In hemapheresis, whole blood is removed from a donor or patient; separated into components, of which one or more are retained; and recombined so that the remaining elements are returned to the donor or patient. Apheresis means “to remove.” Hemapheresis can be used to collect a component intended for transfusion or to treat a patient’s disease by removing a pathologic component.

This chapter is divided into two sections: component preparation and therapeutic applications. Cell-separator devices can be used for either application. Manual plasmapheresis, in which whole blood is collected in multiple bags and centrifuged off-line, is simple and inexpensive, but time-consuming. It also carries a risk that red cells could be returned to the wrong donor. The manual procedure is described in detail in Method 9.14.

AABB Standards for Blood Banks and Transfusion Services and the Code of Federal Regulations set forth regulations for hemapheresis activities. The Food and Drug Administration (FDA) and the American Society for Apheresis have published guidelines and recommendations. All personnel involved with hemapheresis activities should be familiar with these sources, and should have documentation that they are qualified by training and experience to perform apheresis. Because apheresis is more complex than ordinary blood donation, the apheresis facility must have adequate provisions to care for unusual reactions. These should include equipment, medications, personnel training, and prompt availability of medical care for serious problems.

Separation Devices

Separation by Centrifugation

In most apheresis machines, centrifugal force separates blood into components based on differences in density. A measured amount of anticoagulant solution is added to the whole blood as it is drawn from the donor or patient. The blood is pumped into a rotating bowl, chamber,
or tubular rotor in which layering of components occurs. The desired fraction is diverted and the remaining elements are returned to the donor (or patient) by intermittent or continuous flow.

All such systems require prepackaged sets of sterile bags, tubing, and centrifugal devices unique to the machine. Each machine has a mechanism to allow the separation device to rotate without twisting the attached tubing. In the intermittent flow method, the centrifuge container is alternately filled and emptied, and the same intravenous access line is used for both withdrawing and returning the blood. The continuous flow method requires two venous accesses, one for removal and the other for return. Some instruments can be used in either a continuous or intermittent mode. Depending on the procedure and device used, the time varies from 30 minutes to about 2 hours.

Each manufacturer supplies detailed information and operational protocols. Each facility must have, in a manual readily available to nursing and technical personnel, detailed descriptions of each type of procedure performed, specific for each type of cell separator.

**Separation by Membrane Filtration**

Filtration of plasma through a membrane allows collection of plasma from healthy donors or therapeutic removal of abnormal plasma constituents, but does not partition cellular elements. In these instruments, whole blood flows across a membrane containing pores of a defined size. Higher pressure in the blood phase than in the filtrate pushes plasma constituents smaller than the pore size through the membrane into the filtrate. Most instruments have the membranes arranged as hollow fibers but some have flat plates. Surface properties of the inner membrane surface repel cellular elements in the laminar flow of blood so that platelets are not activated and red cell survival is not shortened. Plasma permeates the membrane matrix and escapes at right angles to the stream of flow. Varying the pore size allows a degree of selection in the removal of plasma proteins.

**Separation by Adsorption**

Selective removal of a pathologic material has theoretical advantages over the depletion of all plasma constituents. Both membrane and centrifugal devices can be adapted to protocols that selectively remove specific soluble plasma constituents by exploiting the principles of affinity chromatography. Selective removal of low-density lipoproteins (LDLs) in patients with familial hypercholesterolemia has been accomplished using both immunoaffinity (anti-LDL) and chemical affinity (dextran sulfate) columns. Sorbents such as staphylococcal protein A (SPA), monoclonal antibodies, blood group substances, DNA-collodion, and polymers with aggregated IgG attached, can extract antibodies, protein antigens, and immune complexes. Returning the depleted plasma along with the cellular components reduces or eliminates the need for replacement fluids. Immunoadsorption may be performed in-line, or the plasma may be separated from the cellular components, passed through an off-line column, and then reinfused.

Uncontrolled studies suggest that SPA immunoadsorption may be effective in the treatment of acute and chronic immune thrombocytopenic purpura, thrombocytopenia associated with human immunodeficiency virus (HIV) infection, alloimmune platelet refractoriness, hemolytic uremic syndrome, and selected malignancies such as Kaposi’s sarcoma and breast cancer. Patients taking agents that inhibit angiotensin-converting enzyme (ACE inhibitors) have
experienced severe hypotensive episodes when treated with SPA columns and with other immunosorbents. Many of these protocols are still experimental and randomized trials have not been done. Patients with these complex immune-related conditions frequently receive multiple treatments simultaneously. Because controlled trials of immunoabsorption have not been performed, it is difficult to evaluate the efficacy of this technique. Because adsorption methods can remove only a proportion of the pathologic factor they are designed to retain, and because the treated plasma is returned to the patient’s circulation, adsorption techniques would be expected to be less effective than techniques that divert plasma for discard.

Component Collection by Apheresis

Whenever components intended for transfusion are collected by apheresis, the donor must provide informed consent. The facility must maintain written protocols for all procedures used and must keep records for each cytapheresis procedure. These records include data on the identity of the donor and the results of laboratory tests that qualify the donor; the drugs or other agents administered to the donor; the duration of the procedure, the volume of components collected, and the lot numbers of disposables and replacement fluids; and any reactions that occurred, with information about treatment and follow-up.

Platelet Concentrates

Cytapheresis is used to obtain platelets from unselected volunteer donors, from patients’ family members, or from donors with selected HLA phenotypes. Because large numbers of platelets can be obtained from a single individual, collection by hemapheresis helps limit the number of donor exposures that patients receive. For alloimmunized patients refractory to random allogeneic platelets (see Chapters 15 and 19), platelets from a hemapheresis donor selected on the basis of a compatible platelet cross-match or matched for HLA antigens may be the only way to achieve a satisfactory increment.

