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Guidelines for the clinical use of blood cell separators

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Summary These Guidelines outline standards of care for the clinical use of cell separators for both patients and donors.

Keywords Cell separators, apheresis, donor apheresis, paediatric apheresis

The following points are recommended:

Clinical management

1 Clinical decisions regarding the use of cell separators are the responsibility of a medical consultant (or equivalent). Nursing care and responsibilities must adhere to Principles for Adjusting the Scope of Practice (United Kingdom Central Council for Nursing, Midwifery & Health Visiting1992).
2 Informed consent should be obtained from patients (relatives or guardians) and donors.
3 Selection of patients and donors, and their pre-donation medical and laboratory assessment is the responsibility of a medical officer familiar with the use of cell separators. Particular care must be taken in the selection of volunteer donors (related and unrelated) to ensure that they fulfil the appropriate UK Guidelines for selection of donors and that no undue pressure is put upon them to donate.
4 Paediatric patients require special care and should only be selected and managed in close co-operation with medical and nursing staff trained in the clinical assessment and management of children.

General care and management of complications

1 Apheresis procedures involve certain risks to donors/patients. All staff responsible for donor/patient care during apheresis must be aware of the more common complications and be trained to identify when they occur.
2 Staff must also be trained in how to avoid common complications and also in their management should they occur. Problems with vascular access, reactions to citrate, reactions to replacement fluids and chilling are the commonest complications.
3 Paediatric patients and those with renal disease, liver disease, sickle cell disease or immunosuppresion are more prone to problems, extra care must be taken when treating these patients.
4 Staff proficiency in the operation of cell separators and the identification and management of patient/donor complications during apheresis procedures must be maintained by regular use of equipment.

Post-donation care

1 Care of the donor/patient must include observation in the immediate post-apheresis period to minimize the occurrence of delayed complications.
2 A record of any post-apheresis complications must be made and of the length of time for which observations were made.

Facilities

1 Cell separators should be operated in an area reserved exclusively for their use.
2 Adequate space must be provided for routine working and for cardiopulmonary resuscitation.
3 Facilities must comply with Good Manufacturing Practise regulations and with other relevant Guidelines. Appropriate facilities for the management of potentially infective patients must exist.

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Staff

1 Staff responsible for cell separator procedures must be trained to the highest standards of proficiency in the use of all appropriate equipment. Documentary evidence that training has been undertaken must be kept.

2 Staff involved in patient care must be trained in cardiopulmonary resuscitation to include the use of resuscitation equipment retained on site and they must hold a valid certificate as evidence of appropriate training.

Machine safety

1 Care should be taken to ensure that cell separators and other associated equipment conform to relevant British and European safety requirements.

2 Regular servicing should be undertaken according to manufacturers recommendations and service records must be kept.

Introduction

These guidelines replace Guidelines for the Clinical Use of Blood Cell Separators (1991) and supplement the Guidelines for Automated Apheresis of Volunteer donors within the UK Blood Transfusion Service (1996).

Since the 1991 Guidelines for the clinical use of blood cell separators were published there has been an increase in the clinical use of cell separators for the treatment of a greater variety of clinical conditions (Rock *et al.* 1996) and to collect a greater range of therapeutic products. Cell separator technology has also undergone a considerable evolution, which has permitted the introduction of new procedures such as photopheresis and immunadsorption. Donors can now donate a variety of therapeutic products during a single procedure. A wide range of patients including sicker patients is now being actively treated. It is therefore important that careful consideration is given to the likely clinical conditions to be treated, the most suitable type of equipment to use, and the appropriate training of staff when setting up a cell separator service.

These guidelines for the clinical use of cell separators apply both to patients and volunteer donors.

Patient procedures include:

- Cytapheresis; the removal of white cells (progenitor cells, lymphocytes and granulocytes), platelets and red cells (which may be part of an exchange procedure).
- Plasmapheresis (plasma exchange) with or without immunadsorption columns.
- Photopheresis.

Donor procedures include:

- Cytapheresis; the removal of white cells (progenitor cells, lymphocytes and granulocytes), platelets and red cells.
- Plasmapheresis.
- Or any combination of the above.

1 Clinical management of a cell separator service

Clinical decisions regarding the use of cell separators for both patients and volunteer donors are always the responsibility of a medical consultant (or equivalent). In view of the known risks and complications associated with the use of cell separators appropriate medical/nursing staff must always be in attendance (Guidelines for Automated Apheresis of Volunteer Donors within the UK Blood Transfusion Service 1996). Nursing responsibility must adhere to the Principles for adjusting the Scope of Practice (UKCC 1992). The Department of Health has also issued Guidance Notes on the on the Processing, Storage and Issue of Bone Marrow and Blood Stem Cells (1997).

1.1 Informed consent

The routine of obtaining written informed consent from patients and donors represents good clinical practice and is a requirement of the Guidelines for Automated Apheresis of Volunteer Donors (1996) (see Appendix 2 for suggested consent forms). Clearly written explanatory literature must be available to assist in obtaining informed consent. This should include information about any drugs or replacement fluids, which may be used.

1.2 Selection of donors

Donors should be accepted according to the advice given on the selection, medical examination and care of apheresis donors in the Guidelines for Automated Apheresis of Volunteer Donors (1996). First-time donors should not be under 50 kg in weight and they should, preferably, have given at least one routine blood donation without untoward effect within the last 2 years. Occasionally truly first-time donors may be accepted if they are specifically motivated, for example friends, relatives or hospital volunteers, but they must fulfil the remaining criteria for suitability. Normally donors should be recruited from the Blood Transfusion Service donor panels and requests for such unrelated donors should be made to the local blood centre.

