TRANSFUSION MEDICINE
Official Journal of the British Blood Transfusion Society
British Blood Transfusion Society
Transfusion Medicine | GUIDELINES

Guideline on the clinical use of apheresis procedures for the treatment of patients and collection of cellular therapy products

C. Howell,[1] K. Douglas,[2,3] G. Cho,[4] K. El-Ghariani,[5] P. Taylor,[6] D. Potok,[7] T. Rintala[8] & S. Watkins[9]

[1]*Diagnostic & Therapeutic Services, NHS Blood and Transplant, Bristol, UK,* [2]*Beatson West of Scotland Cancer Centre, Glasgow, UK,* [3]*Scottish National Blood Transfusion Service, Glasgow, UK,* [4]*London North West Healthcare NHS Trust, Harrow, UK,* [5]*Therapeutics & Tissue Services, NHS Blood and Transplant, Sheffield, UK,* [6]*The Rotherham NHS Foundation Trust, Rotherham, UK,* [7]*Diagnostic & Therapeutic Services, NHS Blood and Transplant, Leeds, UK,* [8]*Kings College Hospital, London, UK, and* [9]*Cardiff & Vale NHS Trust, Cardiff, UK*

Received 12 March 2015; accepted for publication 21 April 2015

INTRODUCTION

The guideline group was selected to be representative of relevant UK-based medical and nursing experts. Systematic literature searches were conducted between September to December 2012 using MEDLINE, OVID PLUS and EMBASE for publications in English, using keywords: plasma exchange; apheresis; exchange transfusion; extracorporeal photopheresis; lipoprotein apheresis; leucocytapheresis; peripheral blood stem cells (PBSC); peripheral blood progenitor cells (PBPC) and other relevant keywords related to the subsections of this guideline. Relevant recent publications e.g. guideline documents, which came to the attention of the group subsequent to December 2013, were also included in the following discussion with the full writing group.

The draft guideline was reviewed by a sounding board of British haematologists, the BCSH and the British Society for Haematology Committee. The 'GRADE' system was used to quote levels and grades of evidence, details of them can be found at http://www.bcshguidelines.com.

GUIDELINE UPDATE

This guideline is an update to the archived BCSH guideline on the clinical use of cell separators (BCSH Joint Working Party, 1998). The scope has been extended into a comprehensive description of best practise in Clinical Apheresis. The objective of this guideline is to provide healthcare professionals with clear guidance on the use of clinical apheresis.

In 2014, clinical apheresis is a distinct subspecialty overlapping Haematology, Transfusion Medicine and Renal Medicine (Weinstein, 2007), with more procedures being carried out (Stegmayr *et al.*, 2005) and more procedures taking place outside the UK Transfusion Services, such as allogeneic and autologous haemopoietic progenitor cells–apheresis (HPC-A; also known as peripheral blood stem cells or PBSC) collections carried out by Haematology teams, plasma exchange undertaken by Nephrology teams on dialysis equipment, and the development of extracorporeal photopheresis (ECP) as a treatment for graft-versus-host disease and cutaneous T-cell lymphomas. There has also been a move towards 'evidence-based apheresis medicine', with publication of guidelines by the American Society for Apheresis (ASFA) (Schwartz *et al.*, 2013), American Academy of Neurology (AAN) (Cortese *et al.*, 2011) and the 'Kidney Disease: Improving Global Outcomes' group (KDIGO Work Group, 2012). Although these are helpful, the AAN and KDIGO guidelines cover only a few specific indications for plasma exchange. The ASFA guidelines take the form of an extensive alphabeticised list of indications with broad treatment recommendations; some aspects of clinical management of patients/donors undergoing apheresis, and of management of the service as a whole are not considered in detail.

A new guideline is therefore required to address clinical apheresis as practised in the UK. The 1998 BCSH guideline focused on procedures carried out on 'cell separators' (i.e. excluding plasma exchange carried out on renal dialysis equipment) and included collection of donor plasma, platelets and red cells by apheresis, which are excluded from the current guideline, as best practise is described elsewhere by separate publications within the UK Transfusion Services. The remit of the current guideline, covering all plasma exchange regardless of equipment used, all therapeutic procedures undertaken on cell separators, and any autologous or allogeneic donor apheresis

Correspondence: BCSH Secretary, British Society for Haematology, 100 White Lion Street, London, N1 9PF, UK. Tel.: 020 7713 2093; fax: 020 7837 1931; e-mail bcsh@b-s-h.org.uk

First published online 27 May 2015
doi: 10.1111/tme.12205

for procurement of cellular therapy products such as HPC-A, reflects a more contemporary definition of 'Clinical Apheresis'.

SUMMARY OF KEY RECOMMENDATIONS

Recommendations

- Therapeutic apheresis should be carried out only where there is published evidence of efficacy or, occasionally, in very rare conditions whose pathophysiology predicts efficacy.
- Solvent detergent fresh frozen plasma (SD-FFP) should be used as replacement fluid for plasma exchange in thrombotic thrombocytopenic purpura (TTP); otherwise 4.5% or 5% human albumin solution (HAS) should generally be used.
- Patients undergoing a course of plasma exchange should have fibrinogen levels monitored.
- Initiation of apheresis for HPC-A (PBSC) collection should be based on flow-cytometric peripheral blood CD34+ count monitoring, with a count of 10 μL^{-1} being generally recommended as the minimum threshold.
- Before initiating a course of apheresis procedures, clinical assessment and laboratory results must be documented and a written treatment plan should be produced.
- Trusts should identify a single individual as an apheresis lead, regardless of whether apheresis services are provided internally or by another organisation.
- The Lead Clinician of the apheresis service must ensure implementation of a Quality Management Programme to cover all activities undertaken by the service.

INDICATIONS AND TECHNICAL ASPECTS FOR THERAPEUTIC APHERESIS AND PROCUREMENT OF CELLULAR THERAPY PRODUCTS

Plasma exchange

Indications for plasma exchange. Plasma exchange is used to treat diseases caused by pathogenic antibodies or other macromolecules found in the plasma, or more rarely by albumin-bound small molecules (drugs or toxins) that remain predominantly intravascular. The use of plasma exchange should be evidence-based, while recognising the difficulty of conducting randomised controlled trials (RCTs) in apheresis medicine and the resultant lack of RCT data for many conditions. The main indications for plasma exchange, with associated published evidence, are well set out in the ASFA, AAN and KDIGO guidelines and are summarised in Table 1 below. The ASFA guidelines grade indications as Category I (strong evidence for first-line plasma exchange), Category II (strong evidence for second-line plasma exchange) or Category III (some evidence for second-line plasma exchange).

Recommendations

1. Plasma exchange is the main treatment in TTP and can be life-saving. It must be initiated as soon as possible, ideally within 4 h of presentation (1A).
2. Plasma exchange is indicated for conditions listed as Category I (first-line) or Category II (second-line) in the current version of the American Society for Apheresis guidelines (1A to 1C depending on condition).
3. Plasma exchange may be used as second- or third-line treatment for conditions listed as Category III in the current version of the ASFA guidelines, or for unlisted conditions where removal of a pathogenic antibody makes biological sense providing there is no published evidence that plasma exchange is ineffective or detrimental in the condition in question (1C).
4. Plasma exchange should not be used for conditions where published evidence suggests lack of benefit or harm, such as ASFA Category IV conditions (1B).

Technical aspects of plasma exchange. Exchange volume and frequency: Mathematical modelling of the removal of macromolecules such as antibodies by plasma exchange indicates that the optimum treatment volume for each procedure is 100–150% of the patient's plasma volume (Chopek & McCullough, 1980). To avoid excessive hypofibrinogenaemia while maximising removal of the target macromolecule, many centres initially perform a run of five exchanges at 100% plasma volume at daily or alternate-day intervals for the majority of indications, avoiding weekend days unless there is clinical urgency. Exceptions when more intensive exchange regimes are necessary include: TTP; anti-glomerular basement membrane (GBM) disease; prophylaxis and treatment of solid organ transplant rejection due to anti-ABO or anti-HLA antibodies and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides. In these situations, more intensive regimes are recommended: details are summarised in Table 1. In Waldenström macroglobulinaemia, less intensive plasma exchange may be appropriate (Table 1).

Maintenance plasma exchange is generally not recommended except in certain situations for hyperviscosity or cryoproteinaemias (Table 1), and for a few other rare indications as discussed in the ASFA guidelines (Schwartz *et al.*, 2013). Occasionally, maintenance of plasma exchange may be indicated in antibody-mediated conditions that are refractory to drug therapy or where patients are intolerant of drug therapy; in such situations, the frequency of exchanges may vary from once every 2 weeks to once every 6 weeks, guided by symptoms and (where available) by measuring levels of the target molecule or other objective measurements of the patient's condition.

In certain clinical situations, it may be desirable to reduce a patient's antibody levels very rapidly to as low a level as feasible. In such circumstances, novel column-based extracorporeal immunoadsorption technologies are now available as an alternative to standard centrifugation or filtration plasma exchange,

Table 1. Ten most frequent indications for plasma exchange, with suggested treatment regimes

Indication	Suggested regime (UK consensus)	Replacement fluid	Relevant publications
TTP or atypical HUS	Treat as emergency: aim to initiate apheresis within 4 h of presentation. Daily plasma exchange until platelet count is normal for three consecutive days. Treat by 150% plasma volume exchange until evidence of response, and then reduce to 100% plasma volume.	SD-FFP ONLY	Scully *et al.* (2012)
Myasthenia gravis	For myasthenic crisis: five exchanges (100% plasma volume) at daily or alternate-day intervals. For *stabilisation before thymectomy or other surgery*: three to five exchanges at alternate-day intervals; minimum 48-h gap between last plasma exchange and surgery to allow fibrinogen recovery.	4.5% or 5% HAS	Schwartz *et al.* (2013); Cortese *et al.* (2011); Gajdos *et al.* (2003)
Guillain-Barré syndrome	Five exchanges (100% plasma volume) at daily or alternate-day intervals.	4.5% or 5% HAS	Schwartz *et al.* (2013); Cortese *et al.* (2011); Raphael *et al.* (2002)
Anti-GBM disease (Goodpasture's syndrome)	No benefit from plasma exchange if already dialysis-dependent and no evidence of pulmonary haemorrhage.	4.5% or 5% HAS – but consider FFP for last litre of exchange if patient has pulmonary haemorrhage or has had a recent renal biopsy.	Schwartz *et al.* (2013); KDIGO Work Group (2012); Levy *et al.* (2001)
	If evidence of pulmonary haemorrhage, or if still dialysis-independent, 10 exchanges (100% plasma volume) over 14 days at daily or alternate-day intervals; first three procedures at daily intervals		
	Avoid plasma exchange for 24 h after renal biopsy, to reduce haemorrhagic risk.	Consider FFP for whole exchange if life-threatening pulmonary haemorrhage.	
ANCA-associated vasculitis	Seven to eight exchanges (100% plasma volume) at daily or alternate-day intervals over 10–12 days.	4.5% or 5% HAS – but consider FFP for last litre of exchange if patient has pulmonary haemorrhage or has had a recent renal biopsy.	Schwartz *et al.* (2013); KDIGO Work Group (2012); Jayne *et al.* (2007)
	Avoid plasma exchange for 24 h after renal biopsy, to reduce haemorrhagic risk.	Consider FFP for whole exchange if life-threatening pulmonary haemorrhage.	
ABO-incompatible (ABOi) living donor renal transplantation	Daily to alternate-day exchanges (100 to 150% plasma volume) for *recipient* pre-transplant until anti-A/anti-B antibody titre falls to a pre-determined threshold, usually 1:4 to 1:8 depending on centre and protocol. Low-dose IV immunoglobulin usually given after each plasma exchange. Consider use of column technology (Glycorex® or Therasorb®) to increase efficiency of antibody removal. Centres carrying out ABOi renal transplantation should develop detailed local written desensitisation protocols, incorporating the use of plasma exchange	4.5% or 5% HAS. Fibrinogen levels must be adequate for surgery at the time of transplant.	Schwartz *et al.* (2013); Wilpert *et al.* (2007); Tydén *et al.* (2007); Magee (2006); Morath *et al.* (2012)