Donor Selection and Monitoring

Plateletpheresis donors may donate more frequently than whole blood donors, but must meet all other donor criteria. The interval between donations should be at least 48 hours and donors should not undergo plateletpheresis more than twice in a week or 24 times in a year. If the donor donates a unit of Whole Blood or if it becomes impossible to return the donor’s red cells during plateletpheresis, at least 4 weeks should elapse before a subsequent cytapheresis procedure. Donors who have taken aspirin, or other medications that alter platelet function, within the previous 3 days are usually deferred, because the platelets obtained by apheresis are often the single source of platelets given to a patient. Platelets may be collected from donors who do not meet these requirements if the component is expected to be of particular value to a specific intended recipient and if a physician certifies in writing that the donor’s health will not be compromised. Vasovagal and hypovolemic reactions are rare in apheresis donors, but paresthesias and other reactions to citrate are not uncommon. Serious reactions occur no more often among apheresis donors than among whole blood donors.

Plateletpheresis donors should meet usual donor requirements, including hemoglobin or hematocrit level. A platelet
count is not required before the first apheresis collection or if 4 weeks or more have elapsed since the last procedure. If the donation interval is less than 4 weeks, the donor’s platelet count should be above 150,000/µL before subsequent plateletpheresis occurs. AABB permits this to be documented from a sample collected immediately before the procedure or from a sample obtained either before or after the previous procedure. The FDA specifies that the total volume of plasma collected should be no more than 500 mL (or 600 mL for donors weighing more than 175 pounds). The platelet count of each unit should be determined and kept on record, but need not be written on the product label.

Some plateletpheresis programs collect plasma for use as Fresh Frozen Plasma (FFP) in a separate bag during platelet collection. Apheresis can also be used to collect plasma for FFP without platelets. In both instances a total serum or plasma protein determination and a quantitative determination of IgG and IgM must be determined at 4-month intervals for donors undergoing plasma and platelet collection more often than once every 8 weeks, unless a variance is obtained from the FDA.

### Laboratory Testing of the Unit

Tests for ABO and Rh type, unexpected alloantibodies, and markers for transfusion-transmitted diseases must be done by the collecting facility in the same manner as for other blood components. Each unit must be tested unless the donor is undergoing repeated procedures for the support of a single patient, in which case testing for disease markers need be repeated only at 10-day intervals. AABB requirements are more stringent in this respect than those of the FDA, which require testing only once at the beginning of a donation period not to exceed 30 days.

If a cytapheresis unit contains visible red cells, a hematocrit should be determined. FDA guidelines require that, if the component contains more than 2 mL of red cells, a sample of donor blood for compatibility testing be attached to the container. AABB requires crossmatching if the unit contains more than 5 mL of red cells, and permits the crossmatch to be performed on red cells from a properly identified sample collected from the donor at the time of phlebotomy. It is desirable for the donor plasma to be ABO-compatible with the recipient’s red cells, especially if the recipient is a small infant. Quality control of plateletpheresis components is discussed in Chapter 7.

### Records

Complete records (see Chapter 1) must be kept for each procedure. All adverse reactions should be documented along with the results of their investigation and follow-up. For donors undergoing hemapheresis more often than once every 4 weeks, records of all laboratory findings and collection data must be periodically reviewed by a knowledgeable physician and found to be within acceptable limits. FDA guidelines call for review at least once every 4 months; if values are outside accepted limits, there must be a signed statement explaining exceptions. A cumulative record of red-cell losses is required for each donor, to ensure that red-cell loss in a year does not exceed the level of loss permitted for whole blood collection.

### Plasma

Apheresis can be used to collect plasma for transfusion as FFP or for Source Plasma for further manufacturing. FDA requirements for plasma collection are
different from those for whole blood or plateletpheresis; personnel who perform serial plasmapheresis must be familiar with both AABB and FDA standards. If plasma is intended for transfusion, testing requirements are the same as those for red cell components. Plasma collected for manufacture of plasma derivatives is subject to different requirements for viral testing.

A distinction is made between “occasional plasmapheresis,” in which the donor undergoes plasmapheresis no more often than once in 4 weeks, and “serial plasmapheresis,” in which donation is more frequent than every 4 weeks. For donors in an occasional plasmapheresis program, donor selection and monitoring is the same as for Whole Blood donation. For serial plasmapheresis using either automated instruments or manual techniques, the following principles apply:

1. Donors must provide informed consent. They must be observed closely during the procedure and emergency medical care must be available.

2. Red cell loss incidental to the procedure, including samples collected for testing, should not exceed 25 mL per week, so that no more than 200 mL of red cells are removed per 8 weeks. If the donor’s red cells cannot be returned during an apheresis procedure, hemapheresis or whole blood donation should be deferred for 4 weeks.

3. In manual plasma collection systems, there must be a mechanism to ensure safe reinfusion of the autologous red cells. Before the blood container is separated from the donor for processing, there should be two separate, independent means of identification, so that both the donor and the phlebotomist can ascertain that the contents are those of the donor. Often the donor’s signature is one identifier, along with a unique number.

4. In manual procedures on donors weighing between 50 and 80 kg (110-176 lbs), no more than 500 mL of whole blood should be removed for processing at one time, or 1000 mL during the session or within a 48-hour period. The limits for donors above 80 kg are 600 mL and 1200 mL, respectively. For automated procedures, allowable volume is determined for each instrument by the FDA approval process.

