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BACKGROUND

Apheresis involves the removal of whole blood from an individual and its separation into components. A specified component is retained and the remainder is returned to the individual. Therapeutic apheresis is used to treat patients with a variety of disorders and has become a relatively common treatment modality. The rationale and techniques for therapeutic apheresis, as well as the care of the apheresis patient, will be discussed in this chapter.

PRINCIPLES OF APHERESIS

Therapeutic apheresis includes therapeutic plasma exchange (TPE), cytapheresis and photopheresis.

TPE is used for treatment of conditions caused by a harmful substance found in plasma. It may be used as a primary therapy for a disorder (for example, in immune thrombotic thrombocytopenic purpura, TTP) or as an adjunct to other therapies (for example, in anti-glomerular basement membrane disease). Treatment with TPE is based on the assumptions that 1) disease is caused by a pathogenic substance (e.g. antibody) found in blood; 2) the pathogenic substance can be efficiently removed from the blood and 3) removal or reduction of the amount of pathogenic substance will lead to resolution or improvement of disease manifestations. The effectiveness of TPE depends on the volume of plasma removed relative to the patient total plasma volume, the volume of distribution of the substance, the plasma protein binding affinity of the substance to be removed, and the number of procedures. TPE is much more effective at removing predominantly intravascular proteins and those which equilibrate rapidly between the intravascular and extravascular spaces. Finally, the rate at which the pathogenic substance is synthesized is important, with best therapeutic results of TPE when synthesis is slow.¹

Cytapheresis is used to deplete an overabundant or abnormal cellular blood component and includes erythrocytapheresis (depletion of red blood cells), leukopheresis (depletion of leukocytes or white blood cells) and thrombocytapheresis, also known as plateletpheresis (depletion of platelets). Cytapheresis may also involve collection of a specific subset of cells for therapeutic purposes (e.g. mononuclear cell (MNC) collection for stem cell transplantation or dendritic cells for cancer vaccines).

Erythrocytapheresis, or red cell exchange (RCE), is a procedure in which the patient's red blood cells are replaced with donor red blood cells. This can be performed manually or using a cell separator. For description of a manual RCE, refer to Swerdlow² and the text box below (Table 2) for sample calculations of volume of red blood cell units required. Usually 1.5 red cell volumes (RCV) are exchanged. For automated RCE, the device will calculate the volume of donor red blood cells required on the basis of patient's sex, height, weight, initial and final desired hematocrits, desired fluid balance, and desired fraction of cells remaining (FCR) – the percentage of the patient's red blood cells remaining in the circulation post-procedure. The average hematocrit of the donor units must also be entered into the device. The red blood cell volume to be exchanged depends on the desired FCR for the procedure, which in turn depends on the underlying condition. Indications for red cell exchange include: sickle cell disease with acute stroke (Category I), acute chest syndrome (Category II) and primary or secondary stroke prophylaxis (Category I); and severe babesiosis (Category II). Patients with sickle cell disease should ideally receive red blood cell units that are negative for hemoglobin S and phenotypically matched to the patient.

Leukocytapheresis may be indicated in patients with hyperleukocytosis and symptomatic leukostasis (Category II indication; see Indications section below). Leukostasis results from microvascular obstruction by leukocytes and may lead to endothelial injury, thrombosis and/or hemorrhage in various tissues and organs.

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Clinical signs and symptoms most often involve the brain and/or lungs. Leukostasis may arise in patients with acute myeloid leukemia and circulating white blood cell count exceeding 50,000–100,000 per microlitre. Leukocytapheresis can quickly lower white blood cell count and potentially reverse the symptoms of leukostasis, particularly if there is a delay in starting cytoreductive chemotherapy. In addition, leukocytapheresis may rarely be used to mitigate the extent of tumor lysis syndrome when it occurs with cytoreductive therapy. Usually a vascular catheter is required and 1.5–2.0 blood volumes are processed; an intra-procedural complete blood count (CBC) may be of value to confirm that the desired target reduction in white blood cell count has been achieved. Depending on the volume removed, the patient may or may not need to receive fluid replacement. Leukocytapheresis may need to be repeated daily and must be followed by initiation of chemotherapy to prevent hyperleukocytosis from re-occurring. Note that the ASFA guidelines indicate that there is no advantage to prophylactic leukocytapheresis.