Table 1. continued

Indication	Suggested regime (UK consensus)	Replacement fluid	Relevant publications
Antibody-mediated rejection in association with renal transplant, due to donor-specific HLA antibody (DSA)	*Prophylaxis prior to living-donor transplant for recipient with donor-specific antibody:* Daily to alternate-day exchanges (100–150% plasma volume) for recipient pre-transplant until DSA titre falls below a pre-determined threshold. Low-dose IV immunoglobulin usually given after each plasma exchange. Centres carrying out ABOi renal transplantation should develop detailed local written desensitisation protocols, incorporating the use of plasma exchange *Treatment of rejection post-transplant*: five to six exchanges initially (100–150% plasma volume) over approximately two weeks; often Monday/Wednesday/Friday. Ongoing treatment may be guided by improvement in renal function and/or decrease in donor-specific antibody titres. Consider low-dose IV immunoglobulin after each plasma exchange, and additionally consider rituximab therapy. Renal transplant centres should develop detailed local written protocols. Avoid plasma exchange for 24 h after renal biopsy, to reduce haemorrhagic risk.	4.5% or 5% HAS – but consider FFP for last litre of exchange if recent renal biopsy.	Schwartz *et al.* (2013); Faguer *et al.* (2007); Magee (2006)
Cryoproteinaemias (cryoglobulinaemia or cryofibrinogenaemia)	Five exchanges (100% plasma volume) initially, over approximately two weeks, for patients with acute symptoms e.g. digital or limb ischaemia. Maintenance plasma exchange may be indicated along with immunosuppressive medication, particularly for patients with an ongoing risk of critical digital or limb ischaemia, at a frequency guided by symptoms.	4.5% or 5% HAS	Schwartz *et al.* (2013); Auzerie *et al.* (2003)
Waldenström macroglobulinaemia with symptomatic hyperviscosity	One to three exchanges (100% plasma volume) initially, weekly to twice-weekly, generally as bridging therapy while definitive cytoreductive therapy takes effect, or to reduce IgM levels prior to rituximab therapy. Chemotherapy-refractory patients may require maintenance plasma exchange, at a frequency guided by symptoms and by plasma viscosity (trying to maintain pre-apheresis viscosity results below 4.0 mPa where possible).	4.5% or 5% HAS	Schwartz *et al.* (2013); Johnson *et al.* (2006); Bjorkholm *et al.* (2003)
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Five to six exchanges initially (100% plasma volume), over two weeks. Maintenance treatment is used by some centres and makes biological sense, but published evidence for efficacy is limited.	4.5% or 5% HAS	Schwartz *et al.* (2013); Cortese *et al.* (2011); Mehndiratta *et al.* (2004)

From NHSBT and SNBTS data on referrals for plasma exchange in England and in Scotland respectively, 2010–2013. Note that this is not an exhaustive list of indications. For full details of additional accepted indications for plasma exchange, see ASFA guidelines (Schwartz *et al.*, 2013).

particularly in the context of ABO-incompatible kidney transplantation (Tydén *et al.*, 2007; Morath *et al.*, 2012). However, it is noted that no randomised comparisons with standard plasma exchange have been published and centres choosing to use these technologies should therefore carry out their own risk assessments on comparative efficacy, safety and cost-effectiveness.

Recommendations

1. For TTP, at least daily plasma exchange should be performed until the platelet count has been normal for three consecutive days, with exchange volume being 150% plasma volume initially and reducing to 100% plasma volume on clinical response (1A). In occasional patients with very severe TTP, plasma exchange may be required twice a day initially.
2. For anti-GBM disease, ANCA-associated vasculitides, prophylaxis and treatment of solid organ transplant rejection due to anti-ABO or anti-HLA antibodies and Waldenström macroglobulinaemia, specific advice on plasma exchange regimes is given in Table 1.
3. For prophylaxis and treatment of solid organ transplant rejection due to anti-ABO or anti-HLA antibodies, Transplant Units should establish detailed local written protocols for plasma exchange based on ASFA guidelines and other published evidence (1B).
4. For most other indications (see Table 1 and ASFA guidelines for exceptions), an initial series of five exchanges at 100% plasma volume is recommended at daily or alternate-day intervals (1C).

Replacement fluid. Except for TTP and related thrombotic microangiopathies in which SD-FFP must be used as the sole replacement fluid for plasma exchange (Scully *et al.*, 2012), 4.5% to 5% HAS is the most widely-used replacement fluid for plasma exchange in the UK (UK Transfusion Services, unpublished data) and also worldwide (Weinstein, 2010). In contrast to crystalloids such as 0.9% normal saline, HAS maintains the patient's whole blood viscosity and physiological albumin levels. Some centres also use crystalloid solutions as partial replacement fluid for plasma exchange, to reduce cost and minimise blood product exposure, but there is a lack of published data to demonstrate equivalent safety to HAS, and the incidence of vasovagal faints may be increased (Shemin *et al.*, 2007). Use of a combination of 5% HAS with Gelofusine as replacement fluid may also be considered: if this approach is adopted, careful ongoing surveillance of safety and efficacy is recommended.

Dilutional coagulopathy resulting in hypofibrinogenaemia can be a particular concern if intensive plasma exchange is performed on patients with a pre-existing haemorrhagic risk (e.g. pulmonary haemorrhage; recent renal biopsy), or in ABO-incompatible renal transplantation if plasma exchange is performed shortly before surgery. For such patients, fibrinogen levels must be monitored carefully during a course of plasma exchange, and FFP may be used as part of the replacement fluid (Schwartz *et al.*, 2013). Standard FFP may generally be used, but for patients who are expected to require more than 50 units of FFP in total to support a course of plasma exchange, SD-FFP may be preferred for reasons of prion safety (this is the reason for the recommendation to use SD-FFP in TTP; Scully *et al.*, 2012). Alternatively, cryoprecipitate may be administered *after* plasma exchange to maintain fibrinogen levels above $1.0\,g\,L^{-1}$ (Duguid *et al.*, 2004). For patients without specific risk factors for haemorrhage, extending the interval between plasma exchanges may prevent hypofibrinogenaemia, and is acceptable providing that it is not likely to affect the patient's overall outcome.

Recommendations

1. For TTP, atypical haemolytic uraemic syndrome (HUS) and related thrombotic microangiopathies, Solvent-Detergent-treated Fresh Frozen Plasma (SD-FFP, Octaplas®) must be the sole replacement fluid for plasma exchange (1A).
2. For other indications, 4.5% or 5% HAS is generally the preferred replacement fluid (2C).
3. Alternative colloid solutions such as Gelofusine may be used for patients who are allergic to HAS or who have a religious objection to blood products (2C).
4. Patients undergoing a course of plasma exchange treatment should have fibrinogen levels monitored (1B).
5. Patients undergoing plasma exchange who are at significant risk of haemorrhage (e.g. recent kidney biopsy or pulmonary haemorrhage) should have fibrinogen levels maintained above $1.0\,g\,L^{-1}$ either by the use of FFP as partial replacement fluid for plasma exchange or by the use of cryoprecipitate after plasma exchange (1B).
6. Drugs which are albumin-bound, or any drugs given by continuous intravenous infusion, may be removed by plasma exchange to a substantial extent. The referring clinician should be made aware of this, to allow dosage adjustment as appropriate. Any intravenous medications should be given post-procedure where possible (1B).

Red cell apheresis

Indications for red cell apheresis. Sickle cell disease (SCD) is the main indication for red cell apheresis. Transfusions in sickle cell disease can be used in emergency situations or electively, and may be either top-up or exchange transfusions. Exchange transfusions may be carried out by apheresis or manually. Apheresis red cell exchange has several advantages over manual exchange transfusion, primarily being more effective in preventing transfusional iron overload. Self-evidently, apheresis red cell exchange is also much less likely to lead to transfusional iron overload for patients requiring regular transfusions, compared to top-up transfusion. Other advantages include faster HbS reduction during acute events, and longer gaps between transfusions for patients on a chronic transfusion programme (Swerdlow, 2006).

Emergency red cell exchange is primarily used in SCD, most commonly in acute chest syndrome (ACS) (Vichinsky *et al.*,

2000), although it is used in other severe acute complications including sickle stroke. Initial top-up transfusion should be used for patients with severe anaemia or a significant drop in steady state haemoglobin concentration. The early institution of exchange transfusion for severe ACS is accepted as best practise, particularly in children (Velasquez *et al.*, 2009), although short-term outcomes may not be superior to standard transfusion in adults (Turner *et al.*, 2009). Standard top-up transfusion to reduce HbS percentage cannot be used if the patient's haemoglobin is within or above the normal range, as this will lead to hyperviscosity.

Acute stroke in SCD can be treated with initial top up transfusion if the patient is severely anaemic, but urgent exchange transfusion lowers the risk of subsequent stroke compared to top-up transfusion. Patients with thrombotic stroke should receive regular blood transfusion, ideally exchange, to keep the HbS percentage below 30% indefinitely (Sickle Cell Society, 2008).

For other life-threatening events in SCD, evidence from controlled trials is limited. Emergency exchange transfusion is indicated in severe sepsis, acute hepatic sequestration (Ahn *et al.*, 2005), acute multi-organ failure (Hiran, 2005) and progressive intrahepatic cholestasis (Sickle Cell Society, 2008). Preparation for urgent surgery may also be an indication (NHS SCTSP, 2010; Howard *et al.*, 2013).

Emergency red cell exchange has also been used in severely ill malaria patients and in babesiosis (Schwartz *et al.*, 2013) and occasionally together with anti-D immunoglobulin to reduce Rh(D) sensitisation risk following erroneous large-volume transfusion of Rh(D) positive blood to a Rh(D) negative female child or woman of childbearing years (Laspina *et al.*, 2005).

Elective red cell exchange in SCD may be considered for primary stroke prevention (Adams *et al.*, 1998; Lee *et al.*, 2006), secondary stroke prevention (Scothorn *et al.*, 2002; Hulbert *et al.*, 2006), elective surgery (Vichinsky *et al.*, 1995; Howard *et al.*, 2013), patients with severe disease who have not responded to or cannot take hydroxycarbamide, and painful crises in pregnancy (Sickle Cell Society, 2008).

Red cell exchange in severely ill *malaria* patients with hyperparasitaemia (>10%) may be clinically useful according to case reports and case series publications. A meta-analysis did not find survival benefit from *manual* exchange transfusion compared to antimalarials and aggressive supportive care alone (Riddle *et al.*, 2002). UK treatment guidelines for malaria suggest that exchange transfusion may be considered after discussion with an expert in the management of malaria in patients with hyperparasitaemia (>30% red blood cells parasitized) or >10% parasitaemia and other manifestations of severe disease (Lalloo *et al.*, 2007).

In *polycythaemia vera* the use of *automated erythrocytapheresis* ('isovolaemic haemoreduction') corrects hyperviscosity by lowering the haematocrit. Therapeutic erythrocytapheresis may be preferable to large volume venesection in some situations such as the haemodynamically unstable patient, for elective pre-operative reduction when cytoreductive therapy has been suboptimal, or for emergency pre-operative preparation. Erythrocytapheresis has also been used in haemochromatosis (Grabmer *et al.*, 2014).

Technical aspects of Red Cell Apheresis. Red cell units should be sickle test negative, crossmatch compatible and antigen-negative for any clinically significant red cell antigens against which the patient has antibodies. Units should also be fully Rh and K compatible (Vichinsky *et al.*, 2001). Extended red cell antigen phenotypic matching (LaSalle-Williams *et al.*, 2011) is not currently recommended, though all patients should have an extended red cell phenotype prior to being transfused. Red cell genotyping can be performed if the patient has already received blood, and has the advantage of detecting Rh variants. It is preferable to use red cell units with as short a time interval from donation as possible (less than 8 days) due to longer half-life and therefore more lasting HbS reduction, as well as avoidance of hyperkalaemia, particularly in small children, although comparative studies on this point are currently lacking (Sickle Cell Society, 2008). The aim in the acute setting should generally be to reduce post-procedure HbS levels to below 30% (Schwartz *et al.*, 2013), typically requiring 8–10 red cell units for an adult for those on a long-term programme. It is important to consider the option of automated depletion exchanges (available on modern cell separator platforms), as this can decrease blood exposure while maintaining clinical and laboratory outcomes (Quirolo *et al.*, 2014).

