Clinical Applications of Therapeutic Apheresis

Rasheed A. Balogun,1* Andre Kaplan,2 David M. Ward,3 Chidi Okafor,1 Ted M. Burns,4 A. Sergio Torloni,5 B. Gail Macik,6 and Emaad M. Abdel-Rahman1

1Department of Medicine, Division of Nephrology, University of Virginia Health System, Charlottesville, Virginia
2Department of Medicine, University of Connecticut Health Center, Farmington, Connecticut
3Department of Medicine, University of California, San Diego, California
4Department of Neurology, University of Virginia, Charlottesville, Virginia
5Department of Laboratory Medicine and Pathology, Mayo Clinic, Scottsdale, Arizona
6Division of Hematology, Department of Medicine, University of Virginia, Charlottesville, Virginia

THERAPEUTIC APHERESIS FOR RENAL DISORDERS

The vast majority of the renal indications for plasma exchange are related to immunoglobulin removal. Immunoglobulins, especially IgG, have a relatively long half-life. Thus in antibody-mediated disease, there could be persistence of significant amounts of antibody in the circulation despite cessation of antibody production. The aim of plasma exchange is to significantly reduce circulating antibodies. Removal of the circulating antibodies constitutes the rationale for using plasmapheresis to treat antibody-associated glomerulonephritis (GN). Although small molecular weight substances are removed by plasma exchange, their large volume of distribution and short half-lives make plasma exchange an inefficient means of extracorporeal removal of these substances. For instance, some complement proteins have a half-life of 2 days. If the goal were to be to deplete plasma complement levels, virtually daily plasma exchanges would be needed. Discontinuation of daily plasma exchange would be followed by rapid resurgence to normal complement titers. Hence the shorter the half-life of the molecule being removed, the more aggressive has to be the apheresis schedule.

Plasma volume can be estimated using the following formula:

\[
\text{EPV} = 0.065 \times \text{TBW} \times [1 - \text{Hct}]
\]

where EPV is the estimated plasma volume, TBW is the total body water, and Hct is hematocrit.

The removal of large molecular weight substances from the plasma compartment follows first-order kinetics. Repetitive treatments should be spaced every 24–48 h to allow for extravascular to intravascular equilibration.

Apheresis has been used to treat several renal conditions including primary renal diseases as well as renal manifestations of systemic conditions (Table I).

PRIMARY RENAL DISEASES

Antiglomerular Basement Membrane Antibody Disease/Goodpasture’s Syndrome

Glomerular basement membrane (GBM) antibodies are pathogenic antibodies capable of causing alveolar hemorrhage and rapidly progressive glomerulonephritis (RPGN). There is only one randomized, controlled trial [1] that showed that plasmapheresis results in rapid lowering of anti-GBM antibody, lower post-treatment creatinine, and reduced incidence of end-stage renal disease (ESRD). Thus, plasmapheresis is now accepted as one of the therapeutic modalities used to treat anti-GBM disease.

IgA Nephropathy

Although the vast majority of patients with IgA nephropathy run a benign renal course, IgA nephropathy is sometimes associated with RPGN. Removal of circulating IgA-containing immune complexes may prevent worsening of renal function in such patients with IgA nephropathy.

*Correspondence to: Rasheed A. Balogun, Division of Nephrology, University of Virginia Health System, Box 800133, Charlottesville, VA 22908. E-mail: rb8mh@virginia.edu

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nephropathy [2,3]. Several studies showed that plasmapheresis can result in successful treatment of IgA nephropathy, even without immunosuppression [4,5].

**Henoch–Schoenlein Purpura**

Plasmapheresis has been used as the sole therapy for RPGN in Henoch–Schoenlein purpura [6]. Hattori et al. examined nine children with RPGN secondary to HSP with a mean urine protein of 4.9 g/m²/day and glomerular filtration rate (GFR) of 46.5 mL/min. Renal biopsy showed crescents in >56% of glomeruli. Therapeutic plasma exchange (TPE) was used as the sole therapy for these patients with TPE done thrice weekly for 2 weeks then weekly for 6 weeks. At the end of therapy, there was improvement in renal function, purpuric rash, and abdominal pain. On comparing the renal long-term survival in this study to previous studies, 87% showed long-term renal survival (9.6 years) versus less than 33% in previous studies.

**Idiopathic Rapidly Progressive Glomerulonephritis**

TPE has been suggested to play a role in idiopathic RPGN. Although a randomized controlled study has shown that TPE has no additional therapeutic benefit in patients with idiopathic RPGN [7], the implication of antineutrophil cytoplasmic antibody (ANCA) in the pathogenesis of idiopathic RPGN may give credence to the possibility that TPE may have a beneficial role in treatment of RPGN which were formerly considered idiopathic [8] (Table II).