5. At least 48 hours should elapse between successive procedures and donors should not, ordinarily, undergo more than two procedures within a 7-day period. Exceptions may be permissible when plasma is expected to have special therapeutic value for a single recipient or if the collection is part of an investigational procedure.

6. At the time of initial plasmapheresis and at 4-month intervals thereafter for donors undergoing plasmapheresis more often than once every 4 weeks, serum or plasma must be tested for total protein and IgG and IgM content. Results must be within normal limits.

7. A qualified, licensed physician, well-versed in all aspects of hemapheresis, must be responsible for the program.

Granulocyte Concentrates

The therapeutic efficacy and indications for granulocyte transfusion are not well-defined. Although early studies showed benefit in adults with reversible neutropenia and documented gram-negative infections that did not respond to adequate antibiotic treatment, subsequent experience in marrow-transplant patients with fungal infections has been disappointing.

Granulocyte con-
centrates can induce HLA alloimmunization, may transmit CMV infection, and if not irradiated may cause graft-vs-host disease in susceptible recipients. Alloimmunized recipients may sequester HLA-incompatible transfused granulocytes in the pulmonary vasculature. Prophylactic granulocyte transfusions to adults were abandoned due to excessive pulmonary toxicity and lack of demonstrable efficacy. Better antimicrobial agents and the use of hematologic growth factors such as granulocyte and granulocyte-macrophage colony-stimulating factors (G-CSF and GM-CSF) have largely supplanted granulocyte transfusion as therapy for adults. Better success with granulocyte transfusions has been observed in the treatment of septic infants, possibly because the dose is relatively larger in tiny recipients or because HLA alloimmunization is absent.

**Drugs Administered for Leukapheresis**

A daily dose of $10^{10}$ functional granulocytes and, preferably more if possible, is necessary to achieve a therapeutic effect. Collection of this many cells, with most available equipment, requires administration of drugs or other adjuvants to the donor.

**Hydroxyethyl Starch.** Granulocyte harvest can be improved by more complete separation between granulocytes in the lower, denser portion of theuffy coat and the underlying red cells. Rouleaux-promoting agents cause red cells to aggregate and thereby sediment more completely than single cells during centrifugation. This enhances granulocyte harvest and minimizes red-cell contamination of the component. Hydroxyethyl starch (HES) is a synthetic polymer of amylopectin that, when present in the donor’s circulation, greatly increases separation between red cells and granulocytes. Although cleared by macrophages from the circulation with an intravascular half-life of 24-29 hours, residual HES can be detected for as long as a year after injection. Facilities performing granulocyte collections must have a written policy indicating the maximal cumulative dose of any sedimenting agent administered to the donor within a given interval. Since HES is a colloid, it acts as a volume expander, and donors who have received HES may experience headaches or peripheral edema because of expanded circulatory volume.

**Corticosteroids.** Granulocyte yields depend upon the level of cells circulating at the time of leukapheresis, so raising the circulating cell count increases the number of cells collected. Corticosteroids cause granulocytes in the storage pool to enter the circulation and also decrease egress of granulocytes from the peripheral blood. Oral corticosteroid preparations (hydrocortisone, prednisone, methylprednisolone or dexamethasone) may be given before cytapheresis to increase the donor’s circulating granulocyte count. Corticosteroids can double the number of circulating granulocytes, but total granulocyte harvest is affected by variables of dosage, timing, and route of administration. A protocol using 20 mg of oral prednisone at 17, 12, and 2 hours before donation gives superior granulocyte harvests with minimal systemic steroid activity. Before administration of predonation corticosteroids, donors should be questioned about history of symptoms of hypertension, diabetes, and peptic ulcer. Steroids should not be given to donors with previous or current disease that might be exacerbated by these agents. The consent must include specific permission for any drugs or sedimenting agents to be used.

**Growth Factors.** Hematopoietic growth factors such as G-CSF or GM-CSF may be effective agents to increase granulocyte yields. Administration of G-CSF can result in collection of up to $10 \times 10^{10}$ granulocytes per apheresis.
Preliminary evidence suggests that in-vivo recovery and survival of these granulocytes is excellent and that G-CSF is well tolerated by donors.

**Laboratory Testing of Granulocyte Concentrates**

Testing for ABO and Rh type, antibody screening, and testing for infectious disease markers on a sample drawn at the time of phlebotomy are required. If possible, testing should be accomplished during the donation, to avoid delay in administration of the granulocyte concentrate. Red cell contamination of granulocyte concentrates is inevitable; the red cells should be ABO-compatible with the recipient’s plasma and, if more than 5 mL are present, the component should be crossmatched. D-negative recipients should, ideally, receive granulocyte concentrates from D-negative donors. Each facility should have a written policy about management of D-negative patients exposed to D-positive red cells in component preparations.

Records must be kept of concentrate volume, white blood cell count, differential leukocyte count, and calculation of total number of granulocytes. The donor’s red cell loss and the amount of HES given with each procedure should be documented in records of both the apheresis procedure and of the individual donor. Standards requires granulocyte content of at least $1 \times 10^{10}$ in 75% of the units tested.

**Storage and Infusion of Granulocytes**

Because granulocyte function deteriorates during storage, concentrates should be transfused as soon as possible after preparation. Standards prescribes a storage temperature of 20-24 °C, for no longer than 24 hours. Agitation during storage is probably undesirable. Irradiation is required before administration to immunodeficient recipients and will probably be indicated for nearly all recipients because of their primary disease. Infusion through a microaggregate filter may impair clinical efficacy and should be avoided.