Recommendations

1. Indications for Red Cell Apheresis include complications of sickle cell disease such as acute chest syndrome with hypoxaemia (1B), severe sepsis (1C), acute hepatic sequestration (1C), acute multi-organ failure (1C), progressive intrahepatic cholestasis (1C), primary stroke prevention (1A) and secondary stroke prevention (1B) and acute stroke (1C). In SCD it is also acceptable in preparation for elective surgery (1B) and by extrapolation prior to urgent surgery (2C), and where hydroxycarbamide use is contraindicated or has failed (1C).
2. Other potential indications are: exchange transfusion in severely ill malaria patients (1C) and in babesiosis (1C); isovolaemic haemoreduction in polycythaemia vera and erythrocytosis (1C) and in hereditary haemochromatosis (1C).
3. Red cell apheresis is a better option where transfusional iron overload from simple (top up) transfusions or manual exchange could be expected to be a problem (1B).
4. For exchange transfusion in sickle cell disease, in addition to standard transfusion requirements, red cells should be fully ABO, Rh and K compatible (1B). The red cells should be sickle test negative and less than 8 days old if possible (1C).

Extracorporeal photopheresis

Definition. Extracorporeal photopheresis (ECP) involves collecting a small proportion (5%) of a patient's mononuclear cells

by apheresis, exposing them to ultraviolet (UV) A light in the presence of psoralen, and re-infusing them.

The current methods for delivery of ECP use 'closed' or 'open' systems. Open ECP necessitates collection of a buffy coat on a cell separator, separation of the buffy coat from the system and subsequent UVA irradiation in a separate device, before reinfusion to the patient. By contrast the closed system incorporates an internal UVA source in the apheresis device with no separation of the buffy coat from the device, before return to the patient. While the open system has the potential advantages of increased cell dose and the ability to manipulate the cells further, there is an increased risk of microbial contamination with this technology. The closed system devices have integrated mononuclear cell collection and 8-methoxypsoralen/UVA irradiation, and regulatory approval for treating patients (Wong, 2012).

Indications for extracorporeal photopheresis. Cutaneous T-cell lymphomas (CTCL): ECP has been shown, in a large number of clinical studies, to be an effective treatment with induction of remission in early and late stages of mycosis fungoides and Sézary syndrome. ECP is a recommended therapy for erythrodermic CTCL in several guidelines, including the European Organisation for the Treatment of Cancer (EORTC) mycosis fungoides/Sézary guidelines and the Joint British Association of Dermatology and UK Cutaneous Lymphoma Group guidelines. The latter is endorsed in the Improving Outcomes Guidance in Skin Cancer by NICE (2011). Several US bodies have also endorsed ECP for CTCL (Whittaker *et al.*, 2003; Trautinger *et al.*, 2006; National Comprehensive Cancer Network, 2011; Olsen *et al.*, 2011; National Cancer Institute, 2012).

Chronic Graft-versus-*Host Disease (cGvHD):* Chronic graft-versus-host disease affects approximately 60% of patients undergoing allogeneic transplantation.

Second line therapy with ECP has been advocated for skin, mucosal or liver cGvHD with evidence of steroid intolerance, refractoriness or dependence, by the BCSH, the German Austrian and Swiss consensus and the UK consensus groups (Scarisbrick *et al.*, 2008; Wolff *et al.*, 2011; Dignan *et al.*, 2012a).

Other organ sites respond less well and there is currently insufficient published evidence to recommend ECP for cGvHD of the eyes, joints or lungs (Couriel *et al.*, 2006).

Acute Graft-versus-*Host Disease (aGvHD):* ECP has been used in the treatment and prevention of acute graft-versus-host disease, with encouraging results in steroid-refractory patients who would otherwise have very unfavourable outcomes (Dignan *et al.*, 2012b; Das-Gupta *et al.*, 2014).

Other indications: There is published evidence to support ECP for prevention of graft rejection in heart and lung transplantation (Barr *et al.*, 1998; Christie *et al.*, 2010; Morrell *et al.*, 2010), in the prevention of renal transplant rejection (Dall'Amico *et al.*, 1998), and in the prevention of rejection in face transplantation (Petruzzo *et al.*, 2012).

There are small published series of ECP use in Crohn's disease, and in a variety of immunologically mediated skin conditions, including bullous pemphigoid and eczema, although published evidence for efficacy currently remains limited (Reinisch *et al.*, 2001; Sanli *et al.*, 2010; Rubegni *et al.*, 2013).

Recommendations

1. ECP is recommended as first line therapy for erythrodermic CTCL (1A).
2. ECP may be considered as second line treatment in skin, mucosal and liver cGvHD (1B).
3. ECP schedule should be paired treatments on consecutive days, repeated fortnightly for a minimum assessment period of 3 months (1C).
4. Patients managed by ECP for cGvHD should have their disease monitored by staff trained in the application of the National Institutes of Health (NIH) assessment standards (Pavletic *et al.*, 2006) (1C).
5. ECP is suggested as one of a number of second line agents for steroid-refractory acute GvHD (2C).
6. ECP may be considered for prophylaxis or treatment of graft rejection in heart or lung transplantation (2C).
7. Application of ECP in alternative settings should be considered in the context of appropriate clinical trials (1C).

Cytoreductive Apheresis

Indications for leucocytapheresis. Leucocytapheresis may be undertaken to treat hyperleucocytosis in patients with leukaemia or myeloproliferative neoplasms. Hyperleucocytosis is usually considered if the white blood cell count is more than $100 \times 10^9\ L^{-1}$ (Gancel *et al.*, 2012; Schwartz *et al.*, 2013). Leucocytapheresis may worsen the coagulopathy associated with acute promyelocytic leukaemia and so is not recommended for this type of leukaemia (Vahdat *et al.*, 1994).

Several retrospective analyses of patients with hyperleukocytosis treated with leucocytapheresis have been published (Tan *et al.*, 2005; Bug *et al.*, 2007; Chang *et al.*, 2007; De Santis *et al.*, 2011). Some, but not all, of these analyses showed decreased early mortality. None showed improvement of overall survival.

Leucocytapheresis should be carried out using an apheresis technology that has been validated for this procedure. The use of hydroxyethyl starch as a red cell sedimenting agent is not generally recommended (Schwartz *et al.*, 2013). Response to treatment is monitored by its effects on clinical symptoms and/or reduction of cell count by at least 20%. Most patients require one procedure; others may need two or three.

Recommendations

1. When treating hyperleucocytosis, clinicians must aim for early initiation of suitable chemotherapy and good supportive care irrespective of the use of leucocytapheresis (1A).
2. Leucocytapheresis may be used as part of the management of hyperleucocytosis complicated by clinical leucostasis (pulmonary, cerebral and/or renal leucostasis or priapism), or when the use of chemotherapy is problematic e.g. during pregnancy (1C).

Thrombocytaphereis

Indications for thrombocytapheresis. There are a few case series and case reports describing thrombocytapheresis to treat myeloproliferative neoplasms, particularly during pregnancy (Koh *et al.*, 2002; Elliott & Tefferi, 2005). Thrombocytapheresis has only rarely been used to manage secondary thrombocytosis.

Recommendation

1. Thrombocytapheresis may be used in selected patients who require immediate reduction of platelet count in myeloproliferative neoplasms, e.g. uncontrolled thrombocytosis associated with an acute serious event or prior to urgent surgery, or pregnant women with myeloproliferative neoplasms and high risk of foetal loss (1C).

Cellular therapy product collection by apheresis

Optimising collection. Allogeneic HPC-A (PBSC) donors should have cells mobilised with a non-biosimilar granulocyte colony-stimulating factor (G-CSF) only (EBMT, 2011). For autologous HPC-A mobilisation, G-CSF may be used alone or in combination with chemotherapy. Plerixafor is effective along with G-CSF for patients failing to mobilise autologous HPC-A successfully by conventional means (Jantunen & Lemoli, 2012).

So as not to subject a patient undergoing autologous HPC-A collection to apheresis when there is little or no prospect of achieving a transplantable cell dose, most centres perform a peripheral CD34+ cell count by flow cytometry (either after 4 days of G-CSF alone, or at the time of white blood cell count (WBC) recovery following chemomobilisation) before initiating apheresis. Apheresis should not be performed if the peripheral CD34+ count is less than $5\,\mu L^{-1}$, and most UK centres use a peripheral CD34+ count 'trigger' of $10\,\mu L^{-1}$ to initiate apheresis (UK Stem Cell Users' Group survey, December 2013). Although differential WBC and Sysmex 'Progenitor Cell Count' have both been used as alternatives to peripheral CD34+ count for initiation of apheresis for autologous HPC-A collection, peripheral CD34+ count is more reliable (Meehan *et al.*, 2006).

Most cell separators will default to process two blood volumes in a standard HPC-A collection. However, larger-volume apheresis (i.e. processing of three blood volumes or more) should be considered in patients undergoing autologous HPC-A collection with peripheral CD34+ count below $20\,\mu L^{-1}$ at the time of apheresis (Moog & Moog, 2008; Majado *et al.*, 2009)

Therapeutic T Cells (TC-T; 'Donor Lymphocytes') from the original donor are effective for treatment of mixed chimaerism and/or minimal residual disease following allogeneic HPC transplant. They are collected by apheresis using a standard mononuclear cell collection procedure, processing two to three blood volumes. Prior G-CSF is not used, and CD34+ counts are not required.

Recommendations

1. Allogeneic HPC-A donors should always have cells mobilised using a non-biosimilar G-CSF alone at a dose of $10\,\mu g\,kg^{-1}\,day^{-1}$ for four days prior to apheresis, and with apheresis performed from day 5 onwards, unless in an ethically approved study (1A).
2. Autologous HPC-A patients may be mobilised either with G-CSF alone or with mobilising chemotherapy plus G-CSF (1B).
3. Plerixafor may be used pre-emptively (based on poor peripheral CD34+ counts, below $15\,\mu L^{-1}$), either at the time of haematopoietic recovery after mobilising chemotherapy, or after four days of G-CSF if used without prior chemotherapy; or second-line along with G-CSF for patients who have previously mobilised autologous HPC-A poorly (1B).
4. Initiation of autologous HPC-A collection should be based on flow-cytometric peripheral CD34+ count monitoring at the time of mobilisation (1B).
5. A peripheral CD34+ count of $10\,\mu L^{-1}$ is recommended as the general minimum threshold for initiation of apheresis (2C).
6. Larger volume apheresis (processing of 3 blood volumes or more) should be considered in autologous HPC-A patients with peripheral CD34+ counts of less than $20\,\mu L^{-1}$.

Lipoprotein apheresis

Indications for lipoprotein apheresis. Lipoprotein (Lp) apheresis is a treatment option for severe familial hypercholesterolaemia (FH) (NICE, 2008). It involves removal of atherogenic low density lipoprotein (LDL) and lipoprotein(a) (Lp(a)) particles from either whole blood or plasma.

Lp apheresis is an effective treatment for a small population who have a high cardiovascular risk and in whom conventional therapy has failed (Thompson *et al.*, 2008; Datta & Thompson, 2012).

Recommendations

1. Lipoprotein apheresis is required for patients with homozygous FH or for compound heterozygotes, when serum cholesterol remains $>9\,mM\,L^{-1}$ or decreases by $<50\%$ despite treatment with high dose statin, plus ezetimibe and/or bile acid sequestrants and/or nicotinic acid-containing compounds (1A).
2. Lp apheresis should be considered for patients with heterozygous FH or other forms of severe hypercholesterolaemia and with progressive coronary heart disease (CHD) whose LDL cholesterol remains $>5\,mM\,L^{-1}$ or decreases by $<40\%$ on maximally tolerable doses of combined drug therapy (1B).
3. Lp apheresis should be considered for patients with a raised Lp(a) level and progressive CHD despite treatment with maximally tolerable combined drug therapy (1B).

