 24 hours
Moderate bleeding, e.g. joint and dental surgery ceases	Raise levels to 50% and maintain at 30-60% for 3-5 days after bleeding ceases
Major bleeding, surgical procedures/head injury	Raise levels to 100% and maintain at minimum levels of 50-60% for 10 days

Table 12: Empirical dosage regimen if monitoring is not available

TYPE OF BLEED	UNITS REQUIRED	FREQUENCY
Minor bleed (epistaxis, ecchymoses, cuts)	10 iu/kg	Single dose usually suffices
Moderate bleeds (small joints, dental surgery)	10-20 iu/kg	Single dose; repeat 8-12 hourly if adequate clinical effect is not maintained
Severe bleeds (retroperitoneal haemorrhage, joint bleeding, possible intracranial bleed)	20 iu/kg	Initial single dose repeat 8-12 hourly, depending on perceived or monitored major clinical effect
Pre and post operative schedules for major surgery or trauma	30-60 iu/kg pulse dose immediately prior to surgery, thereafter maintain plasma levels by transfusion of 10 iu/kg every 12 hours for 3-5 days, follow with 20 iu/kg single dose transfusion for 5-7 days	

NOTE:

All elective surgery should be undertaken in a specialist centre.

Transfusion of factor should be rapid. Patients should be observed carefully for any untoward reaction to the product, particularly those of allergic nature. **See Reactions "Allergic/Anaphylactic" (Section 11).**

When monitoring is available (recommended for all major operations) more exact regimens can be followed. Continuous transfusion regimens are also efficacious and may well provide more consistent haemostatis levels. These regimens should, however, be under specialist supervision.

It should be borne in mind that about 10% of Haemophilia A patients have antibodies (inhibitors) to Factor VIII and these patients may not respond to the therapy described above. These patients must be referred to a specialist haemophilia treatment centre as an emergency.

4 VON WILLEBRAND DISEASE (VWD)

Intermediate purity Factor VIII concentrates are the treatment of choice where DDAVP (vasopressin analogue) is not effective. The local products contain adequate amounts of high molecular weight multimers.

a) Dosage

- i. Use Factor VIII units as a measurable entity.
- ii. Using 30 iu units of Factor VIII per kg.
- iii. Monitor every 24 hours.
- iv. If bleeding persists despite adequate levels of Factor VIII, then transfuse Cryoprecipitate (10-20 iu units FVIII per kg) or Random platelet concentrate (1 concentrate per 10 kg).

5 HAEMOPHILIA B

The clinical picture of Haemophilia B is identical to that of Haemophilia A, and the levels required are similar to those of Haemophilia A, although slightly lower levels of Factor IX are usually adequate for normal haemostasis. Factor IX has a longer half-life than Factor VIII (up to 24 hours) and therefore only daily doses may be required. For prolonged therapy (> 5 days) a pure Factor IX concentrate is preferable since prolonged Factor IX complex transfusion has been reported to lead to thrombosis. The reports however only refer to concentrates manufactured outside South Africa. There have been no reports of thrombosis with the local product. When haematological monitoring is available the number of Factor IX units required may be calculated from the following formula:

$$\text{Factor IX dose} = \text{Patient's Mass (kg)} \times \text{Desired increase in Factor IX} \times 1.2$$

Table 13: Haemophilia B target factor levels

PRODUCT	VOLUME	FREQUENCY
Haemosolvex Factor IX	10 ml after reconstitution with sterile water for injection	Factor IX has a half life of 24 hours so daily doses may be required

If monitoring is not available, give 10-20 iu/kg as a daily or twice daily dose regime. Do not give in conjunction with Cyclokapron® or Amicar®.

6 HYPOFIBRINOGENAEMIA

Table 14: Hypofibrinogenemia treatment guidelines

PRODUCT	TYPE OF DEFICIENCY	
Cryoprecipitate: Each unit has 150-200 mg fibrinogen 10 units = 1,5-2,0 g	Acquired	
	As in cases of abruptio placenta, and massive transfusion syndrome	2-6 g per average adult
	Congenital.	4-8 Cryoprecipitate
		units will raise the fibrinogen level to homeostatic levels effective for

7 OTHER PLASMA PRODUCTS

a) *Albumin 20% Solution*

Prepared by fractionation of a large pool of plasma. The process involves steps like pasteurisation and cold ethanol fractionation, which inactivates viruses such as HIV and hepatitis virus.