**Hematopoietic Progenitor Cells**

Cytapheresis for collection of hematopoietic progenitor cells is especially useful in obtaining autologous progenitor cells for bone marrow reconstitution in patients with cancer, leukemia in remission, and various lymphomas. See Chapter 23. Multiple collections are made before the patient receives high-dose myelosuppressive chemotherapy and/or irradiation. The number and frequency of the apheresis procedures are determined for each donor-patient based on the yield of cells obtained and the clinical condition of the patient. The use of single or multiple growth factors generally improves the yield of hematopoietic stem cells.

Progenitor cells can be collected from the circulating blood of healthy donors for allogeneic bone marrow reconstitution. Selection criteria are comparable to those for cytapheresis donors, with allowance for the special importance of HLA matching of donors for bone marrow reconstitution. Prospective donors of hematopoietic progenitor cells must be given the same information as blood donors about the importance of medical history and testing in reducing disease transmission. The procedure must ensure that consent is truly informed and that there is appropriate care of autologous or allogeneic donors during apheresis.

For all progenitor cell collections, the apheresis facility must maintain complete records. See Chapters 1 and 23. The facility’s procedures manual should include protocols for the manipulation and storage of the peripheral blood pro-
genitor cells collected and for the procedures used to evaluate the quantity and quality of the preparations. Initial testing of the donor’s blood should be identical to that done on Whole Blood intended for transfusion. When there are repeated collections from a single donor to support a single recipient, testing is performed at least every 10 days. The system for labeling, storage, and record-keeping must be consistent with AABB Standards. Progenitor cells intended for hematopoietic reconstitution must not be irradiated, but they may be processed and cryopreserved.

Therapeutic Apheresis

Therapeutic apheresis has been used to treat many different diseases. Cells, plasma, or plasma constituents may be removed from the circulation, and replaced by normal plasma or solutions of electrolytes or albumin. The extensive literature on therapeutic apheresis provides no consistent use of terms “plasmapheresis” and “plasma exchange.” Sometimes the term “plasmapheresis” is used to connote volume replacement with crystalloid and/or albumin, with “plasma exchange” reserved for procedures in which extracted plasma is replaced with plasma. Others use the term “therapeutic plasma exchange” to include all therapeutic procedures regardless of the replacement solution. In this chapter, the term “therapeutic apheresis” will be used for the general procedure and the term “therapeutic plasma exchange” (TPE) will be used for procedures in which the goal is removal of plasma, regardless of which solution is used for replacement.

The theoretical basis for therapeutic apheresis is to reduce the patient’s load of some pathologic substance to levels that will allow improvement in the course of the disease. In some conditions, replacement with normal plasma is intended to supply an essential substance that is absent. Other possible outcomes of therapeutic apheresis include alteration of the antigen-to-antibody ratio, modification of mediators of inflammation or immunity, clearance of immune complexes, and a placebo effect. Despite difficulties in documentation, there is general agreement that therapeutic apheresis is effective treatment for certain conditions as listed below:

- Hematology/oncology conditions
  - Paraproteinemias
  - Hyperleukocytosis
  - Thrombocytopenia
  - Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)
- Sickle cell disease
- Posttransfusion purpura
- Neurology conditions
  - Acute Guillain-Barré syndrome
  - Chronic inflammatory polyneuropathy
  - Myasthenia gravis
- Other conditions
  - Cryoglobulinemia
  - Rapidly progressive glomerulonephritis associated with antibody to neutrophil cytoplasmic antigen
  - Homozygous Type II familial hypercholesterolemia
  - Refsum’s disease

General Considerations for Therapeutic Apheresis

Avoiding overuse or underuse of therapeutic apheresis requires considerable medical knowledge and judgment. The patient should be evaluated for the treatment by his or her personal physician and by the physician in charge of the apheresis team. Close consultation between these physicians is important, especially if the patient is small or elderly,
has poor vascular access or cardiovascular instability, or has a condition for which apheresis is of uncertain benefit. The physician responsible for the apheresis team should make the final determination about appropriateness of the procedure and suitability of the patient.

When therapeutic apheresis is planned, those involved with the patient’s care should establish a treatment plan and the goal of therapy. The endpoint may be an agreed-upon objective outcome or a predetermined duration for the therapy, whichever is achieved first. It is helpful to document these mutually acceptable goals in the patient’s medical record. The nature of the procedure, its expected benefits, its possible risks, and the available alternatives should be explained to the patient by a knowledgeable individual, and the patient’s decision should be documented. The procedure should be performed only in a setting where there is ready access to care for untoward reactions, including equipment, medications, and trained personnel appropriate for managing serious problems.

**Vascular Access**

For most adult patients needing a limited number of procedures, the antecubital veins are suitable for removal of blood; for continuous flow procedures, blood can be returned via an indwelling peripheral intravenous line. For critically ill adults and for children, indwelling central or peripheral venous catheters are typically used. Especially effective are rigid-wall, large-lumen, double-bore catheters placed in the subclavian or internal jugular vein. These catheters, of the type used for temporary hemodialysis, allow both removal and return of blood at high flow rates. Central catheters can be maintained for weeks if multiple procedures are necessary.

**Removal of Pathologic Substances**

During TPE, there is continuous removal of plasma that contains the pathologic substance and infusion of replacement fluid. The efficiency with which material is removed can be estimated by calculating the patient’s plasma volume and using [Fig 6-1] Such
estimation depends on the following assumptions: 1) the patient’s blood volume does not change; 2) mixing occurs immediately; and 3) there is relatively little production or mobilization of the pathologic material during the procedure. As seen in Fig 6-1, removal is greatest early in the procedure and diminishes progressively during the exchange. Exchange is usually limited to 1-1.5 plasma volumes, approximately 40 mL plasma exchanged per kg of body weight, depending upon the hematocrit. This maximizes the efficacy per procedure but may make it necessary to repeat the process. Rarely, two or three plasma volumes are exchanged in one procedure. This causes greater initial diminution of the pathologic substance, but overall is less efficient and requires considerably more time to complete. There are no clinical data to indicate that exchange of multiple volumes is more efficacious than removal of one plasma volume per treatment.