For platelet donations, the donors should not have taken any aspirin or other platelet-active drugs for an appropriate period. For aspirin, this is 5 days, but for other drugs this may be shorter.

Care must be taken that undue pressure is not put on

persons to donate, particularly if they are related to the patient or are an HLA matched donor. Donors must not be placed in a position where it is difficult for them to discontinue making further donations although they wish to stop.

Patients or related donors may fail to meet the criteria laid down by the UK Blood Transfusion Service for acceptance as an apheresis donor (Guidelines for Automated Apheresis of Volunteer Donors 1996). The consultant in charge of the unit or his/her deputy must make the final decision regarding an individuals suitability as a donor.

1.3 Medical examination

1.3.1 Patients The doctor in charge of the procedure must ensure that the patient is fit to undergo the procedure and particular account should be taken of pulse and blood pressure, cardiorespiratory status and whether any severe autonomic neuropathy is present.

A record must be made in the patient's case notes of all these findings.

Certain laboratory investigations should be performed before and after all procedures. These investigations are to ensure not only the efficacy of the procedure undertaken but also the patient's well being.

A full blood count should be undertaken to monitor red cell and platelet loss during apheresis procedures in order that replacement transfusion can be instituted as appropriate.

Mandatory microbiological screening tests (Guidelines for the Blood Transfusion Service 1996) should be undertaken on a sample collected at the time of donation, or a few days prior to donation, if a product is being collected for subsequent transfusion, such as progenitor cells. Currently informed consent for HIV testing is required.

A coagulation profile (to include at a minimum a prothrombin time (PT) and activated partial prothrombin time (APPT)) as a baseline assessment is important for certain groups of patients, particularly those undergoing plasma exchange. This is done to indicate whether a pre-existing coagulopathy is present as this may influence the choice of replacement fluid.

Baseline biochemistry to include electrolyte measurement is of especial importance in renal patients and paediatric patients who are more prone to electrolyte disturbances during apheresis.

Plasma viscosity, immunoglobulin levels or specific antibody levels may need to be measured regularly, if they are implicated in the patients pathology, as an important part of assessing efficacy of apheresis. Similarly total white cell count, differential white cell count and CD34+ cell count may need to be measured in order to determine the timing of peripheral progenitor cell collections.

1.3.2 Donors A medical examination should be carried out, preferably by the medical officer who obtains informed consent.

A doctor who does not have primary care responsibilities for the patient to whom the donation will be given should ideally undertake this examination. This examination is to ensure that the donor meets the required standard of health as laid down by the Guidelines for Automated Apheresis of Volunteer Donors (1996).

If there is clinical suspicion of cardiorespiratory disease (as indicated by the donor's history and/or the clinical examination) a specialist opinion should be sought.

Mandatory microbiological screening tests (Guidelines for the Blood Transfusion Service 1996) must be performed on all volunteer donors.

Baseline biochemistry, full blood count, coagulation screen and immunoglobulins may be measured. A CD34+ cell measurement may be required to optimize progenitor cell collection.

The results should be within the normal range for the age and sex of the donor.

Before white cell collections (granulocytes, lymphocytes, progenitor cells) ABO/RhD typing must be performed and donor/patient compatibility must be assessed. A red cell cross match must be performed if major ABO incompatibility is present and if donor/patient incompatibility is detected some form of red cell depletion may be required in order to avoid a haemolytic transfusion reaction.

1.4 Frequency and volume of procedures

1.4.1 Patients The consequences of multiple apheresis on patients must be considered whenever repeated procedures are required. Few medical conditions require more than five consecutive days apheresis and usually fewer procedures are necessary during the first week of treatment. The volume of plasma removed during a plasma exchange should be related to the patient's estimated plasma volume. Each procedure normally involves a 1–1.5 times plasma volume exchange, which in an adult usually involves a 2–4 litre exchange per procedure.

Peripheral blood progenitor cell collections should be timed for individual patients depending on their peripheral white count response to growth factor administration. To harvest sufficient progenitor cells for engraftment between 10 and 15 L of blood needs to be processed. Sufficient progenitor cells are often collected from a single procedure but

for some patients two or more daily collections may be required.

A worksheet should be kept of the details of each procedure. Special note must be made of any adverse patient reactions (see Appendix 1).

1.4.2 Donors Recommendations regarding frequency, volume and duration of donor apheresis procedures are laid out in Guidelines for the Blood Transfusion Service (1996) and should be adhered to. Donors should not regularly donate plasma more often than once a fortnight. A donor should not generally undergo a total of more than 24 plateletpheresis procedures per annum and not more than 12 leucopheresis procedures per annum. There should normally be a minimum of 48 h between procedures and a donor should not normally undergo more than two procedures within a 7 day period. Not more than 15 litres of plasma should be donated by one donor in a year.

For any single donor apheresis procedure, the final collection volume should not exceed 15% of the total blood volume excluding anticoagulant.

Donors should have a full blood count, total serum proteins and serum albumin measured when they first attend for apheresis and annually thereafter. A system should be in operation for regular review of these results together with a documented protocol of the action to be taken in the light of any abnormal findings.

1.5 Special considerations for paediatric patients

Advances in cell separator technology and an increase in the number of clinical indications for apheresis has led to an increase in the applicability of apheresis procedures for children mainly in the field of peripheral blood progenitor cell collections.

1.5.1 Informed consent The nature of the procedure must be explained to the parents/guardian and informed consent obtained on behalf of the child (see consent form Appendix 2).

