Journal of Clinical Apheresis 26:230–238 (2011)

Conventional Apheresis Therapies: A Review

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This article reviews advances in the scientific basis and medical practice of plasmapheresis and cytapheresis therapies. Newly-characterized autoantibodies in neuromyelitis optica, Guillain-Barre variants, anti-neutrophil cytoplasmic antibody (ANCA) vasculitides, etc., exemplify the modern molecular biology which now provides a rigorous framework of understanding for the clinical practice of plasmapheresis. Clinical trials continue to clarify the appropriate use of therapeutic plasmapheresis (TPE) in these and other diseases. Centrifugal (cTPE) and membrane filtration (mTPE) types of plasmapheresis are compared, with details of the plasmapheresis prescription, anticoagulation choices, replacement fluids and other practical considerations. Plasma removal is more efficient with cTPE; mTPE systems have a lower plasma extraction ratio, and therefore require higher blood flow rates or longer procedure times. Autoantibodies and other pathogenic macromolecules targeted for removal by plasmapheresis can be depleted predictably when the plasma is discarded, as in conventional TPE. On-line plasma processing to regenerate the patient's own plasma avoids the need for replacement albumin solutions or plasma transfusion, but is inherently less efficient at removing the target molecule, so usually requires a longer procedure. Therapeutic white cell reduction (leukapheresis), platelet reduction (thrombocytapheresis) and red cell exchange (erythrocytapheresis) require centrifugal apheresis systems. J. Clin. Apheresis 26:230–238, 2011. ©2011 Wiley-Liss, Inc.

Key words: plasmapheresis; apheresis; cytapheresis; therapeutic plasma exchange; plasmafiltration; autoantibody

INTRODUCTION

Therapeutic apheresis modalities comprise plasmapheresis, which is the removal or exchange of blood plasma, and cytapheresis, which is a group of procedures for blood cell removal or exchange. Examples of cytapheresis include the removal of excessive white blood cells (leukocytapheresis) or platelets (thrombocytapheresis), or the exchange of diseased red blood cells (erythrocytapheresis). Conventional apheresis methods include centrifugation, which can separate any of the components of the blood, and membrane filtration, which can be used for plasmapheresis only. Plasmapheresis was first described as a manual method, consisting of repeated cycles of blood extraction and ex vivo centrifugation, discarding the plasma and returning the blood cells to the patient together with a suitable replacement solution [1]. This manual method is still occasionally used in pediatric practice. However, most therapeutic apheresis is now performed on modern machines which combine fully disposable extracorporeal blood pathways with safe and efficient automated systems.

Therapeutic plasmapheresis and therapeutic plasma exchange (TPE) are terms that often are used synonymously. The plasma that is removed can be replaced by fresh frozen plasma (FFP), 5% albumin or similar colloidal solution, or the patient's own plasma after a secondary online purification procedure. Such secondary plasma processing comes in many forms, as discussed below. Complex hybrid systems are beyond the scope of this review, as is online processing of the cell products of cytapheresis, such as photopheresis, which is discussed elsewhere.

APPLICATIONS OF PLASMAPHERESIS THERAPY

Rationales for TPE

Most commonly the objective of plasmapheresis therapy (TPE) is to remove antibodies or suspected antibodies implicated in the pathogenesis of autoimmune disease. Other important targets include circulating antigen–antibody complexes that cause vasculitis in conditions such as hepatitis C, alloantibodies in transplant rejection and transfusion situations, paraproteins that cause hyperviscosity or neurologic and renal damage, poorly characterized pathogenic molecules such as

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Received 6 June 2011; Accepted 5 July 2011

Published online 31 August 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/jca.20302

TABLE I. Prominent Indications for Plasmapheresis Therapy

Auto-antibody:
Thrombotic thrombocytopenic purpura (TTP), immune thrombocytopenic purpura (ITP), myasthenia gravis (MG), Guillain-Barré syndrome (GBS), neuromyelitis optica (NMO), anti-GBM glomerulonephritis (and Goodpasture's syndrome), ANCA-associated glomerulonephritis (and Wegener's granulomatosis), antiphospholipid crisis, etc.
Probable auto-antibody:
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multiple sclerosis (MS), etc.
Antigen-antibody complexes:
Hepatitis C vasculitis, systemic lupus erythematosus, etc.
Allo-antibody:
Transplant sensitization, transplant rejection (humoral), transfusion reactions, etc.
Paraproteins:
Waldenstrom's, hyperviscosity, light-chain neuropathy, light-chain glomerulopathy, myeloma cast nephropathy, etc.
Non-Ig proteins:
Focal segmental glomerulosclerosis (FSGS).
Endogenous toxins:
Hypercholesterolemia, liver failure, systemic inflammatory response syndrome (SIRS), etc.
Exogenous poisons:
Amanita (mushroom), drugs, etc.