Table 15: Indications for albumin

APPROPRIATE	OCCASIONAL	UNJUSTIFIED.
<ul style="list-style-type: none"> • Burns • Replacement fluid following paracentesis and therapeutic plasmapheresis • Shock 	<ul style="list-style-type: none"> • Acute liver failure • Acute renal failure • Ascites • Hypoproteinaemia after surgery • Renal dialysis 	<ul style="list-style-type: none"> • Under nutrition • Cirrhosis • Chronic renal failure

PRACTICAL NOTE:

Volume expansion in acute hypovolaemia is more appropriately obtained using crystalloid or synthetic colloid solutions.

In a dehydrated patient it is inappropriate to use 20% Albumin solution as a volume expander. If a physiological albumin solution is required then add 100 ml 20% albumin to 400 ml saline or Ringers lactate. There is a 4% product available from NBI.

In thermal burns the early restoration of fluid volume is best achieved with crystalloids. Albumin may be given 8-12 hours after the onset of the burn

Dosage:

- i. Calculate the patient's plasma volume from the following formula

$$PV = \text{body weight (kg)} \times 0,04$$

- ii. Calculate the number of grams of albumin required for a particular patient as follows:

$$\text{Dose} = \text{Desired Albumin level (g/dl)} - \text{Actual Albumin level (g/dl)} \times \text{plasma volume (l)} \times 2^*$$

*Since half the albumin transfused will diffuse into the extravascular compartment it is necessary to use this multiplication factor to achieve the desired intravascular levels.

Products available.

- i. 4% Albumin in 8 g/200 ml and 16 g/400 ml bottles (NBI).
- ii. 20% albumin in 20 g/100 ml, 10 g/50 ml bottles (WPBTS, NBI).

NOTE:

Assess carefully before administering to any patient with known hypersensitivity to human proteins.

b) Stabilised Human Serum

Stabilised Human Serum is prepared from large pools of donor plasma that is subjected to:

- i. Selective absorption of lipoprotein, coagulation factors, and complement components.
- ii. Reduction of viral content by the above processes and by ultra violet irradiation.
- iii. A heat treatment step that is licensed as a validated viral inactivation procedure for HIV.
- iv. The resultant stable protein solution contains a wide and constant spectrum of antibodies in the IgA, IgM and IgG classes, many of the transport proteins, and albumin. It provides an ideal physiological volume

Table 16: Composition of stabilised human serum

COMPOSITION	PER LITRE	PER 250 ML
Total protein	50 g	12,5 g
Albumin	30 g	7,5 g
Na ⁺	120 mmol	30 mmol
K ⁺	3 mmol	0,75 mmol
Ca ²⁺	2 mmol	0,5 mmol
Cl ⁻	100 mmol	25 mmol

expander in volumes equivalent to that lost.

Usage

- i. Burns.
- ii. Hypovolaemia.

Administration

- i. Adults: Intravenous transfusion to a dosage of up to 8 units of 250 ml per 24 hours.
- ii. Children: 3-6 ml per kg per 24 hours.

Side effects

- i. Transient urticarial reactions.
- ii. Pyrexia.
- iii. Rigors.
- iv. Hypotension.

Treatment of side effects

Stop transfusion, and administer antihistamines, prednisone, or hydrocortisone either intramuscularly, or intravenously, depending on the severity of the symptoms.

IMPORTANT:

Do not give to any patient with a known sensitivity or allergy to human protein solutions.