Thrombocytapheresis may be indicated as a second-line therapy (Category II; see Indications section below) in patients with thrombocytosis due to a myeloproliferative neoplasm with an acute and severe thrombotic or hemorrhagic event. Thrombocytapheresis can quickly lower the platelet count and provide symptomatic relief while waiting for cytoreductive therapy to take effect. The procedure can be repeated as necessary. Usually 1.5–2.0 blood volumes are processed; an intra-procedural CBC may be of value to confirm that the desired target reduction in platelet count (usually below 400,000 per microlitre) has been achieved.

Finally, **photopheresis**, also known as extracorporeal photopheresis, is an immunomodulatory therapy. During photopheresis, peripheral blood MNC are collected, exposed extracorporeally to psoralen followed by UVA light, then re-infused back into the patient. Photopheresis is most commonly used to treat cutaneous T cell lymphoma and graft-versus-host disease (GVHD).

Centrifugation versus membrane filtration

The two main techniques for the separation of blood components during apheresis are centrifugation and membrane filtration.

Centrifugal apheresis can be used to remove cellular components and is very efficient, achieving plasma extraction of nearly 80%. It requires lower blood flow rates and therefore can be performed using either peripheral or central venous access. Centrifugal apheresis usually uses citrate as an anticoagulant. Centrifugation can be intermittent or continuous.

- **Intermittent flow centrifugation** involves the processing of small volumes of blood in cycles (a cycle consists of blood being drawn, processed, and re-infused). The advantage of using an intermittent flow instrument includes use of single site venous access; however, the procedure time is longer and larger fluctuations in extracorporeal blood volume occur as compared with continuous flow centrifugation.
- **Continuous flow centrifugation** involves the simultaneous removal, processing and re-infusion of blood components. Continuous flow instruments have the advantage of faster procedures, but require two sites of vascular access (or a central apheresis line with two lumens).

Membrane filtration devices allow for the selective removal of high molecular weight proteins by altering pore sizes of membranes and can be used as an alternative to centrifugal apheresis. Membrane filtration devices are not suitable for cytapheresis. These devices are less efficient as they have much lower plasma extraction (about 30%), use heparin as an anticoagulant and require much higher blood flow rates necessitating central vascular access.¹

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CARE OF THE THERAPEUTIC APHERESIS PATIENT

Apheresis is an invasive procedure that can have significant physiologic consequences. Apheresis centres should ideally have a quality management system including policies and procedures, qualified apheresis physicians and nurses, appropriately licensed machines with regular preventative maintenance and a mechanism to report and investigate adverse events.

Any patient requiring apheresis needs a medical history (including a medication review), physical examination and laboratory investigations. The medical history should focus on the indication for apheresis (e.g. diagnosis, current symptoms, appropriateness of request, concurrent treatments), and health-care providers should use this information to assess the patient's ability to tolerate the procedure and identify potential complications so they can be mitigated. The physical examination should include, at minimum, vital signs, height and weight, peripheral venous access assessment and volume status. Prior to the first apheresis treatment, laboratory tests should include: a complete blood count; electrolytes and creatinine; calcium, magnesium, phosphate, and albumin. Additional laboratory studies may also be necessary, depending on the indication for apheresis. Serologic testing and biochemical disease markers should be collected prior to apheresis to avoid inaccurate results. Since apheresis patients are exposed to large amounts of blood components and products, consider checking immunity against hepatitis B and offering vaccination if non-immune.

Informed consent for apheresis requires that the patient or substitute decision-maker is fully aware of the risks and potential benefits of this treatment. Furthermore, many jurisdictions also require a separate consent for blood and blood products.

Co-morbidities, concurrent treatments and medications should be taken into account while planning a course of apheresis. The treatment plan should be reviewed and adjusted regularly based on progress and any arising complications.