Several studies have implicated ANCA as being pathogenic [12]. In vitro data showed that ANCA is capable of activating leukocytes [13,14], while animal studies have shown that antimyeloperoxidase antibodies can induce necrotizing GN and vasculitis [15,16]. In humans, a case of transplacental transfer of ANCA resulting in vasculitis in newborn infant was reported [17]. Thus, several randomized trials using plasma exchange or high-dose methylprednisolone as adjunctive therapy for severe renal vasculitis were done. Jayne et al. [18] studied 137 patients with a new diagnosis of ANCA-associated systemic vasculitis with serum creatinine >5.8 mg/dL. Patients were randomly assigned to receive either TPE (seven plasma exchanges) or intravenous methylprednisolone (3,000 mg of IV methylprednisolone). Both groups received oral cyclophosphamide and oral prednisolone. At 3 months, 69% of the patients who received TPE were alive and independent of dialysis versus 49% of the patients who received IV methylprednisolone (95% CI: 18–35; P = 0.02). The risk of ESRD decreased in patients who received TPE, with only 19% of patients receiving TPE developing ESRD after 1 year of therapy versus 43% after IV methylprednisolone (95% CI: 6.1–41). Both patient survival and severe adverse event rates were similar in both groups. They concluded that TPE increased the rate of renal recovery in ANCA-associated systemic vasculitis that presented with renal failure when compared with IV methylprednisolone.

Another indication of plasma exchange is for ANCA-associated pulmonary hemorrhage. Klemmer et al. [19] showed a 100% survival in those patients with alveolar hemorrhage who received prompt treatment with plasma exchange versus 50% mortality of historical controls with diffuse alveolar hemorrhage.

**Focal Segmental Glomerulosclerosis**

Approximately 15–55% of patients with ESRD due to focal segmental glomerulosclerosis (FSGS) will have recurrence of proteinuria after renal transplantation.

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**TABLE I. Renal Indications for Plasmapheresis**

<table>
<thead>
<tr>
<th>Primary renal disease</th>
<th>Secondary renal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. IgA nephritis/Henoch–Schoenlein purpura</td>
<td>2. Antiphospholipid antibody syndrome</td>
</tr>
<tr>
<td>3. Pauci-immune rapidly progressive glomerulonephritis</td>
<td>3. Cryoglobulinemia</td>
</tr>
<tr>
<td>4. Focal segmental glomerulosclerosis</td>
<td>4. Multiple myeloma</td>
</tr>
<tr>
<td>5. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome</td>
<td>6. Transplantation</td>
</tr>
</tbody>
</table>

**TABLE II. Controlled Trials of TPE for Severe RPGN**

<table>
<thead>
<tr>
<th>Study</th>
<th>Index of severity</th>
<th>TPE</th>
<th>No TPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glockner et al. [10]</td>
<td>Creatinine after 3 years</td>
<td>8.7</td>
<td>13.4</td>
</tr>
<tr>
<td>Cole et al. [7]</td>
<td>Dialysis dependent</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Patients off dialysis at 12 months</td>
<td>10</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Initial number of patients on dialysis</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Patients off dialysis at 12 months</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
This subtype of FSGS appears to be mediated by a circulating 30–50,000 Da protein of unknown origin that can increase glomerular permeability and cause proteinuria. Protein adsorption and plasmapheresis can lower proteinuria and maintain normal histology [20,21].

Dall’Amico et al. [22] obtained pretransplant serum from 25 children with FSGS and evaluated them for this glomerular permeability factor. They showed that 11 of 13 children with permeability factor had recurrence of FSGS, whereas only four of 12 without detectable factor had recurrence. They further showed that nine of 11 patients treated with plasmapheresis and cyclophosphamide had reversal of proteinuria, with seven of 11 having long-term remission (up to 32 months). They concluded that permeability factor can predict recurrence and that TPE and cyclophosphamide are effective in post-transplant FSGS [22]. Matalon et al. [23] studied 13 adult patients from three transplant centers who underwent plasmapheresis for recurrent FSGS between 1993 and 1999. One patient (8%) had a complete response, one (8%) had a partial response and three patients (23%) partially responded but remained plasmapheresis dependent. All five responders were started on plasmapheresis within 30 days of recurrence, whereas seven of the eight nonresponders initiated plasmapheresis after a delay of at least 42 days (P = 0.0047). FSGS recurred within 30 days of transplantation in all five responders, whereas four of eight nonresponders had no evidence of recurrence until 42–150 days after transplantation (P = 0.098). They concluded that plasmapheresis is less effective in adults than in children as a treatment for recurrent FSGS in the renal allograft and that predictors of response to plasmapheresis include early initiation of treatment after recurrence. Nevertheless, plasmapheresis is now a standard treatment for post-transplant recurrence of FSGS.

**SECONDARY RENAL DISEASES**

**Systemic Lupus Erythematosus**

Despite early positive reports, randomized, controlled trials have been unable to document a benefit of plasmapheresis as an adjunct to standard immunosuppressive therapy in patients with systemic lupus erythematosus (SLE) [24–26].

**Antiphospholipid Antibody Syndrome**

In conditions such as lupus anticoagulant and anticardiolipin antibody syndrome, which are associated with arterial and venous thrombosis, recurrent fetal loss, and renal disease, plasmapheresis has resulted in successful pregnancy and reversal of renal disease [27–29].