There may be unusual extenuating circumstances when it may be considered necessary for a child to undergo apheresis as a donor (e.g. for a life-threatening event in a sibling or parent). There are major ethical concerns regarding the role of children as 'volunteered' donors, thus it is highly recommended that advice is sought from a local Ethics Committee.

1.5.2 Medical examination Children should be assessed prior to the procedure by medical staff trained in the clinical assessment of children. These staff must be available throughout the procedure.

All apheresis procedures undertaken on children should take place in an area with full paediatric resuscitation equipment and personnel trained in its use must be available.

1.5.3. Volume and access considerations It is recommended that only continuous flow cell separators with minimal extracorporeal volume are used in children. These machines require high flow rates and therefore good venous access. In some children, typically over the age of 10 years, it may be possible to use bilateral antecubital fossa venous access. This may be facilitated by the use of local anaesthetic creams. However, if repeated procedures are anticipated, or in very small children, insertion of a central venous double lumen catheter will be required. Hazards associated with the use of these catheters are outlined below (see Vascular access) and raise further ethical problems in 'volunteered' donors.

Children who weigh less than 30 kg will require the apheresis extracorporeal lines to be primed with homologous donor blood which should have a haematocrit similar to the patient. Compatibility testing must be undertakena and CMV status of the child must be taken into account. Irradiation of this donor blood is required during peripheral progenitor cell collections for both autologous and allogeneic transplant (Guidelines on Gamma Irradiation of Blood Components 1996). For children under one year of age this blood will also require leucodepletion (BCSH Transfusion Task Force 1997).

During lengthy procedures and particularly when replacement fluids are infused it is essential that these fluids (cellular or otherwise) are warmed to prevent complications such as central body cooling or sickling in susceptible patients.

In small children (under 30 kg) it is important to be aware that electrolyte disturbances (hypocalcaemia and hyperkalaemia) may occur and that if repeated procedures are necessary, depletion of plasma proteins, in particular coagulation factors, may also occur.

Recommendation. Clinical decisions regarding the use of cell separators are the responsibility of a medical consultant (or equivalent). Nursing care and responsibilities must adhere to Principles for Adjusting the Scope of Practice (UKCC 1992). Informed consent should be obtained from patients (relatives or guardians) and donors. Selection of patients and donors, and their pre-donation medical and laboratory assessment is the responsibility of a medical

officer familiar with the use of cell separators. Particular care must be taken in the selection of volunteer donors (related and unrelated) to ensure that they fulfil the appropriate UK Guidelines for selection of donors and that no undue pressure is put upon them to donate. Paediatric patients require special care and should only be selected and managed in close co-operation with medical and nursing staff trained in the clinical assessment and management of children.

2 General care during apheresis procedures

Apheresis procedures involve certain risks to donors/patients these include problems related to anticoagulant use, replacement fluids, fluid and electrolyte imbalance, vascular access, haemolysis, air embolus and infection (Westphal 1984). There is a mortality rate associated with therapeutic apheresis of three per 10 000 patients (Huestis 1983). Staff, therefore, must be trained to the highest standards of proficiency in the operation of apheresis equipment and the care of patients/donors during all procedures. The equipment must be used regularly so that staff proficiency in its operation and care is maintained.

Patients and donors should never be left in a room without the attendance of an appropriately trained member of staff. Procedures on children should be undertaken in a designated paediatric area with appropriately trained medical/nursing staff and with paediatric resuscitation facilities.

2.1 Vascular access

The safest venous access is by repeated venepuncture, most commonly of antecubital fossa veins. This is the only way currently permitted for venous access in healthy donors. In some patients peripheral venous access is not practicable and some form of venous catheter will need to be inserted. This should only be undertaken in accordance with current Guidelines on the Insertion & Management of Central Venous Lines (1997) the major recommendations of which are included in Appendix 3. Related volunteer donors may also occasionally require a central line to be inserted for harvesting. This should be done in accordance with the above guidelines and informed consent, specifically for line insertion, should be obtained as part of the procedure.

There are currently a variety of catheters suitable for venous access for apheresis procedures (Table 1). Some catheters are only suitable for emergency procedures, as they are designed to be used only once, or for a short period of time, have a single lumen and are not able to sustain the high flow rates needed for cell separator use. Dual lumen catheters can be left *in situ* for between 5 days (Vascath) and several months (Apheresis Hickman catheter) and are suitable for progenitor cell harvesting. Patency of long-term indwelling catheters can be maintained by instilling Heparin (1000 u/ml (Hepsal)or 5000u/ml) after each use, daily or once or twice weekly, according to manufacturer's instructions, if the line is not in regular use. This Heparin 'lock' must always be discarded when next accessing the catheter.

2.2 Drugs and infusion fluids

It is recommended that the choice of drugs and other substances given to donors/patients should be restricted. Anticoagulants used should be citrate based, acid citrate dextrose (ACD) and sodium citrate being used most frequently. Heparin is used for some procedures. Replacement fluids that may be used include dextran, hydroxyethyl starch, modified fluid gelatin, Haemaccell and crystalloids. Human albumin solutions, FFP and human red cells are also sometimes used usually as part of an exchange procedure. Predosage of donors with corticosteroids to enhance the yield during granulocyte collections is sometimes undertaken. Records of cumulative dose of corticosteroids should be kept for each donor. Recombinant growth factors (G-CSF) are not currently licensed for stimulating granulocytes prior to collection from donors but have been used for this purpose in ethically approved clinical trials.