Table 2. Comparison of lipoprotein apheresis platforms currently available in the UK

Type	Length of treatment	Anticoagulation used	Flexibility of treatment size	Set up complexity: low to high	Storage required: small to large	Maintenance and service
Polyacrylic	2–3 h	Acid citrate dextrose (ACD) 1:20–1:40 ratio.	500, 750, 1000, 1250 size columns available in different configurations.	Low	Medium	National
Whole blood adsorber		Unfractionated heparin 25000 i.u. prime Possible heparin bolus.				
Dextran sulphate plasma cell separator & adsorber	3–3.5 h	Unfractionated heparin 5000 i.u. prime. Possible heparin bolus.	One size columns only.	High	Small	European support
Dextran sulphate whole blood adsorber	2–3 h	ACD 1:20–1:40 ratio. Unfractionated heparin 5000 i.u. prime. Possible heparin bolus.	500, 750, 1000 size columns available in different configurations.	Low	Small	European support
Precipitation/plasma cell separator	Up to 3 h only	Unfractionated heparin 1000–3000 i.u./h. Unfractionated heparin 300,000 i.u. during treatment. Unfractionated heparin 5000 i.u. prime. Possible heparin bolus.	One size treatment only.	High	Large	Regional
Double filtration/plasma cell separation	2–3 h	Unfractionated heparin 1000–3000 i.u./h Unfractionated heparin 5000 i.u. prime. Possible heparin bolus.	One size treatment only.	Medium	Medium	National

Technical aspects of lipoprotein apheresis

Lipoprotein apheresis removes atherogenic lipoproteins via an extracorporeal blood circuit. Several techniques (see Table 2) are used in the UK and these differ in their underlying mechanisms of action i.e. adsorption, precipitation or filtration. The efficacy and safety of all forms of Lp apheresis are broadly equivalent. The efficiency of removal is dependent on the volume of blood or plasma treated and the size of the columns used.

Recommendations

1. Lipoprotein apheresis procedure is performed weekly or bi-weekly in specialised units providing a regional or supra-regional service (1C).
2. Treatment target reduction for LDL cholesterol for all patients on any lipoprotein apheresis treatment is an interval mean of $<2.6\,\text{mM}\,L^{-1}$ or 60–75% reduction target. Lp(a) reduction aim is an interval mean of $<500\,\text{mg}\,L^{-1}$ (1B).
3. There should be quarterly screening and patient review for safety analysis (1C).
4. Patients receiving Lp apheresis who become pregnant can safely continue their treatment during their pregnancy (1B).

CLINICAL MANAGEMENT OF PATIENTS/DONORS

Pre-apheresis care

The decision to offer apheresis: The decision to offer a therapeutic apheresis procedure to a patient/donor must be made by a physician with special interest in therapeutic apheresis (usually a Haematologist or Nephrologist). Such decisions must consider alternative therapies available and weigh expected benefits of the procedure against inconvenience and possible complications (GMC UK, 2008).

Informed consent: Valid informed consent must be obtained by trained staff from patients/donors with capacity to consent. Staff training must also cover assessment of capacity to consent. Special arrangements must be followed for adults lacking capacity to consent, for children, and for participants in research

studies. Guidance is available from the Department of Health (2001) and from the General Medical Council (2008). Consent for the collection of haematopoietic progenitor cells for transplantation must also follow the Human Tissue Authority Codes of Practice (HTA, 2013). Guidance on obtaining consent for blood transfusion is available from the Advisory Committee on the Safety of Blood Tissues and Organs (SaBTO, 2011). Recommendations from this guidance were developed following extensive consultation including from patient groups.

Consent must cover the following points:

- The rationale for using apheresis rather than other treatment modalities, and expected benefits of apheresis.
- Technical explanation of the apheresis procedure, including serious and frequent complications.
- Procedures associated with apheresis therapy such as blood component transfusion.

Consent must be suitably recorded. Clearly written explanatory literature must be available to assist in obtaining informed consent. Allogeneic stem cell donors (particularly related donors) must not be in a position where it is difficult for them to decline from donating if they wish. The counselling of allogeneic stem cell donors must be undertaken by a Healthcare Professional who is not directly involved in the care of the recipient of the donation (JACIE, 2012).

Recommendation

> Informed consent must be obtained by trained staff according to national guidance and documented prior to an apheresis procedure (1A).

Clinical assessment of patients/donors

The apheresis physician should clinically assess patients/donors at the start of a course of treatment. The aim is to weigh apheresis benefits against possible risks and to anticipate any potential complications. Clinical assessment must cover:

- Any concerns related to mental and psychological capacity of patients/donors and ability to consent.
- General health status of patients/donors and the need for extra nursing/medical help.
- Haemodynamic stability and the presence of significant autonomic dysfunction.
- The presence of adequate vascular access, through peripheral veins or central venous catheters (CVCs).
- Review of clinical implications of the use of G-CSF, anticoagulation and replacement fluid, including blood components, on patients/donors.
- For allogeneic haematopoietic progenitor cells donors, a review of lifestyle, travel and vaccination history is required to assess potential microbial transmission.
- Where appropriate, advice should be sought from an expert from another speciality.

Pre-procedural investigations

Certain laboratory blood tests must be carried out to assess the wellbeing of the patient/donor and to set the baseline for monitoring the effect of the apheresis, such as full blood count (FBC), biochemistry and coagulation screen including fibrinogen.

Mandatory microbiology screening tests must be performed for haematopoietic progenitor cell donors as set out in the relevant legislation (Human Tissue Act; Human Tissue Act (Scotland)).

Apheresis treatment plan

The apheresis physician should produce an individual treatment plan that conforms to current clinical evidence and meets the clinical needs of the patient/donor. The treatment plan should specify the following:

- The reasons for initiating apheresis therapy, the expected benefits and how responses to apheresis should be monitored.
- Type of apheresis procedure required and the frequency of treatment.
- Vascular access to be used.
- Clinical observations, as well as laboratory tests (if any), to be completed before and after each apheresis procedure.
- Decisions on how to manage possible effects of apheresis on medications given before the procedure, and on medication that is required during procedures (e.g. insulin pump). Patients/donors on anticoagulants (e.g. warfarin) may require their anticoagulation adjusted or changed prior to a procedure which uses heparin.
- Technical details of the procedure such as blood volume to be processed, replacement fluid and (where different from agreed local Standard Operating Procedures) anticoagulant to be used.
- Therapy end point.

Recommendation

> Prior to the initiation of a course of apheresis procedures, clinical assessment and laboratory results must be suitably documented and a therapeutic apheresis treatment plan must be produced (1C).

Care during procedures

Immediately before starting the apheresis procedure, the operator should undertake a brief health check to include symptoms and vital sign measurements. Any unexpected variation must be discussed with the apheresis physician. The patient/donor must be asked to confirm consent.

Vascular access must be accessed with care and according to institutional guidance. Insertion of CVCs must be undertaken by suitably trained staff (NICE, 2012).

Apheresis machines must be operated according to manufacturers instructions and according to the apheresis treatment plan. A trained healthcare professional must attend the patient/donor during the whole duration of the apheresis procedure including post-procedure period.

For procedures that involve transfusion of blood components, the guidelines for the administration of blood components must be followed (Harris *et al.*, 2010).

Regular monitoring of vital signs is required, particularly for symptomatic patients/donors, or those receiving blood transfusions.

Technical measurements produced by the apheresis machine, such as flow rate, fluid balance and duration of procedure, must be monitored and recorded on a worksheet.

Medication must not be added to replacement fluids. Where possible, administration of medications through the same vascular access used for apheresis should be avoided during a procedure, unless such medications are part of the procedure, e.g. intravenous calcium to treat citrate reaction.

Recommendations

1. The patient/donor must have the apheresis performed by a healthcare professional who is trained in apheresis and its possible complications, remaining in attendance throughout the apheresis procedure and immediately afterwards, with immediate availability of resuscitation facilities (1A).
2. A light meal is encouraged prior to apheresis, and a good oral fluid intake is encouraged the day before treatment (1B).
3. The patient/donor should generally take all medication as prescribed. Angiotensin-converting-enzyme (ACE) inhibitor drugs increase the risk of vasovagal problems for all apheresis procedures: where possible, patients should therefore avoid ACE inhibitors before the apheresis procedure (1B).

Care post-treatment/collection

The patient/donor must be clinically assessed and allowed to rest after the completion of the procedure, and then mobilised in a manner appropriate to their condition to minimise the risk of fainting. Any clinical concerns must be discussed with an Apheresis physician.

Patients/donors who are allowed home following a procedure should be given written information explaining the nature of the apheresis therapy completed, vascular access used and any blood transfusion given.

Apheresis procedures completed for in-patients must be documented in the hospital records.

The clinical outcome of apheresis procedures should be documented. This may require clinical data collection days or weeks after the apheresis procedure.

Recommendation

Following apheresis, the patient/donor must be clinically assessed, post-treatment blood results should be reviewed as appropriate, and completion of the procedure must be documented. Clinical outcome of a course of procedures must also be documented (1B).

Management of complications

The most frequent complications of apheresis procedures relate to venous access, vasovagal reactions, hypocalcaemic symptoms from citrate anticoagulant and allergy ± anaphylaxis caused by replacement fluids. Complications are mostly moderate and easily managed (Shemin *et al.*, 2007; Strauss & McLeod, 2007; Okafor *et al.*, 2010). Table 3 summarises potential complications of apheresis and their management.

Citrate-related hypocalcaemia commonly causes symptoms of tingling around the mouth and nose, more rarely tingling in the fingers (Grade I). More severe toxicity may cause nausea or vomiting (Grade II) or – much more rarely – tetany, hypotension and/or cardiac dysrhythmia (Grade III). Hypocalcaemic toxicity can be significantly ameliorated by reducing the rate of citrate delivery and overall procedure time and/or by the prophylactic administration of calcium.

Vasovagal reactions are relatively common during apheresis procedures. The patient should be put in a head-down tilt and given intravenous 0.9% normal saline.

Other apheresis toxicities: Albumin solution as a replacement fluid in therapeutic plasma exchange (TPE) carries a risk of *dilutional coagulopathy* (Winters, 2012). Around 60% of coagulation factors and 85% of fibrinogen may be removed (Okafor *et al.*, 2010) and this may result in increased risk of bleeding, especially where multiple, large volume or consecutive daily exchanges are performed. Where *heparin* is used as an anticoagulant, it carries potential hazards of *haemorrhage* and of *type II heparin-induced thrombocytopenia*.

Allergic reactions (ranging from mild urticarial reactions to acute anaphylaxis) are most commonly related to replacement fluid. The risk is substantially higher if FFP is used rather than HAS (Okafor *et al.*, 2010).

Adverse reactions may be seen when *albumin-bound drugs are removed* by plasma exchange, or from an *increased effect of certain drugs* after other substances are removed (Ibrahim *et al.*, 2007; Winters, 2012)

Patients undergoing *Lp apheresis* can have reactions due to *bradykinin-induced histamine release*. Symptoms include a feeling of light-headedness, nausea, headaches or chills and a feeling of shortness of breath, back pain and/or a flush. However, these symptoms can generally be resolved quickly, and patients who initially have these reactions usually acclimatise to the treatment over a few procedures. Long term treatment can also cause iron deficiency and serum ferritin should be monitored.