Another form of antiphospholipid antibody syndrome (APS) is catastrophic antiphospholipid antibody syndrome (CAPS). CAPS is a rare life-threatening disease with associated mortality rate >50%. Treatment of CAPS consists of IV heparin, IV steroids, intravenous immunoglobulin (IVIG), and/or TPE.

**Cryoglobulinemia**

The entity that was known historically as essential mixed cryoglobulinemia is now known to be due to hepatitis C in most cases. The cryoglobulinemia may cause vasculitis that can be of life-threatening severity, mainly by progressive necrosis and gangrene of the extremities. Despite the lack of randomized controlled trials, there is a general consensus that plasmapheresis, by removal of cryoglobulins, is an effective treatment of this condition. Antiviral therapy of hepatitis C infection often fails, and immunosuppression with corticosteroids, cyclophosphamide, or rituximab may be of limited or temporary benefit and can be problematic. Thus some patients are left with plasmapheresis as the only available therapeutic option or others may need plasmapheresis until these other therapies take hold. Ferri et al. [30] showed that some patients with cryoglobulinemia may respond to plasmapheresis alone (Table III).

**“Cast Nephropathy” in Multiple Myeloma**

Light chains (Bence Jones protein) can be toxic to the tubules and result in obstruction of nephron lumen and acute renal failure. Plasmapheresis, as an adjunct to chemotherapy, results in a more rapid lowering of serum light chains and a lower post-treatment creatinine [31]. Clark et al. [32] studied 97 patients with acute renal failure at the onset of multiple myeloma. Patients were randomly assigned to conventional therapy plus five to seven plasma exchanges for 10 days or conventional therapy alone. The primary composite outcome was death, dialysis dependence, or GFR <30 mL/min. Results showed that the composite endpoint occurred in 33 of 57 (57.9%) in the plasma exchange group and 27 of 39 (69.2%) in controls. There was no statistically significant difference between the two groups. One-third of patients in each group died. The study had several limitations: small sample size, use of a composite outcome, and lack of use of renal biopsy as an inclusion criterion. Furthermore, recruiting physicians could not be randomized.
were blinded to treatment allocation but not to treatment thereafter. The researchers concluded that in patients with acute renal failure at the onset of multiple myeloma, there is no conclusive evidence that five to seven plasma exchanges substantially reduces the composite outcome of death, dialysis dependence, or GFR <30 mL/min at 6 months [32]. Secondary analysis of the data at 6 months showed that there was no statistically significant difference in the cumulative survival in both groups at that point. Although the GFR at baseline showed no statistical difference between both groups, patients who became dialysis dependant at 6 months were seven of 26 (26.9%) patients in the control group versus only five of 39 (12.8%) patients in the plasma exchange group. Despite 50% reduction in need for dialysis, the study did not find a statistically significant benefit for TPE [difference 14.1% (CI: −5.1 to 34.6); P = 0.20]. Of note, 17 of 97 patients did not have evidence of free light chains. Such patients could not have possibly benefited from plasma exchange, which may explain the lack of significant benefits in the outcomes in the plasma exchange group.

Recently, Hutchison et al. [33] showed that highly permeable hemofilter membranes may allow for light chain removal without significant albumin loss.

Thrombotic Thrombocytopenic Purpura/ Hemolytic Uremic Syndrome

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are microvascular disorders of platelet clumping with similar signs and symptoms. They are associated with unusually large multimers of von Willibrand factors, capable of agglutinating circulating platelets. The similarity of TTP and HUS has resulted in the clumping of both disorders as “thrombotic microangiopathies.” Recent evidence suggests that TTP and HUS can be distinguished by the activity of vWF cleaving protease [34]. Furlan et al. showed that all 24 patients with nonfamilial TTP had deficiency of protease activity, whereas 20 of 24 patients had IgG inhibitor against the protease. On the other hand, all six patients with familial TTP had protease deficiency without an inhibitor, and 11 of 13 patients with HUS had no protease deficiency [34].

Although plasmapheresis has been shown to be clearly beneficial in TTP [35], the benefit of plasmapheresis in HUS is less clear and may depend on associated factors; E. coli 0157 induced verotoxin, cancer, chemotherapy/drug induced, post-renal transplant, etc.

Several controlled trials were done to evaluate the benefits of plasmapheresis in the management of HUS in children. Minimal benefit of plasma infusion was shown [36].

Loirat et al. [37] showed that plasma infusion (10 mL/kg daily for 7 days) resulted in short-term (<6 months) benefit. IVIG showed no benefit at 1 year [38]. There are no randomized controlled trials with TPE, but retrospective studies and anecdotal reports suggest a benefit in those children with HUS at high-risk of renal damage [those without a diarrheal process or older than 5 years of age or with significant central nervous system (CNS) involvement] [39–41].

The role of plasmapheresis in recurrent HUS in renal allografts is not clear. Agarwal et al. [42] reviewed 68 cases with recurrent HUS in renal allografts. The differential diagnoses for HUS in the renal allografts were acute vascular rejection, cyclosporine, FK506, antilymphocyte antibody nephrotoxicity, and malignant hypertension. The results showed that graft recovery after cyclosporin withdrawal and TPE occurred in 19 of 34 cases. The conclusion is that plasmapheresis in conjunction with fresh-frozen plasma (FFP) may reduce morbidity and mortality in recurrent HUS in renal allografts [42].