TABLE II. Autoimmune Diseases with Well-Characterized Autoantibodies that are Treated with Plasmapheresis (Partial List)

Autoimmune disease	Autoantibodies react with	Refs
Thrombotic thrombocytopenic purpura (TTP), sporadic type	ADAMTS13 (von Willebrand factor protease)	2,11
Myasthenia gravis, classic type	Acetylcholine receptor	8
Myasthenia gravis, MuSK type	Muscle-specific kinase	8
Guillain-Barre syndrome (1) Miller-Fisher variant (2) other variants	Neuronal gangliosides: (1) GQ1b (2) GM1, GM1b, GD1a, GalNAcGD1a, GD1b, GD3, etc.	3,6
Neuromyelitis optica (Devic's disease)	Aquaporin 4	4,5
Stiff-person syndrome and related neuropathies	Glutamic acid decarboxylase (GAD65 antigen)	9
Anti-GBM glomerulonephritis (GN), including Goodpasture's syndrome	Alpha-3 chain of collagen type IV	12
ANCA-associated GN (focal necrotizing GN, microscopic polyangiitis, Wegener's granulomatosis)	Myeloperoxidase (MPO), proteinase 3 (PR3), other lysosomal antigens, possibly lysosomal membrane protein 2 (LAMP2)	7,13
Idiopathic dilated cardiomyopathy	Cardiac beta-1 receptors and cardiac myosin	10

in focal segmental glomerulosclerosis (FSGS), low molecular weight lipoproteins that cause premature atherogenesis in homozygous hypercholesterolemia, and other endogenous and exogenous toxins (see Table I).

Insights from Basic Research

Seminal insights into the molecular pathogenesis of many autoimmune diseases have strengthened and expanded the rationales for plasmapheresis in recent years [2–10] (see Table II). For instance, neuromyelitis optica (NMO) has been differentiated from multiple sclerosis by the discovery of a defining autoantibody. This autoantibody is directed at the aquaporin-4 (AQP4) water channel located on astrocyte foot processes in the perivessel and subpial areas of the brain and spinal cord [4]. This discovery has lead to the recognition that this devastating disease may be particularly amenable to treatment with TPE [5]. A second example is Guillain–Barré syndrome, which turns out to be associated with many different autoantibody specificities, all reactive with neuronal gangliosides [3]. The Miller-Fisher variant is associated with antibody to GQ1b ganglioside; other clinical subtypes show reactivity with other gangliosides (see Table II). Formation of such antibodies may sometimes be triggered by Camylopbacter and other infections because of molecular mimicry between epitopes on bacterial lipo-oligo-saccharides (LOS) and gangliosides [6]. Identification of these autoantibodies strengthens the rationale for TPE in Guillain–Barré syndrome. Thirdly, the formation of antineutrophil cytoplasmic antibody (ANCA) has also been linked to bacterial infection by a report, still unconfirmed, of a high prevalence of antibodies to lysosomal membrane protein 2 (LAMP2) in ANCA-positive patients, and of molecular mimicry between LAMP2 and antigens on bacterial fimbriae [7].

Advances in Clinical Practice

The three diseases used above as examples of discoveries in the basic understanding of autoantibody

diseases can also be used to exemplify the expanding clinical applications of plasmapheresis (TPE) therapy. In the case of NMO, there is mounting concern that patients need to be maintained on immunosuppressive agents and should also receive TPE in many instances [4]. Intervention with TPE for acute attacks is effective and is becoming standard practice for this disease [5,14]. TPE may also play a role in prevention of relapses [15]. In ANCA-positive disease, in cases of focal necrotizing glomerulonephritis (GN), including cases associated with microscopic polyangiitis and Wegener's granulomatosis, a controlled trial has demonstrated an important role of TPE in rescuing kidney function when renal failure is already far advanced [7], and a further controlled trial is in progress.