INDICATIONS

Therapeutic apheresis is a modality used for patients with various disorders yet for many there is a paucity of high-quality literature to support its use. The American Society for Apheresis (ASFA) publishes evidence-based guidelines on the therapeutic use of apheresis (last updated in 2016).³ The guidelines describe indications, type of replacement fluid, frequency and duration of apheresis treatment. The clinical disorders for which therapeutic apheresis is considered a standard and acceptable first-line therapy or a valuable adjunct therapy are Category I indications (Table 1). Category II indications are disorders for which apheresis is accepted as a second-line therapy, either alone or in combination with other modalities (e.g. acute disseminated encephalomyelitis). Indications for which an optimum role of apheresis has not been established and those in which apheresis has been found to be ineffective or harmful are designated as categories III and IV, respectively.

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Table 1. Category I indications for therapeutic apheresis (ASFA 2016 guidelines³)

<p>Therapeutic plasma exchange</p> <ul style="list-style-type: none"> • Thrombotic thrombocytopenic purpura • Thrombotic microangiopathy – due to anti-CFH, ticlopidine • Acute inflammatory demyelinating polyneuropathy (AIDP)/Guillain-Barré syndrome • Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) • Paraproteinemic demyelinating polyneuropathy (IgG/IgA, IgM) • Myasthenia gravis • Antiglomerular basement membrane disease (Goodpasture syndrome) • ANCA-associated rapidly progressive glomerulonephritis • Recurrent focal segmental glomerulosclerosis in transplanted kidney • Hyperviscosity syndrome • Desensitization for ABOI living donor liver transplantation • Desensitization for ABOI or ABO living donor kidney transplantation or antibody mediated rejection • NMDA antibody encephalitis • Progressive multifocal leukoencephalopathy post natalizumab • Acute liver failure • Wilson’s disease (fulminant)
<p>Cytapheresis</p> <ul style="list-style-type: none"> • Erythrocytapheresis <ul style="list-style-type: none"> ◦ Babesiosis – severe ◦ Malaria - severe ◦ Sickle cell disease (acute stroke, stroke prophylaxis) ◦ Hereditary hemochromatosis ◦ Polycythemia vera
<p>Photopheresis</p> <ul style="list-style-type: none"> • Cutaneous T-cell lymphoma (CTCL)

VASCULAR ACCESS⁴

Vascular access is required for apheresis. Ideally access should maintain a flow rate that allows a completed exchange to occur in less than three hours. For adults, the flow rate is usually 60-120 ml/minute. For centrifugal apheresis, vascular access may involve peripheral or central veins, or a combination of the two. Access through peripheral veins is preferred because it is associated with fewer infections, thrombotic complications, and insertion-related complications (bleeding or pneumothorax) as compared to central lines. When frequent procedures over a prolonged period of time are required, for example in TTP therapy, a double-lumen central venous catheter designed for apheresis or hemodialysis should be inserted. For patients requiring chronic apheresis, an arteriovenous fistula or an apheresis implantable access device may be used.

Technical problems with apheresis catheters such as leakage and inadequate flow rates can often be resolved by replacing the catheter over a wire and/or repositioning it, or clearing a blockage by using a fibrinolytic agent. Scarring and thrombosis as a result of repeated peripheral access may be reduced by rotating access sites.

TECHNICAL NOTES

Usually 1.0–1.5 plasma volumes are exchanged per apheresis treatment, and this translates into a removal of approximately 65%–80%, respectively, of intravascular plasma constituents. Plasma volume can be calculated

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on the basis of sex, height, weight, and hematocrit using one of the published formulas (e.g. an online calculator based on Nadler's method⁵) or estimated on the basis of sex and weight, as shown in Table 2 below. The frequency and duration of apheresis is dependent on the disease and the patient's response to treatment. Standardized apheresis regimens have been published for only a handful of disorders. To determine the frequency of treatments, the apheresis physician must balance the need for aggressive removal of the pathogenic substance versus allowing the substance to re-equilibrate into the intravascular space and minimizing complications. For example, a typical plasma exchange course of four to six sessions over 10–14 days can reduce immunoglobulin G (IgG) by 70–85%.⁶

A TPE order should include the following information:

- Number of plasma volumes (PV) to be exchanged;
- Replacement fluid to be used;
- Vascular access site;
- Anticoagulant (usually citrate);
- Final desired fluid balance; and
- Frequency and estimated total number of treatments.