Transplant Candidates with Cytotoxic Antibodies/ Antibodies Against ABO Groups

Preformed cytotoxic antibodies preclude renal transplantation due to risk of hyperacute rejection. Immunoadsorption in highly sensitized patients can allow for successful transplant [43,44]. On the other hand, pre-treatment with plasmapheresis to remove anti-A or anti-B antibodies is necessary to prevent acute vascular rejection with renal transplantation across ABO groups. Modlin et al. [45] showed the 5-year graft survival to be as high as 78% when kidneys from donors in blood groups A2 or B subgroups are transplanted into group O recipients.

EXTRACORPOREAL PHOTOPHERESIS AND SOLID ORGAN TRANSPLANT REJECTION: CURRENT INSIGHTS

Immune injury in autoimmunity and transplant rejection can be either antibody mediated or cell mediated. Therapeutic plasmapheresis/plasma exchange involves removal of antibodies, whereas therapeutic ECP, on the other hand, involves down-modulation of cell-mediated immunity. The mechanism of action of photopheresis is complicated, but essentially involves the promotion of immune tolerance by cells which are rendered apoptotic when exposed to the ECP process.

Principles of Photopheresis

Photopheresis, also known as extracorporeal photopheresis, was originally introduced by Edelson et al. [46] for the treatment of cutaneous T-cell lymphoma (CTCL; Sezary syndrome). Modern photopheresis involves the use of a centrifugal apheresis machine to separate white blood cells (WBCs; leukapheresis).

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Then, 8-methoxy psoralen is injected into the collected WBC product, which when exposed to ultraviolet A (UVA) light in an external chamber results in cross-linking and damage of the leukocyte DNA and eventual apoptosis. The apoptotic leukocytes are returned to the patient, where they are taken up by antigen-presenting cells (APCs). APCs have specific recognition receptors for apoptotic T-cells, whose activation triggers a series of events leading to downregulation of cell-mediated immunity. This appears to be a clonal-specific down-regulation, which means that only T-cell clones that are active at the time of treatment are affected, leaving the rest of the cell-mediated immune system intact. Thus as a treatment for autoimmune or alloimmune (transplant) reactivity, photopheresis is well tolerated, selectively shifting the unwanted immune response from an active state toward tolerance, without impairing defenses against infection as occurs with other immunosuppressive therapies.

Photopheresis was developed as an offshoot from cutaneous photochemotherapy for psoriasis whereby psoralen and UVA light were used to crosslink DNA. Cutaneous photochemotherapy involved initial ingestion of 40 mg of psoralen before exposure to UVA light. The original method of ECP required the same oral ingestion of high-dose psoralen. When parenteral psoralen became available, it sufficed to inject a much lower dose (of the order of 0.1 mg) into the WBC collection. This modern use of low-dose psoralen is a safer practice and greatly reduces the risks of skin and eye photosensitivity and the potential long-term complications of skin cancer, cataracts, etc. Nevertheless, it remains essential that patients should be advised to wear sunglasses and avoid sun exposure for at least 24 h following photopheresis.

Applications of Photopheresis

Photopheresis is mainly used for the treatment of CTCL (including Sezary syndrome), graft-versus-host disease (GVHD), and solid organ transplant rejection (particularly heart and lung). Some evidence is accruing for the use of photopheresis for liver and kidney transplant rejection and for other conditions such as Crohn’s disease, scleroderma, and other autoimmune diseases. As of January 2008, the Medicare system in the Unite States approved reimbursement for photopheresis for the treatment of GVHD and heart transplant rejection, in addition to CTCL. However, CTCL remains the only indication approved by the U.S. Federal Drug Administration (FDA); other applications remain technically “off label.”

Automated Photopheresis Machines

Several types of photopheresis machine are in use around the world. In the United States, until recently the only FDA-approved machine has been the Therakos™ UVARTM XTS™. In 2009, a new machine by the same manufacturer, the Therakos™ CellEX™, was approved by the FDA. The most familiar machines use automated white cell collection using a discontinuous centrifugation system. Initial cycles collect WBCs and return the RBCs and plasma to the patient. Typically, the last cycle is an elutriation centrifugation, which ensures that the WBC product has a low hematocrit. This is important because red blood cells interfere with UVA irradiation of WBCs. The photoactivation stage involves addition of 8-methoxy psoralen (20 µg/mL solution) to the WBC product at a dose of 0.017 mL of psoralen per milliliter of WBC product. The WBC product is exposed to UVA for a time determined by machine parameters, usually ~25–45 min, and is then reinfused to the patient. Most experience has been with the use of two treatments on successive days, repeated every 2 weeks. More frequent or less frequent dosing may be used, depending on the desired intensity of treatment, although the best approach is really not known as there has been no controlled trial to study the optimal timing and pattern of treatment.

