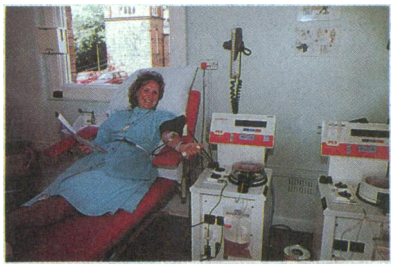
THERAPEUTIC APHERESIS

S J Urbaniak, E A Robinson



Dr Robinson giving her 50th donation of plasma.

Therapeutic apheresis is the removal of blood or one of its components from the body for clinical purposes, usually by automated blood cell separators. Cytapheresis removes cellular constituents, whereas in plasmapheresis the cells are returned and the plasma retained. When large volumes of material are removed some form of replacement is required and the procedure is one of "exchange" (for example, red cell exchange or plasma exchange); the terms plasmapheresis and plasma exchange are often (loosely) used interchangeably.

The procedures are not curative but are adjuncts to conventional treatment in which relief of symptoms or control of pathological processes may be achieved quickly. Rarely, long term control of a disease may be accomplished with less morbidity than with chemotherapy, as in the hyperviscosity of macroglobulinaemia.

Apheresis can affect only the intravascular compartment, and the efficacy of treatment will depend on the volume of blood processed, the rapidity with which the cells or plasma components can be mobilised from the extravascular compartments and the balance between catabolism and synthesis, on the one hand, and the constituents of the replacement fluid on the other.

Cytapheresis

Functions of plasma exchange

Removal of:

• Antibodies—alloantibodies	Anti-Rh(D) (Rh haemolytic disease)
—autoantibodies	Goodpasture's disease; myasthenia gravis
—immune complexes	Systemic lupus erythematosus
• Excessive or abnormal constituents	Paraproteins (multiple myeloma)
	Phytanic acid (Refsum's disease)
	Familial hypercholesterolaemia
• Protein bound toxins and drugs	α-Amanitin (mushroom poisoning)
• Antigens	Drug induced systemic lupus erythematosus

Replacement of:

- Factors in thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome
- Normal immunoglobulin
- Pseudocholinesterase

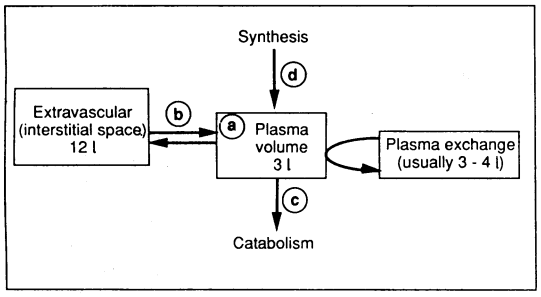
Red cells

In the strict sense, simple venesection or manual exchange transfusion is a form of cytapheresis that has been used for many years to treat polycythaemia, the acute crisis in sickle cell disease, and haemolytic disease of the newborn. Automated procedures aid the rapid, isovolaemic removal of large quantities of abnormal cells or unusually high concentrations of cells, or both. Rarely, patients with life threatening autoimmune haemolysis, severe parasitaemia in malaria or babesiosis, or acute porphyria have been managed successfully by erythrocytapheresis. Harvest of reticulocytes and young red cell "neocytes" for maintenance transfusion in—for example, thalassaemia—is under investigation.

Platelets

Thrombocytapheresis may be used to lower the platelet count rapidly in patients with myeloproliferative disorders and platelet counts of more than 1000×10^9/l, such as polycythaemia rubra vera, primary thrombocythaemia, and chronic granulocytic leukaemia. The main

concern is to prevent the development of thrombotic or haemorrhagic complications before conventional chemotherapy can control platelet production, which usually takes two to three weeks. Two or more procedures—either on consecutive or alternate days—are usually required to achieve adequate reduction in the platelet count. Asymptomatic thrombocytosis does not require removal of platelets unless the patient has a prolonged bleeding time and is about to undergo an operation. Long term thrombocytapheresis in chronic diseases is not effective.