Table 2. Sample calculations for apheresis

Estimated total blood volume (TBV) for adults per kg body weight:	
Male	70 ml/kg
Female	65 ml/kg
Red cell volume (RCV)	hematocrit (Hct) x TBV
Plasma volume (PV)	(1 - Hct) x TBV
<p>Examples:</p> <p>A) For a 70 kg male with Hct 0.35 undergoing 1.0 plasma volume (PV) exchange for TTP: TBV = 70 ml/kg x 70 kg = 4,900 ml PV = (1 - 0.35) x 4,900 ml = 3,185 ml Approximate number of frozen plasma (FP) units required (assuming 1 unit of FP is 250 ml* and 100% fluid replacement): 3185/250 = 12.7, rounded up to 13 units.</p> <p>B) For a 70 kg male with Hct 0.35 undergoing manual 1.5 RCV red cell exchange for acute chest crisis: TBV = 70 ml/kg x 70 kg = 4,900 ml RCV = 0.35 x 4,900 ml = 1,715 ml or 1.5 RCV = 1.5 x 1,715 ml = 2,572.5 ml Approximate number of red blood cell units required (assuming 1 unit of red blood cells is 250 ml* and 100% fluid replacement): 2572.5/250 = 10.3 rounded up to 11 units.</p> <p>*Approximation only. Please refer to Canadian Blood Services' Circular of Information and consult with hospital transfusion service for accurate estimates of the volume of frozen plasma⁷ and red blood cell units.⁸</p>	

ADVERSE EVENTS ASSOCIATED WITH APHERESIS

The rate of adverse events during apheresis is 4–5%, with the risk being slightly higher for the first procedure. Adverse events may be related to the vascular access, replacement fluid or the apheresis procedure itself. The Swedish Apheresis Group assessed more than 20,000 apheresis procedures and observed the following rates of

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adverse events: Grade 1 (mild severity) 1.5%, Grade 2 (moderate severity) 2.8%, Grade 3 (severe) 0.8% and Grade 4 (fatal) 0%.⁹ Adverse events related to vascular access account for about 1% of all adverse events, and include bleeding, pneumothorax, infections, and thrombosis. Adverse events related to replacement fluids may include transmission of infectious agents and transfusion reactions such as fever, allergic reactions and TRALI.

Risks of red blood cell exchange are the same as those of massive red blood cell transfusion: febrile reactions, alloimmunization, allergic reactions, citrate toxicity, TRALI, and transmission of blood pathogens.

The most common adverse event related to apheresis is citrate toxicity which may manifest as hypocalcemia on laboratory testing and clinically as paresthesias, nausea, vomiting, chills, twitching, tetany, seizures and cardiac arrhythmias. In patients with renal insufficiency, infusion of citrate can also lead to metabolic alkalosis. Other complications of apheresis include hypotension due to anemia, hypovolemia or vasovagal reactions; volume overload; cellular losses (iron deficiency anemia and thrombocytopenia); and electrolyte imbalances (hypocalcemia, hypomagnesemia). Furthermore, TPE may remove pharmacologic agents, especially those that are highly protein-bound or have a small volume of distribution. Adverse events and the frequency of these events are listed in Table 3.

The treatment of adverse events depends on the reaction. Mild symptoms of allergic reactions can be treated with antihistamines or corticosteroids. Pre-treatment with antihistamines and/or corticosteroids can be given to patients with previous allergic reactions. Alternatively, patients with thrombotic microangiopathies may be switched to solvent-detergent plasma (SDP). Hypotension can be treated by a fluid bolus, and prevented by withholding blood pressure medications, correcting anemia and hypovolemia prior to initiation of TPE and aiming for positive fluid balance post-apheresis. To prevent citrate toxicity, one can use a higher ratio of citrate-to-product and choose, if possible, non-citrated replacement fluids such as albumin. Prophylactic calcium replacement can also be considered.

TPE with albumin avoids some plasma-related complications but may lead to coagulopathy due to removal of clotting factors, including fibrinogen. Usually, however, the changes in coagulation parameters are not associated with clinically significant bleeding and normalise within 24 to 72 hours. Repeated apheresis procedures with albumin may also lead to severe hypogammaglobulinemia and consequently to increased risk of infection. Immunoglobulin levels usually return to the pre-treatment levels in about 3–4 weeks.