Solid Organ Transplant Rejection

In heart transplantation, early case series reported that among patients at high risk of rejection, photopheresis appeared to reduce the rate of rejection episodes and to allow reduction in standard immunosuppressive doses, thus minimizing associated morbidity and mortality [47,48]. Additional series in patients with severe or recurrent heart transplant rejection reported that the addition of photopheresis reduced or reversed rejection episodes [49–51]. Barr et al. [52] studied the effect of prophylactic photopheresis prospectively and concluded that it is a safe and well-tolerated immunomodulatory technique, and in one study, it is associated with a significant reduction in the frequency and severity of acute heart rejection episodes, and in a second study, it is associated with amelioration of chronic rejection (as judged by a reduction in coronary artery intimal hyperplasia in the transplanted heart) [53]. One of the largest studies of heart transplantation, a retrospective analysis of 343 heart transplant cases from Alabama, reported that photopheresis initiated in a subset of patients with high rejection risk resulted in a reduced rate of hemodynamic compromise and death from rejection [54]. In Alabama, some patients receive a higher intensity of treatment, with two procedures every week for the first month before tapering to a more standard regimen of two treatments on successive days every 2 weeks for the second month.

Lung transplant rejection manifests as bronchiolitis obliterans syndrome. Some early case series reported that ECP may be a safe and efficacious alternative...
therapy for lung transplant rejection [55–57]. The largest single-center study of ECP for bronchiolitis obliterans syndrome and recurrent acute rejection after lung transplantation showed in 24 patients that ECP was associated with clinical stabilization and a marked decrease in the rate of decline of pulmonary function, as documented by serial measurements of the FEV1 (the forced expiratory volume in 1 s) [58].

In liver transplantation, benefit from photopheresis was reported by Lehrer et al. [59] in a 14-year-old patient who had complete reversal of acute cell-mediated rejection following treatment with ECP. Thereafter, Urbani et al. from Pisa have pursued several studies of photopheresis for hepatic transplantation. An initial five patients underwent ECP for biopsy proven liver allograft rejection; all showed reversal of rejection, and three patients could successfully reduce their dose of immunosuppressants [60]. Minimization of dosing of corticosteroids, calcineurin inhibitors, and other immunosuppressants is of special importance in hepatitis-C positive recipients, where progression of viral infection post-transplant is a major factor in subsequent mortality. Urbani et al. [61] prospectively studied 78 such patients in whom antivirals and photopheresis were added to the maintenance post-transplant drug regimen; they found that the immunosuppressive dosages could be successfully reduced and that the 18-month mortality was only 10%, significantly better than historical control groups whose 18-month mortality rates had been 22 and 28%. The same group has successfully used photopheresis prophylaxis in 11 cases of ABO-incompatible liver transplantation, reporting that none developed cellular rejection [62]. Photopheresis appears to be a safe and promising modality that may be able to improve outcomes in hepatic allotransplantation.

Although kidney transplants are by far the most frequent internal organ allografts, photopheresis in this setting has not been extensively studied. Early case reports described successful treatment of recurrent rejection in renal transplant patients [63–65]. Photopheresis was also associated with significant improvement in renal function in renal transplant patients with acute rejection unresponsive to conventional antirejection therapy [66,67]. One study aimed at assessing the biological response to photopheresis when used prophylactically in renal transplant patients and showed induction of regulatory T cells and suggested that prophylactic photopheresis induces a tolerogenic shift in the immune system and may play a role in prevention of chronic kidney transplant rejection [68]. Studies have also shown promising results when photopheresis is used as an adjuvant/salvage therapy in renal allograft rejection [69].

The use of ECP has also transcended to the field of composite tissue allotransplantation. Photopheresis was used in two cases of face transplantation after occurrence of second rejection episodes triggered by viral infections. Photopheresis was shown to reverse the rejection process without development of side effects [70].

Other Applications of Photopheresis

Photopheresis is a well-established treatment for both acute and chronic GVHD as well as CTCL [71–75]. In Crohn’s disease, a recent prospective pilot study of photopheresis in 28 patients showed a clinical response in 50% and remission in 25% of patients with moderate-to-severely active disease unresponsive to immunosuppressants and/or antitumor necrosis factor agents [76].

ECP is establishing itself as a safe and effective modality in the adjunctive treatment or prevention of cellular rejection of solid organ transplants, particularly heart and lung transplants. Results are encouraging for some aspects of the management of liver transplants, but little is yet established about its possible application to kidney transplant management. Photopheresis has an accepted place in the treatment of CTCLs, is gaining similar acceptance for GVHD, and is being explored for its potential efficacy in some autoimmune diseases. It appears to hold promise for promoting the general health as well as the longevity of organ transplant recipients, in part, because of its good safety profile and minimal systemic side effects when compared with conventional antirejection immunosuppressant medications.

NEUROLOGIC INDICATIONS FOR THERAPEUTIC APHERESIS

The two most common neurologic indications for apheresis are myasthenia gravis (MG) and acute inflammatory polyneuropathy [i.e., Guillain-Barré syndrome (GBS)] [77–79]. Multiple sclerosis (MS), neuro-myelitis optica (NMO), acute disseminated encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, Lambert-Eaton myasthenic syndrome, paraproteinemic polyneuropathy, and cryoglobulinemic polyneuropathy are some other neurological conditions sometimes treated with apheresis [80–82]. This review will discuss MG, GBS, MS, and NMO.