Efficiency of depletion by plasmapheresis. Theoretically, 63% of the intravascular substance is removed by a single volume plasma exchange. The duration of reduction depends on: (*a*) intravascular/extravascular distribution of substance; (*b*) transcapillary exchange between intravascular and extravascular compartments; (*c*) fractional catabolic rate (equivalent to synthetic rate at steady state); and (*d*) rate of synthesis.

Leucocytes

Leucocytapheresis is indicated in various forms of leukaemia when white cell count is greater than 100×10^9/l. An extremely high white cell count will promote leucostasis with vascular occlusion in the microcirculation, and this can result in neurological abnormalities, thrombotic episodes, pulmonary dysfunction, and priapism. Leucocytapheresis can rapidly reduce both the white cell count and the blood viscosity and may be of benefit in the early management of leukaemia because it can prevent neurological and respiratory impairment while the cytotoxic chemotherapy is taking effect.

Reducing the number of circulating leukaemia cells ("debulking") before starting chemotherapy will reduce the risks of hyperuricaemia, and may increase the efficacy of chemotherapy in patients with acute myelocytic leukaemia. Even in the absence of leucostasis, early cytapheresis can bring symptomatic relief to a patient with night sweats, pruritis, and abdominal pain as a result of enlargement of the spleen and liver. Long term cytapheresis to maintain a low white count, however, is not justified.

Cytapheresis may also be used to harvest stem cells from blood for subsequent autologous transfusion, as an alternative to bone marrow.

Plasmapheresis/plasma exchange

Plasmapheresis is the selective removal of small volumes (<600 ml) of plasma that does not require intravenous fluid replacement. It is routinely carried out to harvest plasma from blood donors. Plasma exchange is the removal of a larger volume of plasma, which requires replacement by an appropriate fluid to maintain homoeostasis.

Purpose of plasma exchange

The aim is to remove, or reduce to a minimum, those constituents of plasma that cause or aggravate a disease. To be of benefit plasma exchange must remove some pathogenic material that is known to be present in plasma in appreciable quantities, the removal must be more rapid than renewal, the underlying disease should be sufficiently serious to outweigh the risks of exchange, and there should be a reasonable chance of recovery. The most common diseases are immunological, and an antibody (IgG or IgM), an antigen, or an immune complex is removed. To prevent rebound synthesis immunosuppression must be combined with plasma exchange as plasma exchange alone is ineffective. In some instances there is a deficiency of, or defect in, some plasma factors that can effectively be replaced by large volume plasma exchange with fresh frozen plasma—for example, in patients with thrombotic thrombocytopenic purpura.

Many diseases have been treated by plasma exchange, but it is most successful when there is a measurable, well characterised, pathogenic substance present which causes acute tissue or organ damage that is reversible or preventable by timely intervention.

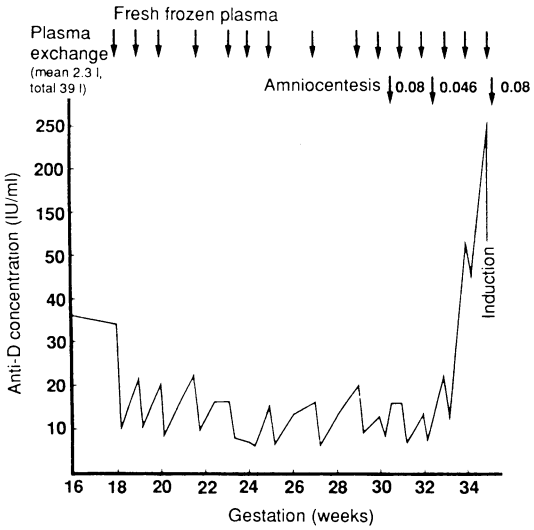
*Diseases in which plasma exchange is often of benefit**