The recent increase in the use of TPE for Guillain–Barré syndrome has a different explanation, reflecting a reduction in utilization of the alternative treatment option, which is high-dose IV immunoglobulin (IVIG). The large trial published in 1997 by the Guillain–Barré study group randomized 379 patients to receive IVIG or TPE or both; the result showed no difference between groups in any primary or secondary outcomes, meaning there is substantial but equal benefit from any of these regimens [16]. Thereafter, IVIG therapy was favored over TPE because IVIG was perceived as of equivalent therapeutic benefit, similar overall cost, but greater convenience [17]. However, since then the cost of IVIG has tripled, so that a typical course of IVIG (five infusions totaling 2 g/kg) is now twice as expensive as five standard TPE procedures (including central venous access, albumin replacement solution, and equipment amortization) (Helmons P, personal communication) [18]. Moreover, TPE avoids the malaise often associated with high-dose IVIG, and the risk of IVIG-associated aseptic meningitis and acute kidney injury [19]. In the UK and Canada, IVIG is being conserved for indications where there are no alternative treatment options, such as immune deficiency states; in the USA the use of IVIG is being discouraged for economic reasons when other treatment alternatives are equally good, such as plasmapheresis for Guillain–Barré syndrome.

Literature Reviews and Practice Guidelines

Most clinical applications of TPE cannot be covered in a review of this size. Reviews of the whole spectrum of indications for apheresis therapy have been published since the 1980s [20]. The American Society for Apheresis has published the ''ASFA Special Issue'' every 7 years from 1986 to 2007, and now every 3 years, most recently in 2010 [21]. This new 2010 version incorporates a structured review of all published literature, with evidence-based ratings for each indication, and with fact sheets that present comprehensive condensed information in a standardized format on apheresis therapy for over 100 diseases. Also available are practice standards for diseases in different subspecialties, and other focused reviews [12,22,23].

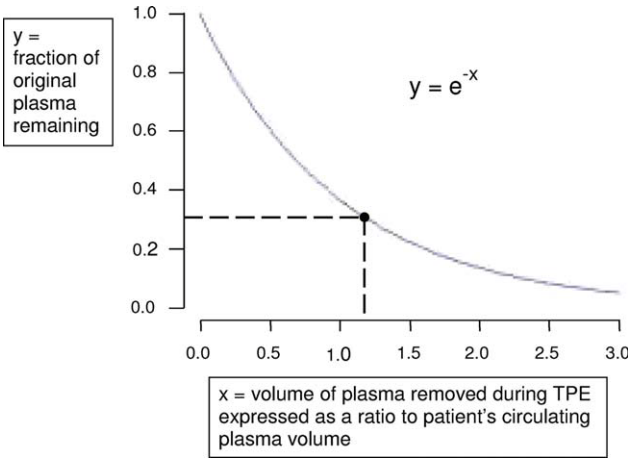

Fig. 1. Relationship of removal of plasma constituents to volume of plasmapheresis. The amount of any nonrenewed plasma constituent remaining in the plasma at the end of plasmapheresis (TPE) can be predicted from the exponential decay formula $y = e^{-x}$, where ''y'' is the percentage of original solute remaining, and ''x'' is the ratio of the volume of plasma removed to the patient's circulating plasma volume. In this example, a typical 70 kg adult with a plasma volume of 3.0 L is treated with a 3.5 L TPE procedure. This gives a ratio ''x'' of 3.5/3.0 = 1.17. Solving the equation $y = e^{-x}$ gives a result ''y'' of 0.31, meaning 31% of original plasma remains, or 69% has been removed. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

STANDARD PLASMAPHERESIS PROCEDURES

Dose of Plasmapheresis

The TPE prescription usually aims to remove a volume of plasma equal to approximately 1.2 times the patient's circulating plasma volume (range 1.0–1.5). This range corresponds to the removal of 63–72% of the original plasma constituents. The amount remaining in the plasma at the end of TPE can be calculated from a simple exponential decay formula (Figure 1). Clearly as the procedure is extended beyond 1.5 plasma volumes, the yield flattens off. This exponential decay curve accurately predicts the amount remaining of a plasma constituent as long as none is added to the plasma during the TPE procedure. This assumption is almost true in many instances. Typically, the pathogenic molecules targeted for removal by TPE are present also in the interstitial fluid (''third space,'' approximately 10–12 L in a 70 kg adult). However, their rate of transfer from the third space into the plasma is slow, so that their reappearance in the plasma occurs mostly after the TPE procedure has been completed. By the next day the rebound is substantial, which is why multiple TPE pro-