Table 3. Complications of apheresis and their management

Complication	Signs/symptoms	Management
Citrate toxicity (hypocalcaemia)	*Mild*: circumoral paraesthesia; 'buzzing' feeling in fingers,	Reduce rate of citrate and/or total volume of citrate infusion. Oral or IV calcium supplements depending on severity of symptoms. Consider changing replacement fluid type/mix if using calcium-avid fluids.
	Moderate: nausea; vomiting; hypotension,	
	Severe: chest tightness; tetany; prolonged QT interval; cardiac dysrhythmia.	Check for metabolic alkalosis and correct if present especially in renal and hepatic insufficiency.
Vasovagal event	*Hypotension and bradycardia*: Pallor; sweating; nausea; agitation; anxiety; hyperventilation. Loss of consciousness (variable).	Trendelenburg positioning; fluid bolus with 250 mL 0.9% normal saline; reassurance and distraction; removal of causative factors.
Hypovolaemia (fluid shift; use of antihypertensive or ACE inhibitors)	Hypotension.	Adjust fluid balance.
	Vasovagal event.	Adjust fluid type. Treat as per vasovagal event. Stop ACE inhibitors 24–72 h before apheresis.
Type II HIT	Low platelet count in clinical context suggesting Type II HIT – use '4Ts' scoring system as per Watson *et al.* (2012).	Procedural anticoagulation with non-heparin anticoagulant (e.g. ACDA) and use of non-heparin central line locking/flushing solutions (e.g. citrate or TPA), in addition to standard treatment for Type II HIT.
Bradykinin-induced histamine release (lipid apheresis)	Light-headedness, nausea, headaches or chills and feeling of shortness of breath, back pain and/or flushing.	Lower flow rates until symptoms subside.
Over-anticoagulation	Bleeding at venous access sites; bleeding elsewhere.	Use citrate-based anticoagulant alone, or heparin in conjunction with citrate anticoagulants to reduce overall amount of heparin.
Allergic reaction	Urticarial rash, itching, wheeze, pyrexia, breathlessness, peri-orbital oedema, stridor and/or oropharyngeal swelling.	Stop transfusion of current blood component or plasma product in progress and manage as per BSCH guidelines. Administer antihistamine, hydrocortisone, salbutamol nebuliser, adrenaline as required. Manage Anaphylaxis as per current UK Resuscitation Council Guidelines. Change replacement fluid unit or type (if possible). Prophylaxis prior to subsequent treatments.
Hypofibrinogenaemia and dilutional coagulopathy	Increased PT and APTT.	Consider: decreased frequency or volume of exchange procedures; use of FFP or cryoprecipitate.
	Decreased fibrinogen and coagulation factors. Bleeding at venous access sites/elsewhere.	
Recirculation	Poor collection yields from otherwise uncomplicated CTP collection procedures.	Use peripheral cannula for return, or use central line with staggered internal ends. CVC placement and care can contribute to recirculation, with biofilm, thrombus and looping of the catheter in the vein causing increases in recirculation. Blood volume processed may be increased to compensate for recirculation.
Line-related thrombosis	Machine alarms indicating inadequate flow through access and/or return side of apheresis circuit.	Peripheral cannulae may be flushed with heparin solution 10 i.u. mL^{-1}. If this is ineffective, re-cannulation will be required. Central venous access devices may also initially be flushed with heparin flush solutions. For more significant thrombosis of central venous access devices, Urokinase may be used according to the manufacturer's recommendations to clear the line.

Recommendations

1. When using citrate anticoagulant: administration of prophylactic calcium supplements should be considered in renal or hepatic impairment; where pre-existing hypocalcaemia or hypomagnesaemia cannot be corrected pre-procedure; in prolonged apheresis procedures such as large-volume leukapheresis for HPC-A collection; and/or where patients have previously experienced apheresis-related citrate toxicity (1C).
2. Oral calcium supplements should be used to treat Grade I or initial Grade II citrate toxicity. Intravenous calcium supplements should be used to treat persistent Grade II or Grade III citrate toxicity.

3. ACE inhibitors should ideally be discontinued 24–72 h prior to plasma exchange procedures using FFP, or Lp apheresis procedures using LDL-A and dextran sulphate cellulose systems (1B).
4. Specific vital sign monitoring regimes for transfusion during apheresis procedures should be incorporated into each organisation's transfusion policy. These should take account of differences in transfusing large volumes as part of exchange procedures and limitations related to measuring blood pressure (1A).
5. Consideration should be given to prophylactic antihistamines and/or hydrocortisone before procedures for patients who have experienced previous apheresis-related allergic reactions (1C).

Paediatric considerations

Treatment principles are no different for children compared to adults, but the extracorporeal blood volume (ECV) and extracorporeal red cell volume may be too great for paediatric patients without procedure modifications (Rogers & Cooling, 2003; Kim, 2010; Wong & Balogun, 2012). Most apheresis machines will not accurately calculate total blood volume (TBV) below a weight of 30 kg and TBV will need to be calculated manually to allow safe treatment below this weight. Priming of circuits with red cell units will be necessary where the extracorporeal blood volume is greater than 15% of TBV. In practise, this means that red cell priming is always required for children less than 20 kg, and often required for children up to 30 kg depending on haemoglobin concentration. A prime with 5% albumin (rather than red cells) may be considered where ECV is between 10 and 15% of TBV (Wong & Balogun, 2012). Continuous flow technology circuits have lower ECVs than intermittent flow technology and are more suitable for use with children.

Circulatory overload and polycythaemia may occur when rinse-back of the apheresis circuit is undertaken in paediatric procedures following a blood prime. Rinse-back should therefore be avoided.

Symptoms of hypocalcaemic toxicity are exhibited differently in children than in adults, with children commonly experiencing abdominal pain, vomiting and pallor as initial signs.

Recommendations

1. Red cell (RBC) prime of apheresis circuits should be undertaken in paediatric procedures where the ECV will represent more than 15% of the TBV. RBC prime should be considered in children who are significantly anaemic even when the ECV is not greater than 15% of TBV (1A).
2. Continuous flow technology should be used in paediatric procedures (1B).
3. Rinse-back should be omitted in paediatric procedures where RBC prime has been carried out (1A).
4. Careful monitoring is required of paediatric patients for non-verbal signs of reactions such as hypocalcaemic toxicity (1A).
5. Indications for paediatric Lp apheresis: children with homozygous FH in whom drug treatment is insufficient should be started on Lp apheresis before they reach 7 years of age or 50 kg (1B).
6. Paediatric procedures should be carried out in an appropriate environment, generally a children's hospital, with access to a paediatric resuscitation team and equipment (1A)

Vascular considerations

All apheresis procedures require adequate venous access (see Table 4 for a summary of available options). Peripheral veins are the safest option (Kalantari, 2012). Where CVCs are required, arrangements for insertion and use should conform to current BCSH guidelines (Bishop *et al.*, 2007).

Shorter catheters/needles with wider lumens provide better flow. Actual flow rates will depend on other physiological factors. In children, CVC length and French diameter should be based on body size and weight (Wong & Balogun, 2012).

Recirculation is a particular problem when using dual-lumen CVCs with non-staggered ends for both access and return, and a peripheral cannula should therefore be inserted for return when using a CVC with non-staggered ends for access.

Internal jugular (IJ) and subclavian catheters carry risk of pneumothorax and haemothorax. Although infection rates are lower in subclavian than IJ catheters, mechanical complications in placement and use are less frequent with IJ placement (Bambauer & Latza, 2004). In general, femoral placement of CVCs carries a higher risk of thrombosis, infection and kinking than IJ and subclavian placement. However, IJ and subclavian catheters require insertion by expert practitioners under controlled conditions as well as imaging for placement (Bishop *et al.*, 2007); therefore for urgent or short-duration procedures femoral lines may be chosen despite their higher infection risk (Moreiras-Plaza *et al.*, 2004; Kalantari, 2012).

Recommendations

1. Peripheral veins should always be used where possible for venous access before considering central venous access, as risks related to peripheral access are lower (1A).
2. CVCs for apheresis procedures should be dual lumen, short and rigid bodied, with a gauge large enough to support the desired flow rates (1A).
3. Care and anticoagulation of CVCs used for apheresis should maintain patency for adequate flow rates and minimise the risk of infection and build-up of fibrin via evidence-based protocols (1A).
4. Initial insertion of a femoral CVC should be considered to allow urgent or emergency apheresis without delay when peripheral venous access is inadequate, even if femoral venous access may be undesirable or not suitable for the complete programme of procedures (1C).

Table 4. Vascular access options for apheresis procedures

Option	Considerations	Pros	Cons
Peripheral veins	Veins will need to be large enough to support a 16G or 17G fixed dialysis-type needle for access flow. Veins may not support consecutive treatments. Ultrasound-guided placement of peripheral cannulas may be helpful for patients with suboptimal veins.	Lower risk than central access.	If peak PBSC mobilisation periods are missed as a result of venous access problems, adequate stem cell yields may not be collected. Patients/donors unable to move arm with fixed needle for extended period of time.
Large lumen CVC	Risks associated with the placement and care of CVCs (infection; pneumothorax) must be factored when weighing the risk and benefits.	Good flow rates allow for faster procedures and less time on machines for patients. Increased mobility for patients during procedures.	Risk associated with placement: pneumo- and haemothorax and cardiac arrhythmias for IJ and SC placements; arterial puncture and air embolus. High risk of infection esp. femoral lines. Prone to mechanical occlusion due to kinking, pinch-off and fibrin sheath build up. Individual trust policy may require inpatient admission. Requires arrangements for line flushing in long-term use to maintain adequate patency. Loss of procedure efficiency if recirculation occurs (use CVC with staggered internal ends).
Combination of central plus peripheral access	Normally used where there is existing long term CVC (e.g. Hickman line in a patient with haematological malignancy undergoing PBSC collection). If having CVC placed specifically for apheresis, large-gauge hard-bodied dialysis type catheter is better option.	Making use of pre-existing CVC saves patient from additional CVC placement and its associated risks. Facilitates two arm technique in closed system photopheresis.	Narrow-gauge, soft-bodied CVCs used for infusion and drug therapy will often not flow at return speeds required, and seldom give good enough flow rates to be used for access.
Implantable ports	Invasive procedure requiring surgical placement of device. Even port types that have been shown capable of supporting apheresis (e.g. Vortex port) are not licenced for apheresis.	Can achieve good flow rates if well maintained.	Requires specific port type (most ports are unsuitable for apheresis) and non-coring needles for use with apheresis equipment. Need regular flushing, and sometimes urokinase, to ensure good function.
Arteriovenous fistula (AVF)	Permanent, body-altering, requires surgical procedure.	Good flow rates once matured; allows single arm procedure without time constraints of single needle procedure; more mobility for patient than two arm procedure.	Requires extended venipuncture skill. Can take longer to establish haemostasis post procedure. Risk of stenosis and arterial steal syndrome. May give poorer results in sickle cell patients.
Gore-tex Grafts	Permanent, body-altering, requires surgical placement. Not routinely used but may be appropriate where previous AVFs have failed.	Good flow rates; permits long term use for frequent or long-term treatment. Placed in leg allowing patient full use of arms.	Requires extended venipuncture skill. Can take longer to establish haemostasis post procedure. Risk of thrombosis and infection.

Table 5. Aspects of a Quality Management Programme (QMP) in Clinical Apheresis

Element of the QMP	Definition	Examples in clinical apheresis practise
Quality Manager	A single designated person with overall responsibility for operation of the QMP.	Depending on the size and complexity of the apheresis service, this can either be an additional role taken on by an existing staff member, or the service can appoint a Quality Manager who does not have additional clinical duties.
Standard operating procedures (SOPs)	Detailed, written instructions to achieve uniformity of the performance of a specific task or process by appropriately trained staff.	SOPs for the performance of Apheresis procedures by trained nursing staff, e.g. machine set-up, machine operation during procedure and post-run rinse back. SOPs for pre-donation assessment of allogeneic HPC donors, and for pre-collection assessment of patients undergoing autologous PBSC collection. SOPs describing the local QMP, including procedures for incident reporting, for validation, and for the development of new SOPs.
Disaster Plan	A comprehensive statement of actions to be taken before, during and after a disaster to minimise impact on an organisation or service, usually in written SOP format.	'Disaster' can cover a variety of events that might include: flooding/storm damage; temporary interruptions in power and water supply; major financial difficulties within an NHS Trust significantly affecting service provision; significant interruptions in routine IT support; pandemic of influenza or similar infectious disease. The impact on the apheresis service can be mitigated by planning for unforeseen disasters in advance. The Disaster Plan should include planning for the event of complete discontinuation of the apheresis service's activities, such that apheresis provision to patients/donors is taken over by other services as far as possible.
Staff training records	Written training records for all staff members, for all critical tasks relevant to their roles.	Both nursing staff and medical staff working in Clinical Apheresis should have a personal training record, documenting competency in all critical tasks relevant to their roles. Competency should be periodically re-assessed. Staff should sign current versions of SOPs relevant to their role as having been read and understood.
Incident reporting system	A defined system to identify non-conformities and other untoward events, particularly where there has been harm or risk of harm to patients/donors, to minimise both the impact of the event and the risk of recurrence.	Incident reporting must include reporting both of clinical incidents resulting in actual harm to patients or donors, and of 'near-miss' incidents. There should be written documentation of Corrective Action (what is done to minimise the impact of what has already gone wrong) and, wherever possible, of Preventative Action (any changes to the apheresis service's processes to minimise the risk of something similar happening again in the future)
Validation	The activity required to prove that any procedure, process, equipment, material, activity or system leads to the expected results.	Any new apheresis equipment or new apheresis processes must be subjected to validation. The validation process might for instance involve initial 'dry runs' without a patient attached to the machine, then close observation of a pre-determined number of procedures after introduction of the new equipment or process, examining the patient's post-procedure blood results, the weight and / or composition of the apheresis product, the machine alarm history, machine operator satisfaction, etc.
Change control	A formal process used to ensure that changes to a system are introduced in a controlled and co-ordinated manner, reducing the risk that changes will cause unforeseen problems for other parts of the service or organisation, or for its clients.	Change Control documentation should ideally be completed in advance when any major changes are made to an apheresis service. For instance, if the apheresis service introduces a new PBSC collection programme at a nearby hospital in addition to an existing PBSC collection programme at the base hospital, the Change Control process should ensure that prior consideration is given to any HTA licencing implications, impact on apheresis nursing staffing resources, safe transport of cell separators and of materials such as ACDA anticoagulant between hospitals, safe transport of the PBSC product, Stem Cell Laboratory workload implications, Clinical Governance implications, etc.