Guillain-Barré Syndrome

GBS represents a group of polyradiculoneuropathies that are acute onset, monophasic, and autoimmune [80,81,83–85]. The classic pattern of GBS is an acute-onset demyelinating polyradiculoneuropathy, manifesting as progressive limb weakness, positive neuropathic sensory symptoms, and hypo- or areflexia. Patients with GBS reach clinical nadir within 4 weeks. Cranial nerves (e.g., facial nerves), phrenic nerves, and auto-
nomic nerves are also commonly affected [85]. Electrodiagnostic testing (EDX) of patients with classic GBS will reveal hallmarks of acquired peripheral nerve demyelination, particularly if the EDX is performed in the second week of illness [86,87]. Variants of classic GBS include those caused by immune attack directed at the axons (e.g., acute motor and sensory axonal polyneuropathy), at motor nerves and nerve terminals (e.g., acute motor axonal neuropathy) or at autonomic nerves (e.g., autoimmune autonomic neuropathy), and those cases demonstrating an unusual geographic distribution of immune attack (e.g., Miller Fisher syndrome manifesting as acute-onset ophthalmoplegia, ataxia, and areflexia) [83,84].

In two-thirds of cases, GBS develops within weeks of an otherwise trivial infection, most commonly an upper respiratory infection or diarrheal illness [88]. The infectious agents that can trigger GBS (e.g., *C. jejuni*, cytomegalovirus) have epitopes on their surface that are similar to epitopes on the surface of peripheral nerves (e.g., gangliosides and glycolipids) [89]. Paraneoplastic myelin, exposed axolemma at nodes of Ranvier, and the presynaptic neuromuscular junction are some common sites of antibody attack [89]. Activation of the complement pathway leads to membrane attack complex formation. Macrophage-mediated stripping of myelin also occurs, mediated by antibody and complement deposition [89,90].

Plasma exchange and IVIG are effective immunotherapy for adult and pediatric patients with GBS if given during the first few weeks of disease [91–97]. For patients with GBS, plasma exchange is usually administered as one plasma volume, 50 mL/kg, on five separate occasions for more than 1–2 weeks [91–95,98,99]. The cost of plasma exchange has been shown to be offset by the savings of a shorter hospital stay [100,101]. The Quality Substandards Subcommittee of the American Academy of Neurology concluded in 2003 that plasma exchange hastens recovery in nonambulant patients with GBS who seek treatment within 4 weeks of onset and that plasma exchange hastens recovery of ambulant patients with GBS who are examined within 2 weeks [91]. The optimum number of plasma exchanges has not been established, but many physicians use the protocol of the North America Trial in which a total of 200 to 250 mL/kg were exchanged for more than 7–10 days [102]. The French Cooperative Group on Plasma Exchange in GBS demonstrated that for adult patients with mild GBS (i.e., able to walk unaided but could not run), two exchanges were better than none, and for patients with moderate (i.e., unable to walk) or severe (i.e., ventilated) GBS, four exchanges were better than two and that six exchanges were no better than four [92].

Plasma exchange and IVIG are probably of equal efficacy and no compelling evidence favors one treatment over the other [102]. The decision to use plasma exchange or IVIG must be based on multiple factors, including availability of treatments and the side-effect profiles in the context of the patient’s severity of GBS and comorbidities. Significant adverse events associated with plasma exchange include hypotension, septicemia, pneumonia, abnormal clotting, complications from central venous access, and hypocalcemia. Citrate infused for anticoagulation or as part of FFP may lead to hypocalcemia or metabolic acidosis. Symptoms of hypocalcemia include paresthesias, muscle cramps, and, in severe cases, cardiac arrhythmias [83]. Major hemostatic disorders, unstable cardiovascular status, active infection, and pregnancy are contraindications to plasma exchange [95].

### Myasthenia Gravis

MG is a chronic autoimmune disorder of neuromuscular junction transmission. Almost all patients with MG initially present with ocular involvement manifesting as asymmetrical, fatigable, and fluctuating ptosis and diplopia [103]. Many patients will generalize within 1 year so that bulbar, respiratory, limb, and/or axial muscles also weaken. Patients frequently develop bulbar muscle weakness manifesting as fluctuating and fatigable dysphagia and dysarthria. It is estimated that ~20–30% of patients with generalized MG will experience clinically significant respiratory weakness, sometimes requiring mechanical ventilation (termed “myasthenic crisis”). Myasthenic crisis is most common during the first few years of disease and is often associated with an upper respiratory infection or other trigger.

MG is a T-cell dependent, antibody-mediated disorder. Approximately 85% of patients with generalized MG have circulating autoantibodies to the acetylcholine receptor (AChR) of the muscle endplate of the neuromuscular junction [103]. Another 7% of patients with generalized MG have antibodies to muscle-specific tyrosine kinase (MuSK) rather than to AChR [104]. MuSK is another protein expressed on the muscle endplate of the neuromuscular junction. The remaining ~8% of patients with generalized MG are classified as “seronegative” or “double seronegative,” although it has recently been reported that many of these patients in fact have autoantibodies to AChR that are only detectable when a newly developed cell-based assay is used to measure antibodies instead of the conventional method [105].