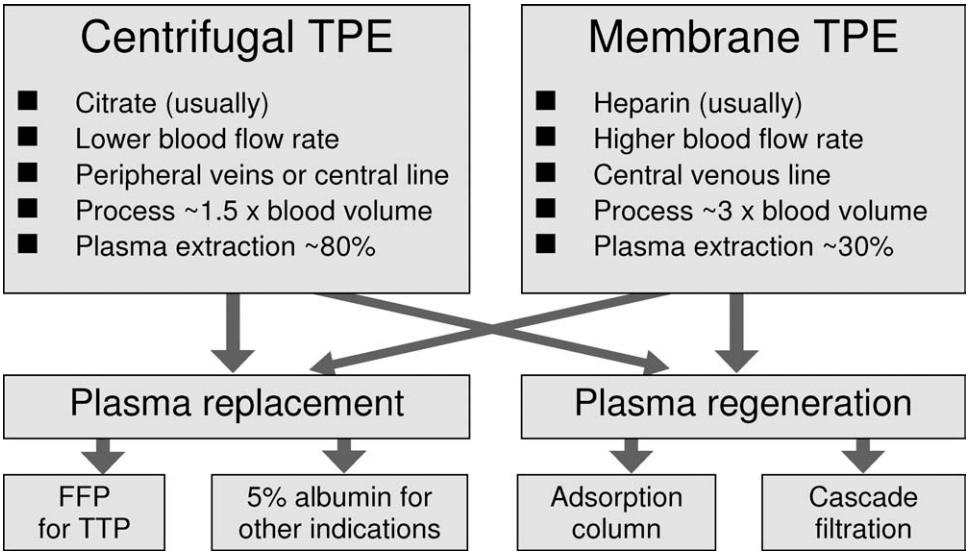

Fig. 2. Comparison of characteristics of centrifugal and membrane plasmapheresis, with choices of plasma replacement or plasma regeneration. Typical prescriptions for centrifugal plasmapheresis (cTPE) and membrane plasmapheresis (mTPE) differ markedly. The risk of hemolysis in mTPE filters requires the plasma extraction ratio to be lower; therefore more blood must be processed to extract the same amount of plasma. This requires a higher blood flow rate (and higher-flow vascular access) or may take longer than cTPE. Citrate or heparin anticoagulation can be used in either, although citrate is more suited to cTPE, and heparin to mTPE. Secondary plasma processing (plasma regeneration) is an option with either cTPE or mTPE.

cedures are needed to clear out the interstitial fluid compartment as well as the plasma. This situation is typical of autoimmune diseases, since virtually all are mediated by IgG-class antibody (~146 kDa), of which only approximately 30% is in the intravascular compartment when TPE commences. In contrast, IgM is a much larger protein (~970 kDa), and approximately 90% of it stays in the plasma compartment. Thus there is very little rebound of the plasma level of IgM after the end of a TPE procedure. For this reason, high levels of IgM, such as cause hyperviscosity in Waldenstrom's macroglobulinemia, can usually be controlled with just one or two TPE procedures [20].

Machine Type and Vascular Access

Centrifugal (cTPE) and membrane filtration (mTPE) types of plasmapheresis machines differ operationally (see Figure 2). Centrifugal machines can pack red cells to a hematocrit of 80% or higher, and thereby can remove 80% or more of the plasma coming through the machine. Thus to remove 1.2 times the patient's plasma volume they need to process only 1.5 times the blood volume. In contrast, membrane filtration systems (including hollow-fiber devices) cannot extract plasma so efficiently, because red cells within the separator are damaged if the hematocrit gets too high. They usually extract only approximately 30–35% of the plasma, so they need to process three or four times the patient's blood volume to achieve similar plasma removal. Thus membrane filter systems take longer and/or require higher blood flow rates. To achieve this higher flow rate, central venous access is almost always necessary with mTPE. The lower blood flow rate needed for cTPE can often be accomplished through peripheral vein needles, which reduces the risk of bacteremia associated with central lines.