Table 5. continued

Element of the QMP	Definition	Examples in clinical apheresis practise
Audit	Systematic and independent examination of any particular process to ensure fitness for its intended purpose.	Like any other clinical service, an apheresis service should be subjected to regular audit to ensure that procedures are carried out safely and that they achieve their intended clinical results. Audit should ideally be regularly scheduled, independent and transparent. See also Table 6.
Third Party Agreements (TPAs) and Service Level Agreements (SLAs)	Written agreements between two or more organisations, where one is a customer and the others are service providers, or where organisations divide their responsibilities to provide a common service to customers or clients.	Where one NHS Trust provides an apheresis service to a separate NHS Trust, the staff will be under separate Line Management and Clinical Governance systems, and will operate within different QMPs. Organisational responsibilities must be defined to ensure that the process operates safely and reliably, with appropriate corrective and preventative action if anything goes wrong. *Service Level Agreements* are written agreements between organisations where one is providing a service (e.g. apheresis service) to the other, and are generally complex documents covering all aspects of interactions between the organisations, including financial aspects. *Third Party Agreements* are more focussed agreements between organisations, relating to specific activities e.g. PBSC collection, intended mainly to delineate precise organisational responsibilities for the various parts of the process.

5. For long term apheresis or loss of peripheral or CVC access, other options may be considered such as arteriovenous (AV) fistulae and grafts or implantable ports (1C).
6. Local agreements should be in place to allow urgent insertion of CVCs by appropriately-trained staff to facilitate apheresis procedures (1C).
7. Adequate and age-appropriate venous access must be achieved for paediatric apheresis procedures to be undertaken successfully. Consideration must be given to the size and type of CVCs used in paediatrics to ensure adequate flow rates and reasonable procedure completion times.

CLINICAL MANAGEMENT OF PATIENTS/DONORS

Service delivery and design

All Trusts should identify an Apheresis Lead responsible for ensuring that policies and procedures are in place to access Therapeutic Apheresis services, whether within the Trust or if provided by another organisation. This is intended to be directly analogous to the recommendation that Trusts should identify a single Lead Consultant for transfusion (Department of Health, 2007). In a similar way as for a transfusion lead, the recommendation is that a named individual will take overall responsibility for appropriate access to apheresis services for all patients who require this, as well as taking responsibility for implementing evidence-based good apheresis practise within the Trust.

Where an organisation does not provide a Therapeutic Apheresis service it should have a clear policy on how to access the service in another organisation. This policy should include access to both emergency and out-of-hours cover for Therapeutic Apheresis. If Therapeutic Apheresis is provided by a third party, a written agreement must be in place to ensure that the roles and responsibilities of each party are clearly defined. This is a mandatory requirement for Cellular Therapy Product collection (JACIE, 2012; HTA, 2013).

Recommendations

1. The Apheresis Facility should be licenced and accredited as required by the governmental authority for the activities performed and should abide by all applicable laws and regulations. Any facilities collecting Cellular Therapy Products (CTPs) must be licenced by the Human Tissue Authority (HTA) (1A).
2. Trusts should identify a single individual as an Apheresis Lead, regardless of whether apheresis services are provided within the Trust or by another organisation (2C).
3. Where apheresis services are provided by another organisation, written agreements must be in place delineating organisational responsibilities (1A).

Staffing levels and training (medical, nursing and healthcare assistants)

Staffing levels at a Therapeutic Apheresis Facility should be considered in the context of the activity undertaken and the nature of the patients treated. There must be an adequate number of trained personnel available for the procedures relative to the workload.

The lead must be qualified for the scope of activities carried out in the facility. She/he must have overall responsibility for all technical procedures including management of complications, the performance of the therapeutic apheresis procedures,

supervision of staff, administrative activities and supervision of the Quality Management Programme (including compliance with applicable laws and regulations) and this should be reflected in Job Plans to ensure adequate time is allocated for these activities. The lead clinician must participate regularly in educational activities related to Therapeutic Apheresis and (if applicable) to the procurement of Cellular Therapeutic Products (Koetz, 2010; JACIE, 2012).

All personnel must be appropriately qualified and trained in the procedures they regularly perform and competency assessment must be documented. All staff in the Apheresis Facility must follow the Standard Operating Procedures relevant to their positions. A staff member should complete relevant procedural training and that training should be documented before an individual is allowed to perform new or revised procedures. There should be a process for periodic assessment of continued competency (Koetz, 2010; JACIE, 2012).

For Apheresis Facilities that perform procedures on paediatric donors and patients, physicians and collection facility staff must have specific training and experience.

Recommendations

1. There must be an adequate number of trained personnel available for the procedures relative to the workload and the nature of the patients treated (1A).
2. All personnel performing or supervising apheresis procedures should be appropriately qualified and trained for their respective roles and their competencies should be assessed and documented. This must include up-to-date training in cardiopulmonary resuscitation and anaphylaxis treatment as per UK Resuscitation Council guidelines (1A).

Facilities

Apheresis should take place in an appropriate area to ensure the patient/donor's safety, which may involve treatment in an intensive therapy unit (ITU) or high dependency unit (HDU) environment for critically ill patients. Confidential patient/donor examination and evaluation must be possible. Resuscitation facilities must be available.

There must be sufficient space to allow staff to operate all equipment without danger to themselves, patients and donors. The Therapeutic Apheresis Facility must have adequate lighting, ventilation and hand-washing facilities.

There must be good transfusion laboratory support with robust lines of communication, to ensure that SD-FFP, FFP and/or red cells are available rapidly when indicated as replacement fluid, and that FFP, cryoprecipitate and/or platelets are available rapidly when indicated for coagulation factor support pre- or post-procedure.

For services undertaking collection of HPC-A (PBSC) or other CTPs, there should be appropriate designated areas and processes not only for the collection of CTPs, but also for interim storage of the product as necessary and for storage of supplies, reagents and equipment. Records must be kept of ongoing monitoring and maintenance of the facility and equipment (JACIE, 2012)

Recommendations

1. The Therapeutic Apheresis Facility should have adequate, designated space for patient/donor assessment and procedures, minimising risk of transmission of communicable diseases and (where relevant) mix-up of any collected Cellular Therapy Products (1A).
2. Patients should undergo their apheresis sessions on treatment couches or beds, which must be suitable for treatment of hypotensive episodes. Adequate consideration should be given to maintaining patient or donor dignity and privacy (1B).

Quality management

Quality management has been defined as 'an organisation's comprehensive system of quality assessment, assurance, control, and improvement' (JACIE, 2012). A Quality Management Programme (QMP) is designed to prevent, detect and correct deficiencies that may affect patient/donor safety. Additionally, for centres that undertake Cellular Therapy Product collection, the QMP ensures the quality of the product. The QMP should ensure that procedures are carried out by all staff members in line with agreed standards, with effective communication between all parts of the service. Key aspects of a QMP are discussed in Table 5, with particular reference to clinical apheresis.

As part of the QMP, there should be a regular programme of audits. Results should be used to recognise problems, detect trends and identify improvement opportunities. Suitable areas for audit within a clinical apheresis programme are listed in Table 6.

Recommendation

The Lead Clinician will be responsible for ensuring that the Therapeutic Apheresis Facility implements a quality management programme including as a minimum development of standard operating procedures, adverse event reporting, audit and development of third party/service level agreements, where appropriate (1B).

Choice of machine platform/validation

Several cell separator platforms are available for therapeutic apheresis, operating either on continuous-flow or (less commonly) on intermittent-flow principles. Any cell separator must comply with the relevant aspects of the Health and Safety legislation. Equipment must be CE marked, conforming with relevant British and European safety requirements, as well as with any organisational requirements for medical

Table 6. Suggested areas for regular scheduled audit within a Clinical Apheresis service

Subject for audit	Details
Incidence of symptomatic citrate toxicity and other adverse events	Data should be collected routinely on adverse events of apheresis, even if not obviously due to a mistake or non-conformance, and even if not 'serious'. Mild citrate toxicity is a common adverse event of apheresis. The Service may seek to reduce its incidence through measures such as prophylactic oral or IV calcium. Particular patient/donor groups may be at increased risk, and audit will help to identify these groups and to plan the service's policy accordingly.
Type of venous access for plasma exchange, and complications of venous access	Peripheral venous access should be used whenever possible, as it is considerably safer than central venous access. An apheresis service could, for instance, audit the proportion of patients receiving plasma exchange that required central venous access, and could seek to reduce this proportion over time. Re-cannulation rates could also be audited.
Clinical outcomes following plasma exchange	Clinical feedback can be sought routinely from the referring Consultant, particularly where plasma exchange is used for indications where this is a less well established evidence base, to try to improve the evidence base for clinical efficacy for the future, and to avoid performing plasma exchange for conditions where it is ineffective. Did the patient appear to benefit from the plasma exchange, particularly in terms of objective outcome measurements?
CD34+ cell collection efficiency during PBSC collection	This may be calculated routinely for all PBSC collections, using pre-run peripheral CD34+ count, blood volume processed and CD34+ cell dose achieved in the product. Procedures with collection efficiency falling below a pre-determined threshold may be investigated for quality assurance purposes. Median collection efficiencies may be compared between different cell separator machines or between different operators.
Reduction in HbS level after red cell apheresis for sickle cell disease	The aim of red cell apheresis for sickle cell disease is generally to reduce the HbS level below 30%. In what proportion of patients was the planned reduction in HbS achieved?
Engraftment following PBSC transplant	Any apheresis service carrying out either autologous or allogeneic PBSC collection should routinely review post-transplant neutrophil and platelet engraftment data from all transplant centres using its PBSC products.

devices. Equipment should be validated as discussed in Table 5.

Recommendations

1. The decision to purchase or lease a specific cell separator should be taken in the context of the type of procedures carried out in the Facility, the efficiency of the equipment in procedures carried out in the Facility and the maintenance and training support provided by the manufacturer.
2. All equipment and critical procedures should be validated and results reviewed by the lead Clinician.

SUGGESTED TOPICS FOR AUDIT

Refer to Table 6. These audit recommendations are also available in the Audit Template for this Guideline, on the BCSH website: http://www.bcshguidelines.com.

ACKNOWLEDGEMENTS

The Writing Group would like to acknowledge the input from the following for their review of specific clinical sections: Dr David Kluth, Dr Lynn Manson, Professor Gil Thompson, Dr Sara Trompeter, Professor Robert Wynn

REFERENCES

Adams, R.J., McKie, V.C., Hsu, L. *et al.* (1998) Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *New England Journal of Medicine*, **339**, 5–11.

Ahn, H., Li, C.S. & Wang, W. (2005) Sickle cell hepatopathy: clinical presentation, treatment, and outcome in pediatric and adult patients. *Pediatric Blood & Cancer*, **45**, 184–190.

Auzerie, V., Chiali, A., Bussel, A., Brouet, J.C., Fermand, J.P., Dubertret, L. & Senet, P. (2003) Leg ulcers associated with cryoglobulinemia : clinical study of 15 patients and response to treatment. *Archives of Dermatology*, **139**, 391–393.