The two modalities of treatment of MG, commonly used together, are cholinesterase inhibition and immunosuppression/immunomodulation. Pyridostigmine (e.g., Mestinon), a cholinesterase inhibitor, is typically used first for ocular and generalized MG, but it often provides only modest symptomatic benefit and thera-
Multiple Sclerosis and Neuromyelitis Optica

MS and NMO are inflammatory, demyelinating disorders of the CNS. Patients with MS or NMO manifest with neurological symptoms and signs referable to the location of CNS injury. Patients with both disorders usually have acute attacks with relapses.

In MS, self-reactive T cells initiate and mediate events that lead to tissue damage in the CNS, although autoantibodies also likely mediate injury [81]. However, the long-term benefit of plasma exchange in the treatment of chronic progressive forms of MS has not been proven, and thus, plasma exchange cannot be recommended for these patients [80]. In contrast to chronic progressive MS, plasma exchange is beneficial in some patients with acute exacerbations of MS, and its use is currently reserved for patients with acute, fulminant exacerbations who have failed to respond to high-dose intravenous corticosteroids [109,110]. It is of interest that patients with MS who respond to plasma exchange appear to have an immunopathological pattern of disease that is characterized by antibody/complement-associated demyelination, whereas patients with MS who do not respond are more likely to have a different immunopathological pattern [110].

NMO was usually classified as a subtype of MS until the detection of NMO serum autoantibodies in patients with NMO and not in patients with MS, which provided compelling evidence that the two CNS inflammatory diseases were different entities [111]. NMO is the first CNS demyelinating disease to have a defined autoantibody, and serologic testing for the NMO-IgG autoantibody enables diagnosis [112]. NMO predominantly affects the spinal cord and optic nerves. The immunopathological pattern of NMO is characterized by inflammatory infiltrates and perivascular immunoglobulin and complement deposits that surround blood vessels. NMO-IgG targets aquaporin-4, a water channel expressed on the surface of astrocytes. Aquaporin-4 is notably in highest concentration on the domains of perivascular and peripial end feet, both of which are in direct contact with the basal lamina of the endothelium and pia mater, respectively [112]. Aquaporin-4 is found in the highest concentrations in the optic nerves, brainstem, and gray matter of the spinal cord [112]. In case series, both high-dose intravenous corticosteroids and plasma exchange have been shown to be beneficial for the acute attacks of NMO. Plasma exchange is usually administered as one plasma volume, 50 mL/kg, on five separate occasions for more than 1–2 weeks.

Thrombotic Microangiopathies When Therapeutic Apheresis Is the Answer

Thrombocytopenia is one of the most common reasons for inpatient hematology consult. Differential diagnoses for thrombocytopenia are legion and include immune thrombocytopenic purpura (ITP), disseminated intravascular coagulopathy, splenomegaly, APS, hemolytic anemia, elevated liver enzymes, and low platelet count (HELLP) syndrome, drug-induced, viral infection, pseudothrombocytopenia, vasculitis, etc. However, always lurking in the background is the possibility of TTP. TTP is relatively rare but is highly fatal if not treated and hence requires a high level of suspicion to prevent fatal outcomes if it goes unrecognized.

TTP was first recognized by Dr. Moschowitz when he described a syndrome in a 16-year-old female with petechiae, pallor, paralysis, and coma [113]. Amorosi and Ultmann [114] established the clinical pentad (thrombocytopenia, microangiopathic hemolytic anemia, renal failure, neurologic dysfunction, and fever) that became the diagnostic criteria for TTP. Moake et al. [115] described large multimers of von Willebrand factor (vWF) in the plasma of four patients with relapsing TTP. Rock et al. [35] documented the efficacy of extensive plasma exchange in treatment of TTP. This discovery was the most important change in therapy for TTP over the last 50 years. Furlan et al. [116] in Switzerland and Tsai [117] in New York isolated a vWF-cleaving metalloprotease. It was recognized that a deficiency of a plasma protein or a circulating inhibitor was responsible for TTP. Levy et al. characterized the vWF protease as a protein in the metalloprotease family known as ADAMTS-13 [118,119].

The annual incidence of TTP is ~3.7 per one million individuals [120]. The median age is 35 years with a female to male ratio of 3 to 4:1. TTP is seen in all...
O157:H7 could also lead to TTP. Viral and bacterial infections especially induced TTP like syndromes are very severe and difficult to control. Certain drugs such as ticlopidine, clopidogrel, cyclosporine, quinine have been implicated in the etiology of TTP. The drug-induced purpura, autoimmune disorders such as Evans syndrome and underlying malignancies. An attempt has been made to categorize TTP based on etiology. Idiopathic TTP that constitutes a large proportion of cases of TTP is often due to deficiency of the ADAMTS-13 cleaving protein and is thought to be an acquired autoimmune disorder. Patients with idiopathic TTP have an autoantibody to the ADAMTS-13 protease and often respond to plasma exchange, steroids, and rituximab although they often have very long clinical courses with relapses. There is also a hereditary form of TTP known as the Upshaw Shulman syndrome. It is associated with a defect in the ability to produce the ADAMTS-13 protease or production of a defective protein molecule. Patients with Upshaw Shulman Syndrome, often present in their teens. Many female patients with Upshaw Shulman syndrome present for the first during pregnancy and often go into lifelong relapsing and remitting disease course. Secondary TTP encompasses TTP as a result of known factors such as drugs, infections, and chemotherapeutic agents.