Anticoagulation

Anticoagulation for mTPE systems is usually with heparin. Centrifugal systems usually use citrate, although they allow the choice of either heparin or citrate anticoagulation. Nafamostat, a serine protease inhibitor, is often used in Japan [24]. Citrate is always a regional anticoagulant, effective in the extracorporeal blood circuit and neutralized as soon as it returns and mixes with systemic blood. Therefore with citrate there is no systemic bleeding risk, as there is with heparin [25]. Citrate is added where the blood leaves the body, in a fixed ratio to blood flow. Because most of the plasma is discarded in a standard centrifugal TPE, most of the citrate is discarded with it. Nevertheless, citrate toxicity, usually transient, can occur in patients during cTPE. Calcium infusion to the return line counteracts the risk of citrate-induced symptoms, and is standard in many programs. When citrate is used with an mTPE system, citrate toxicity is more likely, because typically more citrate is given in proportion to the higher blood flow rate and volume processed, and a greater fraction of the citrate is returned to the patient because of the lower plasma extraction ratio.

Replacement Fluids and Supplements

When the replacement fluid is FFP, the citrate content of the transfused FFP adds to the citrate load that the patient has to metabolize [26]. Plasma (FFP) replacement is used universally for plasmapheresis treatment of TTP (thrombotic thrombocytopenic purpura), because FFP is currently the only plentiful source of the missing ADAMTS13 enzyme (the von Willebrand factor cleaving enzyme). It appears that virtually all published series of treatment of this disease have employed cTPE rather than mTPE [21].

Most indications for TPE can be performed using albumin replacement or a similar colloid preparation. Commonly, a 5% albumin solution is used. However, this may provide more albumin than is necessary, since it would tend to push the patient's serum albumin level toward 5 g/dL (50 g/L), which is above normal. Thus often it is reasonable to use 0.9% saline solution for replacement during the first quarter of the TPE procedure, and 5% albumin for the remainder. However, when this is done, the saline infusion rate should be at least 20% higher than the plasma removal rate during this phase, to compensate for third space shifting of saline [20]. Albumin solutions, although derived from human plasma, are highly purified, with no risk of virus transmission; allergic reactions are rare and usually mild.

Avoidance of FFP as the replacement solution in most TPE is advisable because of the risk of allergic events with FFP. The incidence and severity of these reactions can be reduced by premedicating with an antihistamine such as diphenhydramine and antipyretic such as acetaminophen (paracetamol). Most FFP reactions are just urticarial, but sometimes more serious reactions occur, including transfusion-related acute lung injury [27]. Despite this risk, and the more remote risk of viral transmission by FFP transfusion, FFP supplementation may be needed in patients whose clotting factor levels have become depleted by frequent TPE with only albumin (±saline) replacement. When this happens, 500 mL of FFP can be given instead of the last 500 mL of 5% albumin replacement. Significant clotting factor depletion can be monitored by measuring fibrinogen levels, and FFP may be indicated if the fibrinogen level at the start of plasmapheresis falls below 120 or 100 mg/dL (because a standard procedure will deplete it a further 65–70%). Fibrinogen and other clotting factors recover rapidly after plasmapheresis in most patients. Patients who become progressively depleted, or who have specific bleeding risks, may be helped by standard daily multivitamins and a weekly vitamin K supplement.

Supplementation with IVIG injection after plasmapheresis has been advocated to counteract progressive immunoglobulin depletion, but in this author's experience this provides only transient increases in levels, and is of questionable benefit.

ONLINE PLASMA PROCESSING

Advantages and Limitations

Online purification of separated plasma is certainly a less ''conventional" technique than is standard plasmapheresis with plasma disposal. However, several methods have been in regular use for decades, especially in Europe and Japan, and others are appearing, so an outline of these techniques is germane to this review.

Regeneration of the patient's own plasma for use as the replacement volume has always been an attractive goal. It offers preservation of the patient's own blood proteins, and can avoid the risk and cost of FFP or replacement solutions. However, its validity depends on effective removal of the specific autoantibody or other toxic molecule from the plasma. Plasmapheresis in which the separated plasma is discarded is reassuring because one can see the collected plasma and know that pathogenic macromolecules are being depleted predictably by the procedure. When clearance of the pathogenic material is dependent on adsorption, the efficacy is less certain. If an adsorption column becomes saturated, or another failure occurs and goes undetected, the whole procedure may be ineffective. Thus online plasma regeneration can work well when the pathogenic molecule can be measured serially to monitor progress, but is less suitable for diseases where the pathogenic molecule is poorly characterized or cannot be measured. Methods for secondary plasma processing include selective filtration, cryogelation, immunoadsorption, and chemical adsorption. Such plasma regeneration systems can be coupled to either type of primary plasma separation, i.e., centrifugal (cTPE) or membrane (mTPE) (see Figure 3). Many secondary processing systems are not FDA-approved for use in the USA.