Bambauer, R. & Latza, R. (2004) Complications in large-bore catheters for extracorporeal detoxification methods. *Artificial Organs*, **28**, 629–633.

Barr, M.L., Meiser, B.M., Eisen, H.J. *et al.* (1998) Photopheresis for the prevention of rejection in cardiac transplantation. Photopheresis Transplantation Study Group. *New England Journal of Medicine*, **339**, 1744–1751.

BCSH Joint Working Party of the Transfusion and Clinical Haematology Task Forces (1998) Guidelines for the clinical use of blood cell separators. *Clinical & Laboratory Haematology*, **20**, 265–278.

Bishop, L., Dougherty, L., Bodenham, A., Mansi, J., Crowe, P., Kibbler, C., Shannon, M. & Treleaven, J. (2007) Guidelines on the insertion and management of central

venous access devices in adults. *International Journal of Laboratory Hematology*, **29**, 261–278.

Bjorkholm, M., Johansson, E., Papamichael, D., Celsing, F., Matthews, J., Lister, T.A. & Rohatiner, A.Z. (2003) Patterns of clinical presentation, treatment and outcome in patients with Waldenström's macroglobulinemia: a two-institution study. *Seminars in Oncology*, **30**, 226–230.

Bug, G., Anargyrou, K., Tonn, T., Bialleck, H., Seifried, E., Hoelzer, D. & Ottmann, O.G. (2007) Impact of leukapheresis on early death rate in adult acute myeloid leukemia presenting with hyperleukocytosis. *Transfusion*, **47**, 1843–1850.

Chang, M.C., Chen, T.Y., Tang, J.L., Lan, Y.J., Chao, T.Y., Chiu, C.F. & Ho, H.T. (2007) Leukapheresis and cranial irradiation in patients with hyperleukocytic acute myeloid leukaemia: no impact on early mortality and intracranial hemorrhage. *American Journal of Hematology*, **82**, 976–980.

Chopek, M. & McCullough, J. (1980) Protein and biochemical changes during plasma exchange. In: *Therapeutic Hemapheresis* (eds Berkman, E.M. & Umlas, J.), 13–52. American Association of Blood Banks (AABB), Washington, DC.

Christie, J.D., Edwards, L.B., Kucheryavaya, A.Y. *et al.* (2010) The registry for the International Society for Heart and Lung Transplantation: twenty seventh official adult lung and heart-lung transplant report – 2010. *Journal of Heart & Lung Transplantation*, **29**, 1104–1118.

Cortese, I., Chaudhry, V., So, Y.T., Cantor, F., Cornblath, D.R., Rae-Grant, A. & On behalf of the American Academy of Neurology (2011) Evidence-based guideline update: plasmapheresis in neurologic disorders. *Neurology*, **76**, 294–300.

Couriel, D.R., Hosing, C., Saliba, R. *et al.* (2006) Extracorporeal photochemotherapy for the treatment of steroid resistant chronic GVHD. *Blood*, **107**, 3074–3080.

Dall'Amico, R., Murer, L., Montini, G., Andreeta, B., Zanon, G.F., Zacchello, G. & Zacchello, F. (1998) Successful treatment of recurrent rejection in renal transplant patients with photopheresis. *Journal of the American Society of Nephrology*, **9**, 121–127.

Das-Gupta, E., Dignan, F., Shaw, B. *et al.* (2014) Extracorporeal photopheresis for treatment of adults and children with acute GvHD: UK consensus statement and review of published literature. *Bone Marrow Transplantation*, **49**, 1251–1258.

Datta, D. & Thompson G.R. (2012) *Lipoprotein Apheresis for Refractory Hyperlipidaemia Clinical Indications and Service Requirements (HEART UK)* [Online]. URL http://heartuk.org.uk/files/uploads/documents/Apheresis_Paper_-_Final_Agreed_version.pdf (Accessed 18/12/2013).

De Santis, G.C., deOliveira, L.C., Romano, L.G., Almeida Prado Jr, B.D., Simoes, B.P., Rego, E.M., Covas, D.T. & Falcao, R.P. (2011) Therapeutic leukapheresis in patients with leukostasis secondary to acute myelogenous leukemia. *Journal of Clinical Apheresis*, **26**, 181–185.

Department of Health. (2001) *Good Practice in Consent Implementation Guide: Consent to Examination or Treatment* [Online]. URL http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4019061.pdf (Accessed 26/10/2012).

Department of Health. (2007) *Better Blood Transfusion: Safe and Appropriate Use of Blood* [Online]. URL http://www.transfusionguidelines.org.uk/uk-transfusion-committees/national-blood-transfusion-committee/better-blood-transfusion/health-service-circulars (Accessed 31/3/2015).

Dignan, F.L., Scarisbrick, J.J., Cornish, J. *et al.* (2012a) Organ-specific management and supportive care in chronic graft vs host disease. *British Journal of Haematology*, **158**, 62–78.

Dignan, F.L., Clark, A., Amrolia, P. *et al.* (2012b) Diagnosis and management of acute Graft-versus-Host disease. *British Journal of Haematology*, **158**, 30–45.

Duguid, J., O'Shaughnessy, D.F., Atterbury, C., Bolton Maggs, P., Murphy, M., Thomas, D., Yates, S. & Williamson, L.M. (2004) British Committee for Standards in Haematology – Blood Transfusion Task Force. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *British Journal of Haematology*, **126**, 11–28.

Elliott, M.A. & Tefferi, A. (2005) Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. *British Journal of Haematology*, **128**, 275–290.

European Group for Blood Marrow Transplantation (EBMT) & Niederwieser, D. (2011) *Biosimilar Granulocyte-Colony Stimulating Factor (G-CSF) for Stem Cell Mobilization in Related and Unrelated Donors* [Online]. URL http://www.gitmo.net/Biosimilars_in%20mobilization%20of%20unrelated%20and%20related%20doors.pdf (Accessed 1/9/2012).

Faguer, S., Kamar, N., Guilbeaud-Frugier, C. *et al.* (2007) Rituximab therapy for acute humoral rejection after kidney transplantation. *Transplantation*, **83**, 1277–1280.

Gajdos, P., Chevret, S. & Tokya, K. (2003) Plasma exchange for myasthenia gravis. *Cochrane Database Systematic Reviews*, **2003**, CD002277.

Gancel, C., Beckerm, J., Mintz, P.D., Lazarus, H.M. & Rowe, J.M. (2012) Hyperleukocytosis, leukostasis and leukapheresis: practice management. *Blood Reviews*, **26**, 117–122.

General Medical Council U.K. (2008) *Consent: Patients and doctors taking decisions together* [online]. URL http://www.gmc-uk.org/Consent___English_0513.pdf_48903482.pdf (Accessed June 2013).

Grabmer, C., Schmid, D., Mayer, G., Aigner, E., Wagner, A., Streif, D., Schallmoser, K. & Rohde, E. (2014) Iron depletion with a novel apheresis system in patients with hemochromatosis. *Transfusion* [Epub ahead of print; DOI: 10.11111/trf.12949].

Harris, A.M., Atterbury, C.L.J., Chaffe, B., Elliott, C., Hawkins, T., Hennem, S.J., Howell, C., Jones, J., Murray, S., New, H.V., Norfolk, D., Pirie, L., Russell, J., Taylor, C. & On behalf of the British Committee for Standards in Haematology Transfusion Task Force. (2010) *Guideline on the Administration of Blood Components* [Online]. URL http://www.bcshguidelines.com/documents/Admin_blood_components_bcsh_05012010.pdf (Accessed 26/10/2012).

Hiran, S. (2005) Multiorgan dysfunction syndrome in sickle cell disease. *Journal of the Association of Physicians of India*, **53**, 19–22.

Howard, J., Malfroy, M., Llewelyn, C. *et al.* (2013) The Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study: a randomised, controlled, multicentre clinical trial. *Lancet*, **381**, 930–938.

Hulbert, M.L., Scothorn, D.J., Panepinto, J.A. *et al.* (2006) Exchange blood transfusion compared with simple transfusion for first overt stroke is associated with a lower risk of subsequent stroke: a retrospective cohort study of 137 children with sickle cell anemia. *Journal of Pediatrics*, **149**, 710–712.

Human Tissue Authority (UK). (2013) *Code of practice 1 – Consent. Code of practice 5 – Disposal of Human Tissue. Code of practice 6 – Donation of allogeneic bone marrow and peripheral blood stem cells for transplantation. Code of practice 9 – Research* [Online]. http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/codesofpractice.cfm (Accessed 12/6/2013).

Ibrahim, R.B., Liu, C., Cronin, S.M., Murphy, B.C., Cha, R., Swerdlow, P. & Edwards, D.J.

(2007) Drug removal by plasmapheresis: an evidence-based review. *Pharmacotherapy*, **27**, 1529–1549.

Jantunen, E. & Lemoli, R.M. (2012) Preemptive use of plerixafor in difficult-to-mobilize patients: an emerging concept. *Transfusion*, **52**, 906–914.

Jayne, D.R., Gaskin, G., Rasmussen, N. *et al.* (2007) Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *Journal of the American Society of Nephrology*, **18**, 2180–2188.

Johnson, S.A., Birchall, J., Luckie, C., Oscier, D.G. & Owen, R.G. (2006) Guidelines on the management of Waldenström macroglobulinaemia. *British Journal of Haematology*, **132**, 683–697.

Joint Accreditation Committee of ISCT and EBMT (JACIE). (2012) *5th Edition JACIE Standards* [Online]. http://www.jacie.org/document-centre (Accessed 2/10/2012).

Kalantari, K. (2012) The choice of vascular access for therapeutic apheresis. *Journal of Clinical Apheresis*, **27**, 153–159.

KDIGO Work Group, Cattran, D.C. & Feehally, J. (2012) KDIGO Clinical Practice Guideline for glomerulonephritis. *Kidney International. Supplement*, **2**, 143–153.

Kim, H.C. (2010) Therapeutic apheresis in pediatric patients. In: *Apheresis: Principles and Practice* (3rd edn) (eds McLeod, B.C., Szczepiorkowski, Z.M., Weinstein, R. & Winters, J.L.), 445–464. AABB Press, Bethesda, MD.

Koetz, W.B. (2010) Quality management of apheresis personnel. In: *Apheresis: Principles and Practice* (3rd edn) (eds McLeod, B.C., Szczepiorkowski, Z.M., Weinstein, R. & Winters, J.L.), 681–690. AABB Press, Bethesda, MD.

Koh, L.P., Devendra, K. & Tien, S.L. (2002) Four pregnancies in two patients with essential thrombocythaemia – a case report. *Annals of the Academy of Medicine, Singapore*, **31**, 353–356.

Lalloo, D.G., Shingadia, D., Pasvol, G. *et al.* (2007) UK malaria treatment guidelines. *Journal of Infection*, **54**, 111–121.

LaSalle-Williams, M., Nuss, R., Le, T., Cole, L., Hassell, K., Murphy, J.R. & Ambruso, D.R. (2011) Extended red blood cell antigen matching for transfusions in sickle cell disease: a review of a 14-year experience from a single center (CME). *Transfusion*, **51**, 1732–1739.

Laspina, S., O'Riordan, J.M., Lawlor, E. & Murphy, W.G. (2005) Prevention of post-transfusion RhD immunisation using red cell exchange and intravenous anti-D immunoglobulin. *Vox Sanguinis*, **89**, 49–51.

Lee, M.T., Piomelli, S., Granger, S., Miller, S.T., Harkness, S., Brambilla, D.J. & Adams, R.J. (2006) Stroke Prevention Trial in Sickle Cell Anemia (STOP): extended follow-up and final results. *Blood*, **108**, 847–852.

Levy, J.B., Turner, A.N., Rees, A.J. & Pusey, C.D. (2001) Long-term outcome of anti-glomerular basement membrane disease treated with plasma exchange and immunosuppression. *Annals of Internal Medicine*, **134**, 1033–1042.

Magee, C.C. (2006) Transplantation across previously incompatible immunological barriers. *Transplant International*, **19**, 87–97.