Disease	Pathogenic factors (which may be used to monitor efficiency of treatment or progress of disease)
Hyperviscosity syndrome (Waldenström's macroglobulinaemia, multiple myeloma)	Monoclonal immunoglobulins (hyperviscosity)
Myasthenia gravis	Anti-ACh receptors
Goodpasture's syndrome	Anti-glomerular basement membrane
Cryoglobulinaemia	Cryoglobulins
Haemophilia with inhibitors	Anti-factor VIII inhibitor
Refsum's disease	Phytanic acid
Thrombotic thrombocytopenic purpura	Unknown
Cold agglutinin haemolytic anaemia	Agglutinin
Poisons (for example, mushrooms)	α-Amanitin
Drugs	Parathion-methyl, digoxin

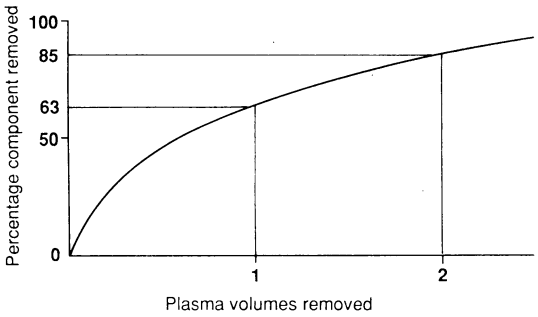
*Not necessarily in all cases and usually only when acute symptoms have not responded to conventional treatment.

Diseases in which plasma exchange may be of benefit

- Familial hypercholesterolaemia
- Acute Guillain-Barré syndrome
- Immune complex vasculitis—
  Systemic lupus erythematosus
  Rheumatoid arthritis
- Rapidly progressive glomerulonephritis
- Rh haemolytic disease
- Post-transfusion purpura
- Bullous pemphigoid

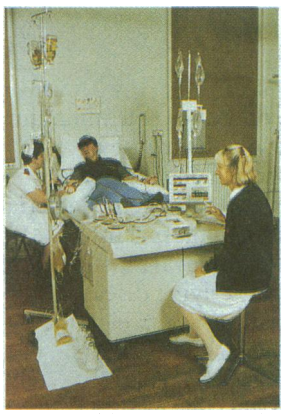


Note rapid rise in anti-D after stimulus of aminocentesis released Rh positive red cells in a pregnant woman undergoing plasma exchange for haemolytic disease of the newborn who was not immunosuppressed.



Efficiency of plasma exchange: removal of constituents of plasma becomes less efficient after 1·5 times plasma volume has been exchanged.

Techniques of apheresis



Patient with myeloma undergoing plasma exchange.

Complications of apheresis

Complications can—and do—occur

Volume and frequency of plasma exchange

Normal healthy donors undergoing plasmapheresis do not require replacement of fluids. If more than 1 litre is removed, however, replacement of albumin is necessary, otherwise vasular colloid osmotic pressure will fall and haemodilution and peripheral oedema will occur. The choice of replacement fluid is based on cost, convenience, availability, and volume removed. Partial substitution with 0·9% saline or colloids (such as hydroxyethyl starch or gelatins), or both, is acceptable.

The volume and frequency of plasma exchange is determined by the pathophysiology of the "undesirable" factors. There may be unwanted side effects from the removal of normal constitutents that may be of sufficient severity to require specific replacement. Albumin, the immunoglobulins, complement, and coagulation factors are the main components of plasma proteins that are affected by large volume plasma exchange. A single volume plasma exchange (40 mg/kg) will reduce the concentrations of immunoglobulins, complement proteins, fibrinogen, and other coagulation factors by 50-60% if the plasma is not replaced. Most constituents, however, return to normal within 24 to 48 hours. The efficiency of removal of antibody is often less than anticipated because of rapid resynthesis during an immune response.

Because of the reduction in efficiency it is usual practice to exchange only 1·5 times the estimated plasma volume during each procedure (about 3-4 litres) and to repeat this daily or on alternate days until the desired reduction is obtained. Effective treatment of the underlying disease (usually by immunosuppression) prevents further production of abnormal constituents. Rarely there is a need to replace immunoglobulins, complement, or coagulation factors, in which case fresh frozen plasma may be used as the exchange fluid (as, for example, in thrombotic thrombocytopenic purpura). Fresh frozen plasma does, however, carry a risk of serious allergic reactions and transmission of viral disease (notably hepatitis).