Selective Filtration

A membrane with a pore size that allows albumin to pass through, but holds back globulins, can be used to fractionate plasma. The fraction containing the albumin can be returned to the patient, and the globulin fraction can be discarded. This is illustrated in Figure 3a. The primary plasma separation in this example uses membrane plasmapheresis (mTPE), but could equally well use centrifugal plasmapheresis (cTPE). When both the primary and secondary stages are membrane-based, the terms ''double-filtration" or ''cascade filtration" can be used. The amount of albumin reclaimed for reinfusion to the patient varies in different systems, and supplementation of volume replacement is often needed. The globulin fraction that is discarded should contain most of the IgG; therefore the system has potential applica-

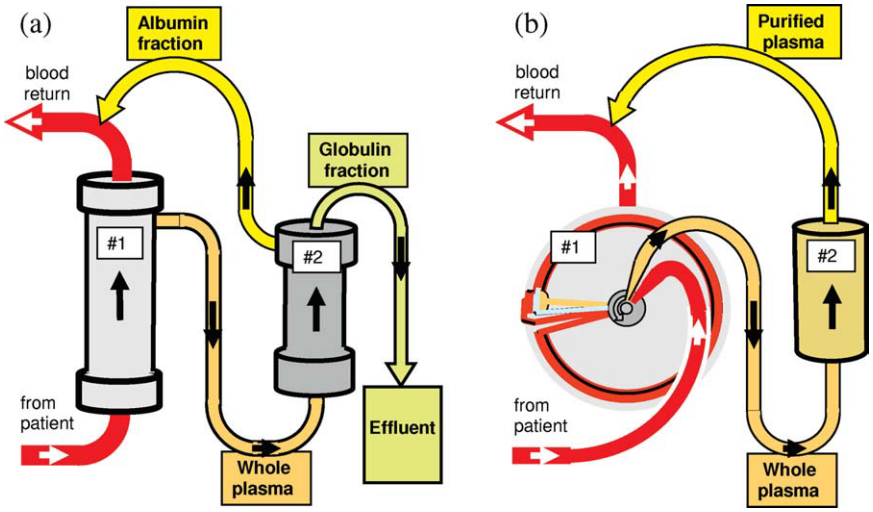

Fig. 3. Circuit diagrams of (**a**) primary membrane plasma separation plus secondary plasma fractionation, and (**b**) primary centrifugal plasma separation plus secondary plasma perfusion column. In the left panel (a), the primary separation of plasma from blood (#1) is in a hollow-fiber membrane plasma filter with a pore size of ~0.3 microns and a molecular weight cut-off in excess of 1,000 kDa. The secondary processing of plasma (#2) is in a hollow-fiber membrane plasma fractionator with a pore size of 0.01–0.03 microns and a molecular weight cut-off of approximately 100 kDa. Albumin (67 kDa) passes through the secondary membrane and can be used as replacement fluid for the patient. Immunoglobulins, including IgG (146 kDa), stay within the hollow-fiber lumen which drains to the effluent bag, thus removing most of the autoantibody present in the plasma. Membrane specifications are those of Asahi® products (Asahi Kasei Kuraray Medical Co., Tokyo 101-8,101, Japan). In the right panel (b), the primary separation of plasma from blood (#1) is by a continuous-flow centrifuge, and the secondary processing of plasma (#2) is in a perfusion column that can contain an immuno-adsorbent or chemical adsorbent (see text). The pathogenic molecule binds to the column, which is replaced when exhausted. Other systems employ pairs of columns that can be regenerated by washing out the bound pathogenic molecule; one column is in active use while the other is being washed clean, and they switch periodically during the procedure. Either type of primary separation (#1) can in principal be coupled to any type of secondary plasma purification (#2). Many secondary devices in use in Europe and Japan, and some primary/secondary combination systems, are not FDA-approved in the USA. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

tion in many types of autoimmune disease [14]. It has also been used to reduce blood viscosity in patients with age-related macular degeneration [28], and other indications. Some systems employ periodic flushing of the secondary filter to remove accumulated large proteins that can clog the membrane.