The use of all drugs and replacement fluids should conform with recommendations outlined in the appropriate data sheet (ABPI Compendium of Data Sheets 1996).

Staff working in cell separator units, with responsibility for patient care must have knowledge of the side-effects of the constituents of the fluids and drugs they are using and also any drugs patients may be already taking which may affect the apheresis procedure, e.g. ACE inhibitors.

The use of fresh frozen plasma (FFP) should conform to current guidelines (Guidelines for the Use of Fresh Frozen Plasma 1992).

Recombinant growth factors (GCSF) are routinely used for patients to stimulate peripheral progenitor cell release and improve collection efficiency. They should be used in accordance with local guidelines and manufacturer's recommendations. Growth factors have also been used for related donors, with local ethical committee approvals, to stimulate peripheral progenitor cell release prior to collection and use for allogeneic transplant. Currently these growth factors cannot be used for unrelated volunteer donors although this is under review.

Table 1. Examples of catheters used for venous access This list is not comprehensive, other catheters are available.Mention of specific trademark names does not represent an endorsement of any given catheter

Maker	Gauge	Lumen	Wall	Duration of use	Position	Indication
BARD	Vascath 10.8Fg	Double	Thick	5 days	IVC, SVC femoral veins	PBSCH, PEX, RBCEX
	Hickman 13.5 Fg	Double	Thick	Months	Tunnelled into SVC	PBSCH, PEX, RBCEX
Terumo Medical Corp.	16Fg	Single backeye needle	Thin	Single use	Antecubital fossa	Single use emergency
Cooke	12Fg	Double Hickman	Thick	Months	Tunnelled into SVC	PBSCH, PEX, RBCEX
Vygon Dualyse catheter	12Fg	Double	Thin	5 days	IVC, SVC femoral veins	PBSCH, PEX, RBCEX
Kimal	8Fg,12.5Fg,15Fg	Double	Medium	Years	SVC	PBSCH, PEX, RBCEX
Ohmeda Venflon	16Fg,14Fg	Single	Thin	Single use	Antecubital fossa	Single use emergency

IVC, Inferior vena cava. PBSCH, Peripheral blood stem (progenitor) cell harvest. PEX, Plasma exchange. RBCEX, Red blood cell exchange. SVC, Superior vena cava.

2.3 Management of complications

Any complications that develop during apheresis procedures (see Table 2) should be treated appropriately. The consultant in charge of apheresis must make recommendations for appropriate treatment with clear indications as to what action must be taken by medical and/or nursing staff.

2.3.1 Anticoagulants (Table 2)

Citrate toxicity This has been recorded in up to 15% of procedures and can lead to cardiac arrrhythmias (Sutton *et al.* 1989). The development of toxicity depends on a variety of factors including the concentration of citrate anticoagulant used, the concentration of citrate in the replacement fluid, the rate of citrate infusion and patient susceptibility. Citrate acts by chelating calcium ions and symptoms are due to hypocalcaemia and include circumoral paraesthesiae, muscle twitching, nausea and/or vomiting, chills, syncope and tetany (rare). Chilling of the patient/donor exacerbates the symptoms of citrate toxicity.

Severe hypocalcaemia can occur without any of the above warning symptoms.

Avoidance • The patient/donor should be warned about symptoms and asked to report any immediately. Oral calcium supplements before/during the procedure may prevent the development of hypocalcaemia

• Use the manufacturers' recommended anticoagulant at the correct ratio to comply with Guidelines for the Blood Transfusion Service (1996).

• If different citrate formulations are to be used, it is essential to monitor the citrate levels in the return line to the patient/donor and to monitor ionized calcium levels in the patient/donor to ensure the maximum citrate dose rate is not exceeded. Advice on the need to undertake such monitoring should be sought from the manufacturer of the cell separator to be used.

• If patient susceptibility is suspected, for example impaired renal or liver function, reinfuse at a slow rate and monitor for signs of hypocalcaemia.

Treatment It is safer to correct hypocalcaemia by stopping or slowing the reinfusion rate than to infuse concentrated calcium solutions – hypercalcaemia induced in this way can be as dangerous as hypocalcaemia. Calcium gluconate 5 ml of 10% given slowly intravenously can be used for the treatment of serious citrate reactions where clinical and electrocardiographic evidence of hypocalcaemia exists and then only under medical supervision (Guidelines on Collection, Processing and Storage of Human Marrow and Peripheral Stem Cells for Transplantation 1994).

Inadequate citration If inadequate levels of citrate are achieved, this may lead to clotting in the extracorporeal cell separator circuit. This may result in either the reinfusion of material with procoagulant activity and potentially precipitate disseminated intravascular coagulation (DIC), or

Table 2. Patient/donor complications associated with use of cell separators

Subject	Sign/symptom	Possible cause	Possible management
Vascular access	High Return Pressure	Haematoma	Check tubing for kinks
	Low Access Pressure	Kink in tubing	Check position of valves
		Valves in closed position	Adjust or resite access or return line
		Vascular inadequacy	Reduce inlet flow
			Stop procedure
Delivery of anti-coagulant	Significant tingling/numbness	Citrate toxicity	Decrease citrate infusion rate
	Hypotension		Pause/stop procedure
	Nausea/vomiting		Consider administration of calcium (oral/IV)
	Fasciculation/carpo-pedalspasm/tetany		
	Unstable interface during PBSC	Under anti-coagulation	Check tubing for kinks
			Increase AC: inlet ratio
	Gross clotting evident		Stop procedure
Fluid balance	Increased blood pressure	Fluid overload	Operate at a negative fluid balance
	Dyspnoea		Stop procedure
	feeling faint	Vasovagal	
	Hypotension	Hypovolaemia	Operate at a positive fluid balance
			Increase colloid: crystalloid ratio
Chilling	Decrease in donor/patient Temp	Cold environment	Increase room temperature
	Decrease access pressure		
	Patient/donor complains of cold	Cold replacement fluids	Use blood warmer
Transfusion Reaction	Urticaria	Plasma products	Administer antihistamine and/or hydrocortisone
			Stop procedure
	Increased patient/donor temperature	Incompatible transfusion	Stop procedure
	Shock	Septicaemia	
	Bronchospasm	Anaphylaxis	
	Rigor		

cause haemolysis in the cell separator leading to reinfusion of haemolysed blood.