Majado, M.J., Minguela, A., Gonzalez-Carcia, C. *et al.* (2009) Large-volume-apheresis facilitates autologous transplantation of hematopoietic progenitors in poor mobilizer patients. *Journal of Clinical Apheresis*, **24**, 12–17.

Meehan, K.R., Hill, J.M., Patchett, L., Webber, S.M., Wu, J., Ely, P. & Szczepiorkowski, Z.M. (2006) Implementation of peripheral blood CD34 analyses to initiate leukapheresis: marked reduction in resource utilization. *Transfusion*, **46**, 523–529.

Mehndiratta, M.M., Hughes, R.A. & Agarwal, P. (2004) Plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Systematic Reviews*, **2004**, CD003906.

Moog, R. & Moog, R. (2008) Management strategies for poor peripheral blood stem cell mobilization. *Transfusion & Apheresis Science*, **38**, 229–236.

Morath, C., Becker, L.E., Leo, A. *et al.* (2012) ABO-incompatible kidney transplantation enabled by non-antigen-specific immunoadsorption. *Transplantation*, **93**, 827–834.

Moreiras-Plaza, M., Albo, C. & Ares, C. (2004) Efficacy and safety of femoral vascular access for peripheral blood stem cell (PBSC) collection. *Bone Marrow Transplantation*, **33**, 347–350.

Morrell, M.R., Despotis, G., Lublin, D., Patterson, G.A., Trulock, E.P. & Hachem, R.R. (2010) The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. *Journal of Heart & Lung Transplantation*, **29**, 424–431.

National Cancer Institute. (2012) *Mycosis Fungoides and the Sézary Syndrome Treatment (PDQ®)* [Online]. URL http://www.cancer.gov/cancertopics/pdq/treatment/mycosisfungoides/HealthProfessional (Accessed 3/4/2013).

National Comprehensive Cancer Network. (2011) *NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas. Version 1.1* [Online]. URL http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf (Accessed 3/4/2013).

National Institute for Clinical Excellence (NICE). (2011) *Improving Outcomes for People with Skin Tumours Including Melanoma: Guidance of Cancer Services* [Online]. URL http://www.nice.org.uk/nicemedia/pdf/CSG_Skin_Manual.pdf (Accessed 3/4/2013).

National Institute for Clinical Excellence (NICE). (2012) *NICE Guidance, TA49 Central Venous Catheters - Ultrasound Locating Devices: Guidance* [Online]. URL http://guidance.nice.org.uk/TA49/Guidance/pdf/English (Accessed 26/10/2012).

National Institute for Health and Clinical Excellence (NICE). (2008) *Identification and Management of Familial Hypercholesterolaemia. NICE Clinical Guideline 71*. http://www.nice.org.uk/guidance/cg71/evidence/cg71-familial-hypercholesterolaemia-full-guideline3 (accessed 3rd April 2013).

NHS Sickle Cell and Thalassaemia Screening Programme (NHSSCTSP), and Sickle Cell Society. (2010). *Sickle Cell Disease in Childhood: Standards and Guidelines for Clinical Care* (2nd edn) [Online]. http://sct.screening.nhs.uk (Accessed 3/4/2013).

Okafor, C., Ward, D.M., Mokrzycki, M.H., Weinstein, R., Clark, P. & Baloquin, R.A. (2010) Introduction and overview of therapeutic apheresis. *Journal of Clinical Apheresis*, **25**, 240–249.

Olsen, E.A., Rook, A.H., Zic, J. *et al.* (2011) Sézary syndrome: immunopathogenesis, literature review of therapeutic options, and recommendations for therapy by the United States Cutaneous Lymphoma consortium (USCLC). *Journal of the American Academy of Dermatology*, **64**, 352–404.

Pavletic, S.Z., Martin, P., Lee, S.J. *et al.* (2006) Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. *Biology of Blood & Marrow Transplantation*, **12**, 252–266.

Petruzzo, P., Testelin, S., Kanitakis, J. *et al.* (2012) First human face transplant: 5 year outcomes. *Transplantation*, **93**, 236–240.

Quirolo, K., Bertolone, S., Hassell, K., Howard, T., King, K.E., Rhodes, D.K. & Bill, J. (2014) The evaluation of a new apheresis device for automated red blood cell exchange procedures in patients with sickle cell disease. *Transfusion* [Epub ahead of print; DOI: 10.11111/trf.12891].

Raphael, J.C., Chevret, S., Hughes, R.A. & Annane, D. (2002) Plasma exchange for Guillain-Barré syndrome. *Cochrane Database Systematic Reviews*, **2002**, CD001798.

Reinisch, W., Nahavandi, H., Santella, R. *et al.* (2001) Extracorporeal photochemotherapy in patients with steroid dependent Crohn's disease: a prospective pilot study. *Alimentary Pharmacology & Therapeutics*, **15**, 1313–1322.

Riddle, M.S., Jackson, J.L., Sanders, J.W. & Blazes, D.L. (2002) Exchange transfusion as an adjunct therapy in severe Plasmodium falciparum malaria: a meta-analysis. *Clinical Infectious Diseases*, **34**, 1192–1198.

Rogers, R.L. & Cooling, L.L.W. (2003) Therapeutic apheresis in pediatric patients. In: *Apheresis: Principles and Practice* (2nd edn) (eds McLeod, B.C., Price, T.H. & Weinstein, R.). AABB Press, Bethesda, MD.

Rubegni, P., Poggiali, S., Cevenini, G., D'Ascenzo, G., Perrone, A., Flori, M.L., Barbini, P. & Firniani, M. (2013) Long term follow-up results on severe recalcitrant atopic dermatitis treated with extracorporeal photochemotherapy. *Journal of the European Academy of Dermatology & Venereology*, **27**, 523–526.

SaBTO (Advisory Committee on the Safety of Blood Tissues and Organs). (2011) *Patient Consent for Blood Transfusion* [Online]. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_130716 (Accessed 26/10/2012).

Sanli, H., Akay, B.N., Ayyildiz, E., Anadolu, R. & Ilhan, O. (2010) Remission of severe autoimmune bullous disorders induced by long term extracorporeal photochemotherapy. *Transfusion & Apheresis Science*, **43**, 353–359.

Scarisbrick, J.J., Taylor, P., Holtick, U., Makar, Y., Douglas, K., Berlin, G., Juvonen, E. & Marshall, S. (2008) UK consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. *British Journal of Dermatology*, **158**, 659–678.

Schwartz, J., Winters, J.L., Padmanabhan, A. *et al.* (2013) Guidelines on the use of therapeutic apheresis in clinical practice – evidence-based approach from the Writing Committee of the American Society for Apheresis: the Sixth Special Issue. *Journal of Clinical Apheresis*, **28**, 145–284.

Scothorn, D.J., Price, C., Schwartz, D. *et al.* (2002) Risk of recurrent stroke in children with sickle cell disease receiving blood transfusion therapy for at least five years after initial stroke. *Journal of Pediatrics*, **140**, 348–354.

Scully, M., Hunt, B.J., Benjamin, S. *et al.* (2012) Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *British Journal of Haematology*, **158**, 323–335.

Shemin, D., Briggs, D. & Greenan, M. (2007) Complications of therapeutic plasma exchange: a prospective study of 1,727 procedures. *Journal of Clinical Apheresis*, **22**, 270–276.

Sickle Cell Society. (2008) *Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK* [Online]. http://www.sicklecellsociety.org (Accessed 3/4/2013).

Stegmayr, B.G., Ivanovich, P., Korach, J.M., Rock, G., Norda, R. & Ramlow, W. (2005) World Apheresis Association – World apheresis registry. *Transfusion & Apheresis Science*, **32**, 205–207.

Strauss, R.G. & McLeod, B.C. (2007) Complications of therapeutic apheresis. In: *Transfusion Reactions* (3rd edn) (ed Popovsky, M.A.). AABB Press, Bethesda, MD.

Swerdlow, P.S. (2006) Red cell exchange in sickle cell disease. *Hematology*, **2006**, 48–53.

Tan, D., Hwang, W. & Goh, Y.T. (2005) Therapeutic leukapheresis in hyperleukocytic leukaemias – the experience of a tertiary institution in Singapore. *Annals of the Academy of Medicine, Singapore*, **34**, 229–234.

Thompson, G.R., Barbir, M., Davies, D. *et al.* (2008) Recommendations for the use of LDL apheresis. *Atherosclerosis*, **198**, 247–255.

Trautinger, F., Knobler, R., Willemze, R. *et al.* (2006) EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome. *European Journal of Cancer*, **42**, 1014–1030.

Turner, J.M., Kaplan, J.B., Cohen, H.W. & Billett, H.H. (2009) Exchange versus simple transfusion for acute chest syndrome in sickle cell anemia adults. *Transfusion*, **49**, 863–868.

Tydén, G., Donauer, J., Wadström, J. *et al.* (2007) Implementation of a protocol for ABO-incompatible kidney transplantation – a Three-Center experience with 60 consecutive transplantations. *Transplantation*, **83**, 1153–1155.

Vahdat, L., Maslak, P., Miller, Q.H. Jr., Eardley, A., Heller, G., Scheinberg, D.A. & Warrell, R.P. Jr. (1994) Early mortality and the retinoic acid syndrome in acute promyelocytic leukemia: impact of leukocytosis, low-dose chemotherapy, PMN/RAR-alpha isoform and CD13 expression in patients treated with all-trans retinoic acid. *Blood*, **84**, 3843–3849.

Velasquez, M.P., Mariscalco, M.M., Goldstein, S.L. & Airewele, G.E. (2009) Erythrocytapheresis in children with sickle cell disease and acute chest syndrome. *Pediatric Blood & Cancer*, **53**, 1060–1063.

Vichinsky, E.P., Haberken, C.M., Neumayr, L. *et al.* (1995) A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. *New England Journal of Medicine*, **333**, 206–213.

Vichinsky, E.P., Neumayr, L.D., Earles, A.N. *et al.* (2000) Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *New England Journal of Medicine*, **342**, 1855–1865.

Vichinsky, E.P., Luban, N.L., Wright, E., Olivieri, N., Driscoll, C., Pegelow, C.H. & Adams, R.J. (2001) Prospective RBC phenotype matching in a stroke-prevention trial in sickle cell anemia: a multicenter transfusion trial. *Transfusion*, **41**, 1086–1092.

Watson, H., Davidson, S. & Keeling, D. (2012) Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition. *British Journal of Haematology*, **159**, 528–540.

Weinstein, R. (2007) Evidence of seriousness in apheresis medicine. *Journal of Clinical Apheresis*, **22**, 95.

Weinstein, R. (2010) Basic principles of therapeutic blood exchange. In: *Apheresis: Principles and Practice* (3rd edn) (eds McLeod, B.C., Szczepiorkowski, Z.M., Weinstein, R. & Winters, J.L.), 269–294. AABB Press, Bethesda MD.

Whittaker, S.J., Marsden, J.R., Spittle, M. & Russell, J.R. (2003) Joint British Society of Dermatology and U.K. Cutaneous Lymphoma group guidelines for the management of primary cutaneous T cell lymphomas. *British Journal of Dermatology*, **149**, 1095–1107.

Wilpert, J., Geyer, M., Teschner, S. *et al.* (2007) ABO-incompatible kidney transplantation – proposal of an intensified

apheresis strategy for patients with high initial isoagglutinine titers. *Journal of Clinical Apheresis*, **22**, 314–322.

Winters, J.L. (2012) Plasma exchange: concepts, mechanisms, and an overview of the American Society for Apheresis guidelines. *Hematology*, **2012**, 7–12.

Wolff, D., Schleuning, M., von, Harsdorf, S. *et al.* (2011) Consensus conference on clinical practice in chronic GVHD: second line treatment of chronic graft versus host disease. *Biology of Blood & Marrow Transplantation*, **17**, 1–17.

Wong, E.C.C. (2012) Techincal aspects. In: *Extracorporeal Photopheresis* (eds Greinix, H.T. & Knobler, R.), 8. De Gruyter, Berlin.

Wong, E.C. & Balogun, R.A. (2012) Therapeutic apheresis in pediatrics: technique adjustments, indications and nonindications – a plasma exchange focus. *Journal of Clinical Apheresis*, **27**, 132–137.