As patients with various clinical disorders are treated with therapeutic apheresis, the care of patients in this setting requires a multidisciplinary approach. Caution exercised during apheresis will limit the adverse effects experienced by patients.

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Table 3. Adverse events associated with TPE

Category	Symptom	Incidence (%)
Common events		<10%
Hypocalcemia	Parasthesias	1.5–9.0
Hypovolemia	Hypotension	0.4–4.2
	Muscle cramps	0.4–2.5
	Headaches	0.3–5.0
Anaphylactoid	Urticaria	0.7–12.0
	Rigors	1.1–8.8
Rare events		~1.5%
Cardiac	Myocardial ischemia or infarction or shock	0.1–1.5
	Arrhythmia	0.1–0.7
Pulmonary	Respiratory arrest/pulmonary edema	0.2–0.3
	Pulmonary embolism	0.1
Hematologic	Thrombosis/hemorrhage	0.02–0.7
Infectious	Hepatitis	0.7
	Other infection	0.3
Neurologic	Seizures	0.03–0.4
	Cerebrovascular ischemia	0.03–0.1
Miscellaneous	Hyperthermia	0.7–1.0

Adapted from Kaplan (1999).¹⁰

REPLACEMENT FLUIDS FOR APHERESIS

For red blood cell exchange, the replacement fluid is red blood cells. Red blood cell matching is important, particularly for sickle cell patients.

For TPE, the most commonly used replacement fluids are 5% human albumin solution and plasma, including cryosupernatant plasma (CSP), SDP, frozen plasma (FP) or fresh frozen plasma, (FFP). Some centres may also use normal saline or starches in combination with albumin or plasma. As 1.0–1.5 plasma volumes are typically removed with each plasma exchange, replacement of the intravascular volume is necessary. A replacement solution that exerts a colloid osmotic pressure equivalent to plasma prevents hypotension and edema.¹

The use of each of these replacement solutions has advantages and disadvantages summarized here:

- **Starches:** Each type of starch has a maximum daily dose that should not be exceeded. TPE with starch may lead to edema, electrolyte imbalances, pruritus and allergic reactions.
- **Albumin** (5% human albumin solution) can be used in a one-to-one replacement ratio, and is a good long-term volume expander with a half-life of 17 days. Albumin is pasteurized to prevent transmission of infectious agents and is usually well-tolerated. Complications may include febrile reactions, hypotension in the setting of angiotensin-converting enzyme (ACE) inhibitor use and hypokalemia.
- **Plasma** replaces coagulation factors and immunoglobulins. Plasma is associated with a higher risk of transmitting an infectious agent relative to starches and albumin. However, this risk is very low in Canada.

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Other complications of plasma include fever, allergic reactions and transfusion-related acute lung injury (TRALI). Furthermore, the substantial amount of citrate contained in plasma can lead to citrate toxicity and hypocalcemia.

- **CSP** is frequently used as a replacement fluid for patients with TTP. As CSP is devoid of the largest von Willebrand factor multimers thought to be pathogenic in TTP, it may offer an advantage over frozen plasma for these patients.¹¹⁻¹³
- **SDP** is used as a replacement fluid for patients with TTP or other thrombotic microangiopathies and when there is a history of allergic transfusion reaction or lung disease. SDP is pathogen inactivated, pooled fresh frozen plasma.

In general, TPE with plasma is reserved for treatment of patients with thrombotic microangiopathies. However, addition of plasma may also be indicated in patients who are coagulopathic, actively bleeding or imminently before or after major surgery.

CONTINUING PROFESSIONAL DEVELOPMENT CREDITS

Fellows and health-care professionals who participate in the Canadian Royal College's Maintenance of Certification (MOC) program can claim the reading of the Clinical Guide to Transfusion as a continuing professional development (CPD) activity under [Section 2: Self-learning credit](#). The reading of one chapter is equivalent to **two credits**.

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We're here to answer your questions about the Clinical Guide to Transfusion. We'd also appreciate your ideas on how to improve the Guide. Please contact us through the [Clinical Guide feedback form](#).

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