Avoidance • Use the manufacturer's recommended anti-coagulant at the correct ratio.

• Monitor the anticoagulant pump, the rate of delivery via the drip chamber and the volume of anticoagulant used throughout the procedure to ensure constant correct delivery of anticoagulant.

• Monitor the separation chamber of the return line filter for evidence of clotting. Also monitor the return line for evidence of negative pressure which can be an early indicator of clotting within the circuit.

• Monitor the colour of the separated plasma for evidence of haemolysis.

Adverse reactions to heparin These include bleeding, allergy/anaphylaxis, thrombocytopenia, dyspnoea and abdominal pain.

If protamine is used to reverse heparin, the following adverse reactions can occur: chills and light headedness, allergy and/or anaphylaxis, dyspnoea and/or chest pain, and flushing.

Because of these adverse reactions and the prolonged effect of heparin, citrate is recommended as the anti-coagulant of choice for most cell separator procedures and the use of heparin in normal donors should be avoided.

2.3.2 Replacement fluids The following materials have been used alone or in combination for fluid replacement in therapeutic exchange procedures:

Human albumin solution 4.5%
Fresh frozen plasma (FFP)
Whole blood and/or packed cells
Volume expanders, e.g. modified fluid gelatin (MFG), hydroxyethyl starch (HES)
Haemaccel, Dextran, Crystalloids, e.g. saline, Hartmans solution.

No therapeutic materials should be added to HAS, blood or other blood products.

For plasma exchange procedures the choice of replacement fluid depends on the frequency and volume of the exchange procedure and the underlying disorder. However, in all patients it is important to maintain adequate levels of protein during the procedure as inadequate protein replacement can rapidly lead to hypovolaemia and hypotension.

Procedures can be done safely for most patients with a mixture of crystalloid, colloid, albumin, depending on the patient's condition. If plasma exchange is to be performed more than once a week, the volume of the exchange is 1.5 × plasma volume, and replacement fluid is part crystalloid part albumin, the patients albumin levels as well as levels of other plasma proteins progressively fall.

If replacement fluid is albumin solution only, the patient's albumin levels will be maintained, but there will be a progressive fall in levels of coagulation factors (including fibrinogen and antithrombin III), immunoglobulins, complement and cholinesterase.

Reduction in coagulation factors can lead to bleeding episodes, particularly if there is a potential bleeding point, for example recent renal biopsy. This will be enhanced if heparin is used as the anticoagulant.

Reduction in antithrombin III levels may predispose to thrombo-embolic episodes post exchange, and also reduces the effectiveness of heparin.

Reduction in cholinesterase levels can lead to prolonged periods of apnoea in response to the muscle relaxant suxamethonium used in general anaesthesia or precipitate a myasthenic crisis.

If volume expanders are used as part replacement, certain problems should be recognized.

(i) Fluid overload precipitating congestive cardiac failure in the susceptible patient.

(ii) Allergic reaction, particularly with dextrans.

(iii) Haemaccel has a high concentration of calcium and should not be mixed with citrated blood as this could produce clotting in the reinfusion blood line.

FFP should not be used as a replacement fluid except in the management of thrombotic thrombocytopenic purpura (TTP). Intensive plasma exchange using coagulation factor-free replacement fluids results in progressive reduction in plasma coagulation factors but FFP should only be used to correct these abnormalities when abnormal bleeding occurs. There are certain adverse effects associated with the use of FFP that may prove hazardous if used inappropriately for plasma exchange, these include the following (and see also Table 2):

(i) Allergic reactions. Urticaria has been reported in 1–3% of patients. Life-threatening anaphylaxis is reported as occurring in 1 in 20 000 transfusion episodes. (Bjerrum & Jersild 1971).

(ii) Transfusion transmitted infection. The risk of infection with human immunodeficiency virus (HIV), hepatitis B and C, and parvovirus following a transfusion of FFP is similar to that following the transfusion of red cells. Two forms of virally inactivated FFP (solvent detergent, Octaplas, Octapharma, Vienna and methylene blue treated FFP, UK BTS) are expected to become available during 1998 and may be used as a replacement fluid to reduce these risks. FFP has not been implicated in cytomegalovirus (CMV) transmission (Bowden R and Sayers M. 1990) nor in transfusion acquired graft vs host disease.

(iii) Haemolysis. ABO incompatible plasmas may contain potent anti-A or anti-B that can cause lysis of recipient cells. FFP of the same ABO group as the recipient should be used whenever possible and if group O FFP has to be used for non-O recipients it must have been screened to exclude donations from high titre anti-A and anti–B group O donors.

(iv) Transfusion related acute lung injury (TRALI) may result from potent donor antibodies to patient granulocytes (Nordhagen *et al.* 1986).

(v) Immune suppression resulting from plasma infusion has also been reported (Blumberg & Heal 1988).