Immunoadsorption Using Bound Antibody

Immunoadsorption columns can extract specific plasma proteins or classes of proteins when used as a secondary device to purify plasma. There has been extensive experience using adsorption columns with centrifugal machines (cTPE) (see Figure 3b), as well as with membrane plasma-separators (mTPE). Columns containing immobilized antibody to apoprotein B have been used in Europe for decades to remove low density lipoprotein (LDL) [29]. This has proved highly successful in the treatment of homozygous familial hypercholesterolemia and severe heterozygous cases. These columns are used in pairs, one active while the other is being regenerated with rinsing fluids, switching periodically during the procedure. The columns can be reused for the same patient multiple times over periods of weeks. Columns containing antibody to human IgG have also proved effective. Immobilized polyclonal anti-IgG effectively depletes all subclasses of IgG from plasma. The method can be used for depletion of alloreactive antibodies in organ transplant rejection (antibody-mediated type), or in autoimmune diseases [30]. None of the antibody-containing plasma-processing devices is FDA-approved.

Immunoadsorption Using Staphylococcal Protein A

Immunoadsorption columns containing immobilized staphylococcal protein A exploit the high avidity of protein A for the Fc portions of IgG_1, IgG_2, and IgG_4. These columns were developed to deplete IgG autoantibodies or circulating immune complexes containing IgG. Initial FDA-approval was obtained because they showed efficacy in idiopathic (immune) thrombocytopenic purpura (ITP). Subsequently in a double-blind, sham-controlled trial they were shown to be an effective treatment for rheumatoid arthritis [31]. The amount of IgG they bind is small compared to regular plasmapheresis with whole plasma removal, so their ability to suppress autoimmune reactivity was not fully understood. Later, protein A was shown to be a B-cell superantigen, postulated to have evolved in staphylococci as a means to impair antibody-mediated defenses in the host that the staphylococcus is invading [32]. Thus exposure of the patient's blood to staphylococcal pro-

tein A may have an immunosuppressive effect because of a pharmacologic mechanism rather than by an apheresis mechanism. Commercial production of these columns has ceased, and the treatment has not been available in recent years.

Immunoadsorption Using Bound Antigen

Perfusion columns containing immobilized antigen have the potential to be the most specific way to remove autoantibodies. This approach was pioneered in the 1970s, first in a canine model using immobilized glomerular basement membrane (GBM) antigens for the treatment of anti-GBM GN, and then in humans using immobilized DNA for the removal of circulating anti-DNA antibodies from patients with systemic lupus erythematosus (SLE) [33,34]. These attempts were clinically unsuccessful, probably frustrated by leaching of antigen from the column into the patient; the antigen presumably stimulated an increased immune response in the patient, thus augmenting production of antibody of the very type that needed to be eradicated. Twenty years later it became feasible to avoid this obstacle; the approach was to construct peptide ligands that mimic the epitope recognized by pathogenic autoantibodies, and covalently couple these to sepharose in a plasma-perfusion column. This has been used in auto-immune type idiopathic dilated cardiomyopathy. The autoantibodies in this disease were characterized initially as reactive with β-1 receptors in the heart, but some have other reactivities including with cardiac myosin. Plasmaperfusion on these specific columns has been shown to be effective in ameliorating cardiac dysfunction in this disease [35]. The system is now undergoing clinical trials in the USA.

Other Adsorption Column Techniques

Many types of affinity adsorption columns have been developed. For instance, tryptophan linked to polyvinyl alcohol gel has specific affinity for IgG3, and has been shown to successfully deplete anticardiac autoantibodies [36]. This and many other devices are not currently approved for use in the USA. Affinity column adsorption has proved most effective when the pathogenic toxin can be accurately measured and reliably extracted. A good example is a Japanese machine for LDL-apheresis which removes low-density lipoprotein (LDL) using dextran sulfate columns, which fortuitously bind LDL, Lp(a) (lipoprotein ''little a'') and VLDL (very low density lipoprotein), but not the beneficial lipoprotein fraction HDL (high density lipoprotein) [37]. A German system for LDL-apheresis treats separated plasma with high dose heparin and an acid buffer; this causes precipitation of lipoprotein complexes that are removed downstream in a column that traps these macromolecular aggregates; further downstream is a column that adsorbs heparin, and finally there is a dialyzer to correct the pH before the lipid-depleted plasma returns to the patient [38]. Both of these LDL-apheresis systems are FDA-approved and are in use in the USA.