The rate at which a pathologic substance is synthesized and its distribution between intravascular and extravascular compartments affect the outcome of TPE. For example, the abnormal IgM of Waldenstrom’s macroglobulinemia is synthesized slowly and remains almost entirely within the bloodstream, making apheresis a particularly effective mode of treatment. In contrast, efforts to prevent hydrops fetalis with intensive TPE to lower the mother’s level of IgG anti-D have been less successful, in part because more than half of IgG is in the extravascular fluid and in part because rapid reduction of IgG may cause antibody synthesis to increase rapidly and overshoot the pretreatment levels. Rebound synthesis may also complicate TPE treatment of autoimmune diseases. Cytotoxic agents such as cyclophosphamide, azathioprine or prednisone may be administered to blunt the IgG rebound response to apheresis.

Plasma collected during TPE should be handled carefully and disposed of properly. Such plasma cannot be used for further manufacture into transfusable plasma derivatives, and must not be shipped interstate without an FDA product license specifically for therapeutic exchange plasma.

Removal of Normal Plasma Constituents

When the quantity of plasma removed during TPE exceeds 1.5 times the plasma volume, different rates of removal and reconstitution are observed for different constituents. For fibrinogen, the third component of complement (C3), and immune complexes, reduction is greater than predicted, with 75-85% of the original substance lost after a one plasma-volume procedure. Normal levels return in 3-4 days. The concentrations of electrolytes, of uric acid, and of Factor VIII and other proteins, are less affected by a one plasma-volume procedure. A 25-30% drop in platelet count generally occurs, with 2-4 days needed for return to preexchange values. Coagulation factors other than fibrinogen generally achieve preapheresis levels within 24 hours. Immunoglobulin removal occurs at about the expected rate of 65% per plasma volume, but recovery patterns vary for different immunoglobulin classes, depending on intravascular distribution and rates of synthesis. (Table 10-3 describes Ig characteristics.) Plasma IgG levels return to approximately 60% of the pretreatment figure within 48 hours because of reequilibration with protein in the extravascular space. These issues are important in planning the frequency of therapeutic procedures. Weekly apheresis permits more complete recovery of normal plasma constituents; daily procedures can be expected to deplete many normal, as well as abnormal, constituents.
**Replacement Fluids**

The three commonly used replacement solutions are: crystalloids, albumin solutions, and FFP. Table 6-1 presents advantages and disadvantages of each. A combination is often used, the relative proportions being determined by the physician on the basis of the patient’s disease and physical condition, the planned frequency of procedures, and cost. Early in the TPE, plasma may be replaced with less expensive crystalloid solution, but as the procedure reaches one-third to one-half of the patient’s plasma volume, colloid fluids are generally used to avoid an excessive drop in the patient’s colloid oncotic pressure. Acute treatment of life-threatening conditions usually requires a series of one plasma-volume procedures, often producing significant reduction of coagulation factors. Monitoring the prothrombin time, activated partial thromboplastin time, and fibrinogen level helps one judge the need for supplemental FFP. Because plasma contains citrate, use of FFP does increase the risk of citrate toxicity.

**Complications**

With careful patient selection and attention to technical details, most therapeutic apheresis procedures are accomplished with few complications. Therapeutic apheresis is often requested, however, for patients who are critically ill and at risk for a variety of complications.

**Vascular Access.** Patients referred for therapeutic apheresis have often been subjected to multiple venipunctures and vascular access may be difficult. Special venous access, such as surgical placement of an indwelling double-lumen catheter, may be required. Venous access devices may cause further vascular damage, sometimes leading to thrombosis; infrequently, they may result in severe complications such as pneumothorax or perforation of the heart or great vessels. Other complications include arterial puncture, dissecting deep hematomas,

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and arteriovenous fistula formation. Bacterial colonization often complicates long-term maintenance of catheters, and may lead to catheter-associated sepsis. Inadvertent disconnection of catheters may produce hemorrhage or air embolism.

**Alteration of Pharmacodynamics.** TPE can lower blood levels of drugs, especially those that bind to albumin. Apheresis reduces plasma levels of antibiotics and anticonvulsants, but as the efficacy of many drugs depends on tissue levels, there have been few clinical data to suggest adverse patient outcomes from apheresis-associated lowering of drug levels. Nevertheless, the pharmacokinetics of all drugs being given to a patient should be considered before starting apheresis therapy, and dosage schedules adjusted if necessary. It is common practice to withhold the administration of drugs scheduled to be given during or up to an hour before apheresis until after the procedure is finished.

**Effects of Citrate.** Most patients with normal parathyroid function maintain calcium homeostasis during TPE. Symptoms of reduced plasma levels of ionized calcium (perioral paresthesias, tingling, a feeling of vibrations) can occur and reflect the rate at which citrate anticoagulant is returned to the patient. Hyperventilation, hypothermia, hypomagnesemia, and the use of FFP as a replacement solution exacerbate citrate toxicity. Citrate effects can usually be controlled by reducing the proportion of citrate or slowing the reinfusion rate. If untreated, symptoms may progress to muscle twitching, chills, pressure in the chest, nausea, vomiting, and collapse. High citrate concentrations can induce severe cardiac arrhythmias. Asking the patient to report any vibrations or tingling sensations can help determine the correct reinfusion rate. Extra precautions must be taken in patients who are unable to communicate during the procedure.