Adverse effects can be minimized by adhering to current Guidelines for the Use of Fresh Frozen Plasma (1992). Major reactions to FFP, such as TRALI, must be reported to the Serious Hazards of Transfusion Office (SHOT Office, Manchester Blood Centre, Plymouth Grove, Manchester M13 9LL).

2.3.3 Fluid and electrolyte balance problems (Table 2) Selection of the type and amount of replacement fluid is an important consideration when undertaking therapeutic plasma exchange (Sutton, Nair & Rock1989). Cytapheresis procedures do not usually require replacement fluids and are therefore not usually complicated by problems associated with their use.

Hypervolaemia This is most commonly seen in renal patients

and can be controlled by maintaining the albumin level and finishing the exchange with the patient in a negative fluid balance. Any plasma exchange must, however, always aim to replace a minimum of 75% of the patient's total calculated plasma volume. Patients with hyperviscosity are often already hypervolaemic and care must be taken in performing plasma exchange on these patients especially when they are anaemic as changes in their haematocrit can acutely change the total blood viscosity and precipitate a hyperviscosity crisis (Beck *et al.* 1982).

Hypovolaemia This is avoided by using protein containing solutions for replacement. In paediatric patients where the extracorporeal volume of the circuit exceeds 12% of the total blood volume a whole blood prime should be used to avoid hypovolaemia. (see paediatric section).

Electrolytes Problems resulting from abnormalities of calcium homeostasis are the most frequently encountered electrolyte disturbance associated with the use of cell separators. They result primarily from the use of citrate containing anticoagulants. The resulting hypocalcaemia is most commonly seen in patients who have severe liver dysfunction, those receiving citrated fresh frozen plasma and during procedures such as T lymphocyte collection where there is a high citrate:blood ratio (Silberstein *et al.* 1986). Management of this problem is discussed under the section concerning anticoagulation.

Other electrolyte abnormalities are uncommon apart from in patients with renal disease who have pre-existing abnormalities. In these cases it is possible to alter the electrolyte composition of the exchange fluid as appropriate.

Children are particularly prone to electrolyte disturbances (see special considerations for paediatric apheresis).

2.3.4 Chilling (Table 2) Rapid reinfusion without using a blood warmer can cause 'chilling' and rigors. Chilling also increases the problems of hypocalcaemia. Certain groups of patients are more prone to complications associated with chilling.

These include patients with:
Sickle cell disease
Paraproteinaemia
Cold haemagglutinin disease
Cryoglobulinaemia
Paediatric patients

Haemolysis, gelling or agglutination may occur in the extracorporeal circuit in these conditions. It is important therefore in these groups of patients to use a blood warmer to:

Warm all solutions used for priming
Warm all replacement fluids
Warm any reinfused blood

and also to increase the temperature of the working environment.

Blood warmers are mechanical devices for warming fluids being returned to the donor/patient to minimize chilling. A variety of different commercially produced blood warmers are available. Such devices must comply with BS 5724 Part 1. Safety of Electrical Equipment (1979, 1989) and BS EN 60601–1 – (1993). They must be operated and maintained according to manufacturer's instructions.

2.3.5 Complications of vascular access (Table 2)

Peripheral venous access Peripheral access may be associated with haematoma formation, bruising and occasionally nerve damage. Poor vascular access may require resiting of the venepuncture or abandonment of a procedure. Careful explanations must be given to the donor/patient when these complications occur and appropriate medical management must be undertaken.

Central venous access The use of central venous catheters can be associated with well described complications and these complications lead to the majority of fatalities associated with apheresis (Sutton *et al.* 1989). Subclavian/superior vena caval catheters can be associated with vessel perforation, haemothorax, pneumothorax, infection and thrombosis. The use of femoral catheters can be associated with the occurrence of haemorrhage, thrombosis and infection.

2.3.6 Haemolysis (Table 2) Forcing blood by pump through a narrow orifice particularly when blood is concentrated to a high haematocrit, may result in haemolysis. Inadequate anticoagulation is also associated with haemolysis.

Avoidance • All the software must be carefully examined prior to setting up the machine to ensure there are no kinks or twists in the tubing.

• Constant observation of the colour of the plasma to detect for the presence of haemolysis.

• When using filtration machines, constant monitoring of the transmembrane pressure is essential and particular care taken if frequent episodes of low flow occur, as in this situation haemolysis is more likely to occur.

If haemolysis is suspected the procedure must be terminated as the return of damaged red cells to the patient/donor could precipitate DIC and mimic a haemolytic transfusion reaction.

2.3.7 Air embolus Most cell separators incorporate air detector devices in the reinfusion line. However, with the use of blood warmers and other software beyond the machine's air detectors, there is a risk of air embolism if all the lines are not fully primed.

Never rely totally on 'fail/safe' alarm systems. Occasionally they can fail and constant monitoring of all reinfusion lines is necessary to prevent air embolism from occurring.

2.3.8 Infection

Equipment contamination Do not leave cell separators and associated equipment primed for longer than necessary and not for more than one hour prior to use.

Bacterial infection If bacterial contamination has occurred during the set-up and priming procedure, there is a risk of causing a severe bacteraemia, which could be fatal in an immunosuppressed patient. Plasma exchange using crystalloid, colloid or albumen as replacement fluid depletes the patient's immunoglobulin level. The combination of low immunoglobulins and immunosuppressive therapy predisposes the patient to infection. Prophylactic administration of intravenous immune globulin to patients particularly at risk should only be considered under special circumstances.