In the past, columns containing resins or activated charcoal were used for hemoperfusion to remove poisons. They can be disruptive to blood cells; this damage can be avoided by using the columns on separated plasma rather than on whole blood. The use of resin columns in this manner has been investigated in the treatment of septicemia with multiple organ failure, sometimes in tandem with high-volume hemofiltration [39]. However, these columns appear to bind many different cytokines, of both pro- and antiinflammatory varieties, and probably other unmeasured mediators, which makes evaluation difficult. It is of interest that the only randomized prospective trial of plasmapheresis therapy in septic shock that has shown significant survival benefit was performed using conventional centrifugal TPE [40].

THERAPEUTIC CYTAPHERESIS MODALITIES

Leukapheresis

White blood cell (WBC) reduction in leukemia was the first intended use when centrifugal apheresis machines were being developed in the 1960s [20]. The procedure is now used when hyperleukocytosis causes (or threatens to cause) cerebral leukostasis syndrome or other organ perfusion problems [41]. The malignant myeloblast is the largest and least deformable cell that ever enters the circulation, and is associated with signs and symptoms attributable to reduced capillary flow in internal organs. Leukapheresis is also used when debulking of the circulating WBC mass seems advisable before lytic therapy, to avoid postlysis complications; this can apply to lymphocytic as well as myelocytic leukemias. When WBC leukapheresis is used for hyperleukocytosis in acute myeloid leukemia, there is a beneficial impact on the overall early mortality rate [42]. Leukapheresis has been recommended in acute myeloblastic states whenever the absolute myeloblast count exceeds 70,000 per mm^3, whether or not the patient is yet symptomatic [20]. When the spleen is enlarged, removal of leukemic cells by leukapheresis may be followed immediately by re-emergence of sequestered cells into the bloodstream. This may necessitate repeated procedures to achieve adequate reduction. Each procedure usually involves processing at least 10 L of blood through a centrifugal machine; because the WBC mass represents a larger than normal fraction of the blood, the WBC collection pump has to be set at a substantially higher flow rate than in other WBC collection procedures.

Leukapheresis is used on patients with normal WBC counts to collect cells for autologous hematopoietic stem cell transplantation (formerly bone marrow

transplantation), and for reinfusion to the patient after experimental gene transfer and immuno-modulation procedures. These modalities, and leukapheresis with online WBC processing such as photopheresis, are beyond the scope of this review.

Thrombocytapheresis

Platelet reduction apheresis is indicated for the treatment of symptomatic thrombocytosis or for prophylaxis when the platelet count exceeds 1,000,000 per mm^3 [43].

Erythrocytapheresis

Red cell exchange apheresis has been used for over 30 years for specific complications of sickle cell disease (SS) and other hemoglobinopathies [44]. It is also indicated in asymptomatic patients with SS or SC disease before elective surgeries of the eye, pulmonary thrombarterectomy surgery, and other surgeries that create periods of organ ischemia. Recently, erythrocytapheresis has been used after ABO marrow transplantation to remove the recipient's red cells before the new marrow starts causing massive immune hemolysis, and replace them with RBCs compatible with the patient's new immune system [45]. Occasionally, erythrocytapheresis is used to remove and replace affected RBCs in malaria and babesiosis [21].

CONCLUSION

Apheresis therapies have an important and growing role in the treatment of many diseases. The predominant use of plasmapheresis is for the removal of autoantibodies, which can be eliminated with certainty when the separated plasma is discarded. Secondary processing to purify the plasma and allow it to be returned to the patient is an objective that has spawned numerous different innovations over many years, but none is yet as efficient or as universally accepted as is conventional plasmapheresis with plasma replacement. In choosing machines, the efficiency and reliability of centrifugal plasma separation has to be weighed against the lower initial investment cost of membrane separators. Also relevant is the ability of centrifugal machines to perform cytapheresis modalities as well as plasmapheresis. Advances in molecular science, clinical validation, and technical sophistication combine to make apheresis medicine an exciting and important therapeutic discipline.

ACKNOWLEDGMENTS

The contents of this review were presented at the September 2010 Therapeutic Apheresis Academy, University of Virginia, Charlottesville, VA.

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