**Circulatory Effects.** Hypovolemia and subsequent hypotension may occur during therapeutic apheresis, especially when the volume of extracorporeal blood exceeds 15% of the patient’s total blood volume. Hypotension tends to occur in children, in the elderly, and in anemic patients treated with intermittent-flow devices that have large extracorporeal volumes. Continuous-flow machines typically do not require large extracorporeal volumes. Continuous-flow machines can produce hypovolemia if return flow is inadvertently diverted to a waste collection bag, either through operator oversight or through mechanical or software failure. During all procedures it is essential to maintain careful and continuous records of the volumes removed and returned. Antihypertensive medications, especially ACE-inhibitors, may aggravate hypovolemic reactions. Because infusion of cold fluids through a central venous catheter has the potential to induce arrhythmias, some programs use blood warmers for selected patients.

**Infections.** Fresh Frozen Plasma is the only commonly used replacement solution with the risk of transmitting infectious viruses. Bacterial infection related to repeated apheresis usually arises from the vascular catheter. Intensive apheresis regimens decrease levels of immunoglobulins and the opsonic components of complement. In addition, immunosuppressive drugs prescribed to prevent rebound antibody production may further compromise defense mechanisms. Induced immunosuppression superimposed on the patient’s underlying condition often results in increased susceptibility to infections.

**Mechanical Hemolysis and Equipment Failures.** Kinked tubing, malfunctioning pinch valves, or improper threading of tubing may damage red cells in the extracorporeal circuit. Machine-related hemolysis was observed in 0.07% of over 195,000 apheresis proce-
dures performed on volunteer donors in the UK. The operator should carefully observe plasma collection lines for pink discoloration suggestive of traumatic hemolysis. Such other types of equipment failure as problems with the rotating seal, leaks in the plastic, and roller pump failure, are rare.

Allergic Reactions and Respiratory Distress. Respiratory embarrassment during or immediately following apheresis can have many causes: pulmonary edema, massive pulmonary embolus, obstruction of the pulmonary microvasculature, anaphylactic reactions, and transfusion-related acute lung injury. Pulmonary edema that results from volume overload or cardiac failure is usually associated with dyspnea, increase in the diastolic blood pressure, and a characteristic chest X-ray picture. Acute pulmonary edema can also arise from damage to alveolar capillary membranes secondary to an immune reaction or to vasoactive substances present in FFP or colloid solutions prepared from human plasma. Use of FFP as a replacement fluid has been associated with complement activation and with allergic reactions that produce urticaria, swelling of oral mucosa, and bronchospasm; these usually respond to antihistamines and corticosteroids. Generalized urticarial reactions have occurred in donors sensitized to the ethylene oxide gas used to sterilize disposable plastic apheresis kits.

Fatalities During Apheresis. Despite the fact that patients undergoing therapeutic apheresis are often critically ill, fatalities during apheresis are comparatively rare. Estimates of case fatality rates have ranged from 3 in 10,000 to 1 in 500. Most deaths were due to cardiac arrhythmias or arrest during or shortly after the procedure or to acute pulmonary edema or adult respiratory distress syndrome occurring during a procedure. Rare fatalities resulted from anaphylaxis, vascular perforation, hepatitis, sepsis, thrombosis, and hemorrhage.

Indications for Therapeutic Apheresis

Although therapeutic apheresis has been applied to many different diseases, most published studies are case reports or small uncontrolled series, providing often insufficient or unreliable evidence of efficacy. Publication bias tends to favor positive results, and physicians must be careful to avoid subjecting patients to the costs and risks of apheresis on the basis of marginal clinical studies. Controlled, randomized, blinded studies of therapeutic apheresis are difficult to conduct, especially since the use of sham treatments as a control is expensive and carries some risk to the patients involved. However, the complicated apheresis machines and associated attention from nursing and medical personnel may well create or amplify a placebo effect and bias evaluation of clinical improvement.

For many of the diseases being treated, the etiology, pathogenesis, and natural history are incompletely understood, and reductions in such measured variables as complement components, rheumatoid factor, or immune complexes cannot reliably be correlated with changes in disease activity. An example is the use of the erythrocyte sedimentation rate (ESR) as an index of rheumatoid activity. The ESR invariably decreases during intensive TPE, but this reflects removal of fibrinogen and not necessarily a decrease in disease activity. The conditions discussed below have been considered by a panel of experts to be appropriately treated by therapeutic apheresis.

Hematologic Conditions

Serum Hyperviscosity Syndrome. Serum hyperviscosity resulting from multiple myeloma or Waldenstrom’s macroglobulinemia can cause congestive heart failure; reduced blood flow to the cere-
bral, cardiac, or pulmonary circulation; or symptoms of headache, vertigo, somnolence, or obtundation. Paraproteins may interfere with hemostasis, leading to hemorrhagic symptoms. Fundoscopic examination may show engorged retinal vessels, hemorrhages or papilledema.

The presence of hyperviscosity correlates only in very general terms with the concentration of paraprotein. Measurement of serum viscosity relative to water is a simple procedure that may provide better objective information. For some pathologic proteins, serum viscosity is highly temperature dependent, so serum viscosity should be measured at physiologically relevant temperatures. Normal serum viscosity ranges from 1.4 to 1.8 relative to water. Since most patients are not symptomatic until relative serum viscosity is more than 4.0 or 5.0, patients with mild elevations may not need treatment. For symptomatic hyperviscosity, a single apheresis procedure is highly effective. TPE has also been used in conjunction with cytotoxic agents to treat patients with multiple myeloma and renal failure.