Recommendation. Apheresis procedures involve certain risks to donors/patients. All staff involved in donor/patient care during apheresis must be aware of the more common complications and be trained to identify them when they occur. Staff must also be trained in how to avoid common complications and also in their management should they occur. Problems with vascular access, reactions to citrate, to replacement fluids and chilling are the commonest complications. Paediatric patients and those with renal disease, liver disease, sickle cell disease or imunosuppresion are more prone to problems, extra care must be taken when treating these patients. Staff proficiency in the operation of cell separators and the identification and management of patient/donor complications during apheresis procedures must be maintained by regular use of equipment.

3 Post donation care

It is important to ensure as far as possible that all donors/patients take the required amount of rest and drink at least one cup of fluid before leaving the apheresis venue and if no adverse reactions have occurred, this information is noted in the relevant notes.

Any adverse reaction must be dealt with promptly, appropriately and sympathetically and must be documented. The patient/donor must have recovered as fully as possible before being allowed to leave the venue.

The nurse/doctor in charge must remain on the unit until the last donor/patient has left the premises.

Recommendation. Care of the donor/patient must include observation in the immediate post-apheresis period to minimize the occurrence of delayed complications. A record of any post-apheresis complications must be made and of the length of time for which observations were made.

4 Facilities

4.1 Accommodation

Ideally, cell separators should be operated in an area reserved exclusively for this work though patients and donors can be managed in the same area. This area should be adequate to allow a cardiac arrest team to operate. There should be sufficient space to allow for staff to operate all equipment without danger to themselves, patients and donors. All cell separator units where products for subsequent transfusion are collected, such as platelets, peripheral blood progenitor cells, lymphocytes or granulocytes, must comply with guidelines for good manufacturing practice (Rules and Guidance for Pharmaceutical Manufacturers & Distributors 1997). Collection and storage of progenitor cells must comply with current Guidelines (1994) and with Department of Health recommendations (1997). Each cell separator unit must have adequate space for patients/donors to rest and be monitored following a procedure, particularly if there have been any adverse reactions.

All procedures must be undertaken with resuscitation facilities available, as agreed by a consultant in charge of a hospital cardiac arrest team. Staff must be trained in cardiopulmonary resuscitation and in the use of the available equipment.

Patients categorized as 'high risk' from the point of view of infection should be managed in collaboration with a local control of infection officer. Local guidelines must be observed to minimize risk of transmission of infection. Advice from manufacturers may need to be obtained regarding appropriate decontamination procedures for apheresis equipment used for such patients.

Recommendation. Cell separators should be operated in an area reserved exclusively for their use.

Adequate space must be provided for routine working and for cardiopulmonary resuscitation. Facilities must comply with Good Manufacturing practise regulations and with other relevant Guideline recommendations. Appropriate facilities for the management of potentially infective patients must exist.

5 Staff

5.1 Training

The Consultant in charge of the unit has responsibility for establishing a programme for initial and continued training of the apheresis staff to ensure an appropriate level of proficiency. Training may take place at a site other than an apheresis unit and may be supervised by a trainer qualified in assessment but the Consultant in charge of the unit and his/her Nurse Manager/Sister must be satisfied that the content of the training is appropriate.

The Consultant in charge of the apheresis unit in consultation with the Nurse Manager or sister in charge of the unit must be satisfied that the appropriate training has been completed before allowing staff to carry out apheresis procedures.

In the absence of a nationally recognized training programme, a suitable comprehensive training programme (3–6 months) should be devised in conjunction with the appropriate machine manufacturers and opportunities provided for regular updating (e.g. study days, conferences, etc.). Training should be done in accordance with standard operating procedures and cover aspects of donor/patient care, operation of machines and trouble shooting, recognition and management of adverse effects. Training in cardiopulmonary resuscitation (CPR) must be undertaken on a regular basis using recognized trainers, a valid CPR certificate must be held by staff who perform patient apheresis procedures.

A suitable assessment designed to determine the level of competence of such staff must be performed and documentation of knowledge and technical ability (training records) must be kept and updated annually.

Recommendation. Staff responsible for cell separator procedures must be trained to the highest standards of proficiency in the use of all appropriate equipment. Documentary evidence that training has been undertaken must be kept. Staff involved in patient care must be trained in cardiopulmonary resuscitation to include the use of resuscitation equipment retained on site and they must hold a valid certificate as evidence of appropriate training.

6 Machine safety

Numerous types of cell separators are now available, but all operate on either a continuous or an intermittent flow principle allowing rapid return of citrated blood.

These systems consist of a device that will carry out whole blood separation, normally using a disposable apheresis set and a citrate and/or heparin anticoagulant solution. Such an integrated system withdraws blood from the donor/patient, mixes it with anticoagulant in the required ratio, separates and collects the component selected, safely returning the remaining blood components to the donor/patient.

The machine shall comply with the relevant aspects of the Health and Safety at Work Act. Additionally such machines must comply with the requirements of British Standard BS 5724: Part I: Safety of Medical Electrical Equipment (1979) and BS EN 60601–1-(1993).

6.1. Machine maintenance

Cell separator machines should be serviced in accordance with manufacturers' instructions. A planned maintenance scheme should be followed.

Machine maintenance and servicing must be in accordance with procedures outlined in Equipment information HEI.98 Management of Medical Equipment, Devices (1990).

Apheresis machines should be routinely cleaned with a suitable decontaminating agent. A standard procedure for dealing with blood spillage must be in operation.

In the event of a mechanical failure of the machine, a service engineer should be able to be contacted by telephone during normal working hours.