Automated apheresis procedures require good venous access with a blood flow of 50-100 ml/minute if efficient processing is going to be accomplished within a reasonable period.

Various blood cell separators have been developed, some of which operate on single vein systems that are better suited to donor apheresis; these are slower than the true continous flow systems that require one vein for withdrawal and a second for return. Centrifugal continuous flow systems are usually multipurpose and can be adapted for cell or plasma removal under operator control. The centrifugal devices separate by differential cell density at different *g* forces, whereas membrane separators operate by different pore sizes in flat bed, cylindrical, or hollow fibre cartridges with blood under pressure. All modern devices have safety features: pressure sensor alarms, microfilters, air detectors, metered pumps, and sensors for filtration pressure or centrifuge speed, depending on the system. Most have microchip controls with preprogrammed settings, which allow comparatively inexpert operators to achieve acceptable results. Training of operators and supervisors is essential, and adequate facilities for resuscitation are required in case there are unexpected side effects, which can be serious.

Apheresis is comparatively safe, many procedures being carried out all over the world without problems; appreciable problems (including death) may, however, occur. Achieving adequate venous access can lead to vascular damage resulting in thrombosis, perforation, infection, and gangrene, leading to amputation of the limb. Replacement with fresh frozen plasma in plasma exchange can give rise to viral hepatitis, anaphylactic

Complications of apheresis

Vascular access
- Haematoma, thrombosis, sclerosis gangrene
- Perforation of artery
- Sepsis through catheter sites
- Surgical shunts or fistulas

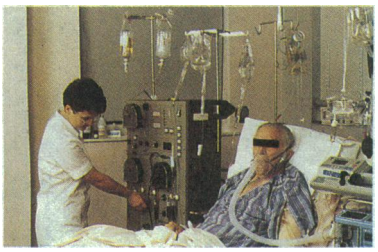
Procedural problems
- Vasovagal, hypovolaemic, hypotensive
- Hypervolaemia (overload)
- Mechanical haemolysis
- Air embolus
- Citrate toxicity
- Chills, rigors, nausea

Effects of replacement fluid
- Allergic reactions, including anaphylaxis
- Electrolyte imbalance
- Viral hepatitis
- Citrate toxicity
- Hypoproteinaemia
- Haemorrhage
- Bacterial infection
- Suxamethonium apnoea

reactions, and citrate toxicity. Some procedural reactions are associated with the rate and volume of removal or replacement by an extracorporeal circuit and with inexperienced operators.

Throughout the world 50 deaths have been reported, principally among patients who received fresh frozen plasma as the exchange fluid, and causes include the adult respiratory distress syndrome, cardiac arrhythmia, and viral hepatitis. The reported overall mortality is about three for every 8000 procedures.

Future applications



Patient with Goodpasture's disease undergoing plasma exchange.

Therapeutic apheresis is no longer the fashionable treatment that is used when all else fails. Controlled trials have shown no benefit from its use in patients with multiple sclerosis, rheumatoid arthritis, or Crohn's disease or in the long term management of systemic lupus erythematosus, myasthenia gravis, or scleroderma. In some diseases high intravenous doses of immunoglobulins seem to be as successful as plasma exchange, if not more so, without the same degree of risk or use of resources.

Technological developments include the use of specific absorbents (for example, staphylococcal protein A for IgG antibodies, DNA collodion charcoal for immune complexes in systemic lupus erythematosus, and anti-low density lipoprotein sepharose for hypercholesterolaemia); with these it is possible to forgo total plasma replacement and remove only the desired constituent.

An alternative approach is cascade filtration with different pore sizes, in which plasma is collected and passed through a second filter that retains macromolecules but allows the passage of albumin.

The diagram of the rise in anti-D after amniocentesis is published by permission of Blackwell Scientific Publications Ltd, and the colour photographs by courtesy of the Audiovisual Department, St James's University Hospital, Leeds.

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