Hyperleukocytosis. Leukapheresis is often used to treat the dramatically elevated white cell count that can occur in acute leukemia. Several different thresholds have been used: fractional volume of leukocytes (leukocrit) above 20%; total circulating leukocytes above 100,000/µL; and circulating blasts above 50,000/µL. The use of a single laboratory value as an indication for treatment is, however, an oversimplification. Such factors as erythrocyte concentration, leukemic cell type, rate at which the count is rising, potential obstructions to cerebral or pulmonary blood flow, and the patient’s coagulation status and general condition must affect the decision. Most leukemic patients with extreme leukocytosis have significant anemia. Reduced red cell mass reduces blood viscosity, so unless there is acute need to increase oxygen-carrying capacity, red cell transfusions should be withheld until the leukocytic hyperviscosity crisis is past.

In some patients with acute blast crisis or in unusual types of leukemia, both the hematocrit and leukocrit are elevated. If there is evidence of impending cerebral or pulmonary symptoms, rapid reduction of leukocyte concentration should be considered. More commonly, however, the white cell count rises over weeks or longer, and leukoreduction can be effected with chemotherapy, with or without leukapheresis. Leukapheresis is sometimes used to reduce the cell burden before the start of chemotherapy, to decrease the chance of tumor lysis syndrome. However, there have been no controlled clinical trials to substantiate this approach, and it must be recognized that more malignant cells are present outside the circulation than within the bloodstream.

Thrombocytopenia. Therapeutic plateletapheresis is usually undertaken only for platelet counts above 1,500,000/µL, but the measured count should not, by itself, determine whether platelet reduction is indicated. In patients with evidence of thrombosis or threatened stroke thought to be due to thrombocytopenia, plateletapheresis can play a therapeutic role. There are no accepted indications for prophylactic plateletapheresis in asymptomatic patients, although the risk of placental infarction and fetal death may justify the procedure in a pregnant woman with severe thrombocytopenia.

TTP/HUS. The conditions described as TTP/HUS are multisystem disorders of unknown cause, in which platelet thrombi occlude the microcirculation. They are characterized by varying degrees of thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, neurologic abnormalities, and fever. Patients presenting with overt TTP usually have platelet counts below
50,000/µL and lactic dehydrogenase (LDH) levels above 1000 IU/mL, resulting from microangiopathic hemolysis. The peripheral blood smear characteristically shows increased numbers of schistocytes. Evidence for disseminated intravascular coagulation is generally absent.

TTP usually develops without obvious cause, although episodes may occur after minor viral infection, pregnancy, organ transplantation, or during the course of HIV infection. Increasingly, cases of recurrent or relapsing TTP are being recognized. HUS is a similar condition that occurs more commonly in children than adults. HUS may follow diarrheal infections with verotoxin, secreting strains of *E. coli* (strain 0157:H7) or *Shigella*. Compared to classical TTP, patients with HUS have more serious renal dysfunction. TTP/HUS can occur after treatment with certain immunosuppressive drugs, including mitomycin C and cyclosporine. Drug-associated TTP/HUS appears to be less responsive to therapy than the other variants. A distinctive constellation has been called the HELLP syndrome of pregnancy, characterized by hemolysis, elevated liver enzymes, and low platelet count.

TPE has become the treatment of choice for TTP/HUS. Although the cause of the condition is unknown, evidence points to abnormal interaction between endothelial cells and platelets, involving endothelial cell damage and factors that affect platelet aggregation. TPE may remove substances injurious to endothelial cells and/or restore a plasma environment that does not promote the development of microthrombi. Other treatments include prednisone, antiplatelet agents, splenectomy, vincristine, and intravenous immunoglobulin. Because platelet transfusions may provoke additional thrombotic damage, they should not be given unless there is severe bleeding along with the thrombocytopenia.

Intensive apheresis will reduce concentration of potentially diagnostic plasma constituents, so specimens for testing should be drawn before TPE. Testing might include tests for pregnancy, HIV infection or other viral markers, and such disorders as systemic lupus erythematosus, disseminated intravascular coagulopathy, Evans syndrome (autoimmune anemia and thrombocytopenia), heparin-induced thrombocytopenia, posttransfusion purpura, and sepsis with multiorgan dysfunction.

TPE is often performed daily for 1-2 weeks, but the intensity and duration of treatment should be guided by the individual patient’s course. Occasionally, prolonged courses of treatment are needed. Different forms of plasma may be used as replacement fluid. Many centers replace with FFP, but stored liquid plasma or supernatant plasma from which cryoprecipitate has been removed have also been used. No controlled studies have shown one form of plasma to be superior.

Therapeutic plasma exchange has impressively improved the survival rate in TTP, from almost universally fatal before 1964 to 80% survival in recent series. Signs of response to therapy include a rising platelet count and diminishing elevation of LDH between procedures, levels rising no higher than 600 IU/mL before the next procedure. As patients recover, some programs switch from intensive TPE to intermittent plasma exchange or simple plasma infusion, or the use of drug therapy. Despite the success of TPE, TTP/HUS remains a serious condition. Treatment failures continue to occur and to cause major organ damage or death.

**Complications of Sickle Cell Disease.**

Several complications of sickle cell disease are syndromes that can be treated by red cell exchange; these include pri-
pism, threatened stroke, and acute chest syndrome. Either manual or automated techniques can be used for red cell exchange, but automated techniques are faster. The goal is to replace red cells containing only hemoglobin S with a sufficient number of red cells containing only hemoglobin A so that the overall concentration of hemoglobin A in the bloodstream is approximately 50%. Many centers select red cells that match the recipient’s phenotype for as many antigens as possible, to avoid alloimmunizing patients likely to need repeated transfusions. At the end of the procedure the hematocrit should be at or below 30% to avoid increased blood viscosity.