Recommendation. Care should be taken to ensure that cell separators and other associated equipment conform to relevant British and European safety requirements. Regular servicing should be undertaken according to manufacturers recommendations and service records must be kept.

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Appendix 1: Guidelines for operators outlining standards of care for patients and donors undergoing blood cell separation

A consultant fully experienced in the operation of cell separators has overall responsibility for the health and welfare of patients/donors, and for the observance of the codes of practice.

Registered general nurses are responsible for nursing care aspects and for preparation and operation of the cell separator.

The nurse in charge has responsibility for:

The physical and psychological needs of the patient/donor

Making sure that support facilities are available and functioning

Completing a comprehensive record/work sheet

Making sure there is instruction on post-procedural care and subsequent follow-up of patient/donor.

Standards and monitoring required to prevent complications

The clinical hazards associated with procedures and the avoidance of such complications are clearly outlined in this document.

To minimize operational errors, the following should apply:

1 Information required with reference to specific patient/donor management.

(a) The physical and psychological condition of the patient/donor

(b) Any associated nursing care required

(c) The basic parameters required to establish the total blood and plasma volume: height, weight and Haematocrit (relevant to the volume to be removed or exchanged and the anticoagulant ratio to be used).

(d) The details of current drug therapy, particularly anticonvulsants, antiarrhythmics and steroids. It may be necessary to modify drug regimens or to give supplemental doses to maintain the desired drug concentration in the blood, especiallywhen large quantities of plasma are to be removed.

(e) If there is a history of cardiac valvular diseases, specialist advice about antibiotic prophylaxis should be sought.

2 A standard operating procedure (SOP) must be available for the machine in use. It should include a detailed description of all procedures likely to be undertaken.

The SOP must clearly lay out details of the following:

- Maintenance of donor/patient records and care plans.
- Checking and prescribing required for drugs, anticoagulants and intravenous solutions also recording all batch numbers of harnesses, packs, intravenous solutions and local anaesthetic (if used).
- A description of the complications which may arise during the procedure and the corrective and preventive action to be taken. This should include details of the following:

(a) Procedures to be undertaken in the event of a respiratory

or cardiac arrest and application of the techniques involved and the equipment in use
(b) Procedures following accident or untoward incident
(c) Action in the event of fire or bomb alert.

A list of appropriate laboratory tests for the procedure concerned so that advice concerning intervention or adjustment to treatment can be sought.

Appendix 2: Donor consent form (cell separators)

1 I .....(full name)

of .....(full address) hereby acknowledge that I have volunteered to donate blood by means of a cell separator. The nature and purpose of the donation of blood by this means and the risks involved to the donor have been explained to me by:

Dr .....*

I hereby consent to the donation of ..... by means of a cell separator and I agree to undergo medical assessment which will also involve giving a sample of my blood for tests including a test for HIV/AIDS. I consent to such further or alternative operative measures or treatment as may be found necessary during the course of the donation.

Signature of volunteer donor .....

Date.....

2 I confirm that I have explained the nature and purpose of this procedure to the person who signed the above form of consent.

Signature of doctor .....

Date.....

*The explanation must be given by a medical practitioner.

Appendix 2. Patient consent form

Please check and complete the following personal details.

SURNAME
FORENAME
ADDRESS

POST CODE
DATE OF BIRTH

CASE SHEET NUMBER.....

To be completed by Patient/Guardian/Parent/Next of Kin

I am the patient/guardian/parent/next of kin (delete where appropriate). I understand the procedure ....., which has been explained by Dr ..... I understand that this will involve the use of a cell separator machine and the infusion of anticoagulant solution whilst blood is being processed. Any other procedure in addition to that named above, will be performed if it is necessary and in the best interests of myself/my child/my next of kin (delete where appropriate).

I agree to the administration of local anaesthetic or to sedation if required.

I agree to the procedure named on this form.

Signature: ..... Date:.....

NAME (Block Caps): .....

To be completed by the Medical Practitioner
I have fully explained to the patient/parent/guardian/next of kin:
1 The procedure named on the consent form
2 Alternatives which are available
3 The significant side effects of this form of therapy

Signature: ..... Date:.....

NAME (Block Caps): .....

Appendix 3: Guidelines on the insertion and management of central venous lines

Major recommendations

1 Tunnelled central venous lines (catheters) are indicated for the repeated administration of chemotherapy, antibiotics, parenteral feeding and blood products, and for frequent blood sampling.

2 Single lumen catheters can be used but additional peripheral access will usually also be required.

3 Fully implantable catheters (ports) are more suitable for children and for less frequent but long-term use, while non fully implantable lines are better for short-term use and intensive access.

4 Insertion should be performed by experienced operators, regardless of speciality. Lines should be inserted in children by paediatric specialists.

5 Imaging facilities (fluoroscopy, intravenous contrast studies and standard radiography) must be available.

6 Line insertion should take place in an operating theatre or similar clean environment.

7 Skin cleansing is of utmost importance.

8 Routine antibiotic prophylaxis should not be used.

9 Dressings are not required in the long term but regular flushing (by protocol according to the type of line) is essential to avoid thrombosis.

10 Pre-existing haemorrhagic, thrombotic or infective problems must be effectively managed before line insertion.

11 Thrombosis and infection must be promptly diagnosed and vigorously treated. Both complications may require removal of the line.

12 Catheters should only be removed by experienced personnel. Catheter breakage requires expert radiological intervention.

13 Patients should receive clear and comprehensive verbal and written information and be encouraged to look after their own lines.

14 Units should audit complications associated with central lines and should use the data to develop preventative measures.