8 IMMUNOGLOBULIN THERAPY

Immunoglobulin is the antibody-containing fraction of human plasma that is obtained by the fractionation of pooled plasma units, all of which have been tested and found non-reactive for HBsAg, anti-HCV, anti-HIV and p24 HIV antigen. Specific hyperimmune immunoglobulin preparations are prepared from plasma from donors with high titres of specific antibodies. The manufacturing process per se for immunoglobulins has virucidal effects and preparations used and manufactured in South Africa have never been reported to transmit hepatitis or HIV. More

Table 17: Indications for intravenous immunoglobins

INDICATION
Agammaglobulinaemia
Immunosuppressed patients
Kawasaki disease
Idiopathic thrombocytopenic purpura

recently introduced intravenous products contain specific viral inactivation steps for lipid enveloped viruses.

PRACTICAL NOTE:

Anaphylactic reactions may occur if an intramuscular product is used intravenously.

Anaphylactic or severe allergic reactions may occur if the patient suffers from IgA deficiency, or has experienced a previous severe reaction to human protein product.

Table 18: Intramuscular immunoglobulin preparations

PRODUCT	COMPOSITION	INDICATION	DOSE
Hebagam IM (Human hepatitis B immunoglobulin)	100 iu/ml	Post exposure prophylaxis	
	2 ml ampoule	Needle-stick injury Mucosal exposure Sexual exposure	>10 years 500 iu 5-9 years 300 iu <5 years 200 iu Treat preferably within 48 hours, and not more than 7 days after exposure. Repeat after 28 days unless recipient has been shown to be immune or has received hepatitis B vaccine
		Newborn babies born to HBsAg positive mothers (especially those who are HBeAg positive)	Treat preferably at birth, and definitely within 48 hours after birth Dose 200 iu

Table 18 continued: Intramuscular immunoglobulin preparations

PRODUCT	COMPOSITION	INDICATION	DOSE
Intragam (Human normal immunoglobulin IM)	2 ml and 5 ml ampoules	Hepatitis A prophylaxis	
		1. Post-exposure prophylaxis:	
		Within one week of household contact	0,02-0,04 ml/kg
		2. Travellers to endemic areas:	
		visit <3 months	0,02 ml/kg
		Visit >3 months continued exposure	0,06 ml/kg every 4-6 months
		Measles prophylaxis	
		Within one week of contact	0,2-0,25 ml/kg (max. 15 ml)
		Susceptible immunocompromised children	0,5 ml/kg (max. 15 ml)
		Replacement therapy	
		Congenital immunoglobulin deficiencies	0,2-0,5 ml/kg repeat every 4-8 weeks
		Transient hypogammaglobulinaemia	0,2-0,5 ml/kg repeat when necessary
Rabigam IM (Human rabies immunoglobulin)	150 iu/ml 2 ml ampoule	Post-exposure prophylaxis Known or suspected exposure to the rabies virus in conjunction with the rabies vaccine	20 iu/kg Infiltrate half the dose into the wound where anatomically feasible and the remainder as a deep IM injection
Rhesugam IM (Human anti-D(Rh ₀) immunoglobulin)	500 iu (100 µg) per 2 ml ampoule	Prevention of Rh disease	500 iu
Tetagam IM (Human tetanus immunoglobulin)	125 iu/ml 2 ml ampoule 500 iu/ml 1 ml ampoule	Post-exposure prophylaxis patients >10years	250 iu. If more than 24 hours since injury use 500 iu
		Treatment of clinical tetanus	3000-6000 iu as a single dose
Vazigam IM (Human varicella zoster immunoglobulin)	100 iu/ml 2 ml ampoule	Post-exposure prophylaxis in high risk patient Administer within 96 hours of the exposure	< 5 years: 2 ml 6-10 years: 4 ml 11-14 years: 5 ml >15 years: 6 ml

Table 19: Intravenous immunoglobulin

PRODUCT	COMPOSITION	INDICATION	DOSE
Polygam	1 g/50 ml (2% solution)	Replacement therapy	100-400 mg/kg
(Lyophilised	3 g/100 ml (3% solution)	for primary antibody	at monthly intervals
human normal	6 g/200 ml (3% solution)	deficiency syndromes	
immuno- globulin IV)	12 g/400 ml (3% solution)	Adjunctive therapy in the prevention of infections in secondary antibody deficiency For immunomodulation in ITP and Kawasaki disease	400 mg/kg/day for 5 days or 1-2 g/kg as a single dose