**Posttransfusion Purpura.** In posttransfusion purpura, there is a precipitous decline in platelet count and diffuse bleeding. Affected patients, more often women than men, are usually negative for the HPA-1 platelet antigen and have circulating anti-HPA-1. For symptomatic or severely thrombocytopenic patients, treatment options include intravenous immunoglobulin, used for immune thrombocytopenic purpura, and corticosteroids. TPE has been used to decrease the titer of anti-HPA-1. Often a single procedure is efficacious and response to TPE tends to be more rapid than response to intravenous immunoglobulin.

**Neurologic Conditions**

**Myasthenia Gravis.** Myasthenia gravis results from autoantibody-mediated attack on the acetylcholine receptor located on the postsynaptic motor end-plate of muscles. Standard treatment includes the use of steroids and acetylcholinesterase inhibitors. TPE is used as adjunctive treatment for patients experiencing exacerbations of disease not controlled by medications, for patients being prepared for surgical thymectomy, and those who experience postoperative respiratory failure. A typical treatment protocol is five or six TPE procedures over 5-10 days. Concurrent immunosuppression to prevent antibody rebound is recommended. For seriously affected patients, a course of intensive TPE can be followed by a series of treatments done once every week or every 2 weeks.

**Acute Guillain-Barré Syndrome.** Guillain-Barré syndrome is an acute autoimmune demyelinating polyneuropathy that can produce dramatic paralysis in otherwise healthy individuals. The cause is unknown; many cases appear to follow benign viral infections. Most patients recover spontaneously, but as many as one in six may become unable to walk or may develop respiratory failure requiring ventilatory support. Early treatment is beneficial for patients with rapidly progressive disease, and response to therapy is less in patients who remain untreated for several weeks. Treatment includes some combination of intensive TPE, steroids, and intravenous immunoglobulin. One controlled study suggested that intravenous immunoglobulin gives results equivalent to TPE. Multicenter trials have suggested that TPE, if initiated early, can decrease the period of minimal sensorimotor function. Patients whose illness is not acute in onset or is not characteristic of Guillain-Barré syndrome, or in whom nerve conduction studies show complete axonal block may have a poorer prognosis and less response to apheresis therapy.

**Chronic Inflammatory Demyelinating Polyneuropathy.** Chronic inflammatory demyelinating polyneuropathy (CIDP) is a group of disorders with slow onset and progressive or intermittent course, characterized by elevated spinal fluid protein, marked slowing of nerve conduction velocity, and segmental demyelination of peripheral nerves. A variety of sensorimotor abnormalities result. A variant condition, called the POEMS syndrome, is characterized by...
Polyneuropathy, organomegaly, endocrinopathy, an M-protein, and skin changes. CIDP responds less well to treatment than acute Guillain-Barré syndrome; it may be idiopathic or associated with benign monoclonal gammopathies. Corticosteroids are the first treatment for CIDP. TPE and intravenous immunoglobulin have shown equivalent efficacy in patients unresponsive to corticosteroids. A controlled trial of TPE in the treatment of neuropathy among patients with monoclonal gammapathies suggested benefit.

**Rheumatologic, Nephrologic and Other Conditions**

TPE has been used as adjunctive treatment for a variety of multisystem diseases. Some vasculitides, for example, may respond to a combination of steroids, cytotoxics, and TPE. Therapeutic apheresis has been used in treating the vasculitis associated with rapidly progressive glomerulonephritis (RPGN) and the presence of antineutrophil cytoplasmic antibody (ANCA-positive RPGN). A combination of steroids, cytotoxic agents, and TPE has been used for severely ill patients with polyarteritis nodosa. Significant elevations of cryoglobulins may cause cold-induced vascular occlusion, abnormalities of coagulation, renal insufficiency, or peripheral nerve damage. Removal of cryoglobulins by apheresis can be used to treat acute symptomatic episodes, but definitive therapy depends on identifying and treating the underlying causative condition. Goodpasture’s disease, in which pulmonary hemorrhage and/or renal failure is associated with antibodies to glomerular basement membrane, has not been subjected to sham-controlled trials of TPE. However, a comparison of immunosuppressive agents alone or with apheresis treatment suggests that apheresis provides additional benefit.

Most rheumatologic conditions are poorly responsive to TPE. Clinical trials have not shown evidence for consistent benefit in the treatment of systemic lupus, polymyositis, dermatomyositis, scleroderma, or rheumatoid arthritis. Homozygous hypercholesterolemia, a rare disorder of the receptor for low-density lipoproteins (LDLs), results in severe premature atherosclerosis and early death from coronary artery disease. Prolonged reduction in circulating lipids can be achieved with repeated TPE, often with selective adsorption or filtration techniques. Heterozygous hypercholesterolemia results from a variety of gene defects in the LDL receptor. Some patients with heterozygous hypercholesterolemia also develop very high levels of circulating cholesterol and are at increased risk for premature atherosclerotic heart disease. Although some of these patients respond to cholesterol-lowering drugs, others may require repeated TPE for control of cholesterol.

**Periodic Review**

A group of responsible physicians (in many institutions, the Hospital Transfusion Committee) should establish and monitor the policies relating to therapeutic apheresis, review the indications for treatment, and maintain surveillance of all adverse outcomes. For a regional blood center, a Medical Advisory Committee could serve the same function.

**References**


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