ADAMTS-13 stands for a disintegrin-like and metalloprotease with thrombospondin type 1 motif, 13th member. The only known physiologic substrate for this enzyme is the ultra large vWF multimer. There are a variety of ADAMTS-13 gene mutations and this explains the wide variation in disease presentation and severity. Ticlopidine and clopidogrel are associated with autoantibodies against ADAMTS-13 [123]. There are commercially available kits for testing the ADAMTS-13 activity, but the drawback is that these kits are not universally available and samples often have to be sent out leading to delay in getting the results back. There is need for the development of rapid assays for ADAMTS-13 to allow for earlier differentiation between autoimmune TTP and secondary causes of thrombocytopenia. Monitoring ADAMTS-13 activity with rapid assays during treatment may guide therapy in relation to the decision to increase, decrease, or discontinue plasma exchange. Also, the rapid assays may be used during remission to identify patients at higher risk of relapsing [124].

Diagnosis of TTP is made with the aid of simple laboratory tests, elevated platelet count, anemia, elevated LDH and bilirubin, low haptoglobin levels, normal prothrombin and partial thromboplastin time, and classically less than 5% ADAMTS-13 activity. However, the most important tool for diagnosis of TTP is a high clinical suspicion.

Plasma exchange remains the standard of care for management of TTP. The duration, volume of exchange, and indication for tapering of the plasma exchange are still some of the issues surrounding plasma exchange for TTP that have not yet been agreed on by experts. The significant decline in the mortality associated with TTP is largely attributed to thrombocytopenic purpura, autoimmune disorders such as Evans syndrome and underlying malignancies. An attempt has been made to categorize TTP based on etiology. Idiopathic TTP that constitutes a large proportion of cases of TTP is often due to deficiency of the ADAMTS-13 cleaving protein and is thought to be an acquired autoimmune disorder. Patients with idiopathic TTP have an autoantibody to the ADAMTS-13 protease and often respond to plasma exchange, steroids, and rituximab although they often have very long clinical courses with relapses. There is also a hereditary form of TTP known as the Upshaw Shulman syndrome. It is associated with a defect in the ability to produce the ADAMTS-13 protease or production of a defective protein molecule. Patients with Upshaw Shulman Syndrome, often present in their teens. Many female patients with Upshaw Shulman syndrome present for the first during pregnancy and often go into lifelong relapsing and remitting disease course. Secondary TTP encompasses TTP as a result of known factors such as drugs, infections, and chemotherapeutic agents.
the use of plasma exchange [125]. Steroids (1 mg/kg prednisone) may play a role in relapse in some patients but is rarely needed especially if patient is responding to plasma exchange. Immunosuppressive agents such as cyclophosphamide and vincristine should be reserved for refractory cases and potentially have long-term side effects and morbidity associated with the therapy. Rituximab is increasingly being used for autoimmune disorders such as ITP, acquired von Willebrand’s disease, acquired hemophilia, and acquired TTP. It has been associated with good outcomes and is less toxic when compared with steroids. Splenectomy is an option if plasma exchange does not work and is often a treatment of last resort. Platelets are relatively contraindicated in TTP because it promotes more platelet clumping and thrombosis due to preponderance of large vWF in the microvasculature. Platelet transfusion is only indicated if there is intracranial hemorrhage that needs to be arrested by infusing platelets to achieve hemostasis. Desmopressin, on the other hand, is absolutely contraindicated because it releases more ultra large vWF from the endothelium and worsens the whole process of occlusive thrombi in the microvasculature.

The therapeutic benefit of plasma exchange in TTP involves removal of toxic factors and replacing with deficient factors. The plasma containing autoantibodies are removed and replaced with plasma containing ADAMTS-13. The concept of plasma exchange grew out of the fact that there was improvement in TTP with plasma infusion only [126,127]. However, in patients who failed to improve with plasma infusion, plasma exchange offered benefits [128]. The superiority of plasma exchange over plasma infusion was shown in the prospective randomized clinical trial by Rock et al. [35]. As mentioned earlier, there are still some gray areas in the use of plasma exchange in the management of TTP. The frequency of plasma exchange varies from institution to institution although most have adopted daily plasma exchange. Twice a day exchanges should be a limited trial in refractory patients. The use of more frequent exchanges is associated with more FFP reaction and citrate toxicity. With more rapid ADAMTS-13 assay kits, plasma exchange therapy could be guided depending on the results from the assay. The precise volume to use for exchange is not very clear; however, based on limited studies, the volume of exchange to be used should be ~40–60 mL/kg. High-volume replacement flow requires large venous access with bleeding risk. The initial suggestion that cryo-poor plasma improves outcome by decreasing vWF was refuted by a randomized clinical trial [129]. On the other hand, cryo-poor plasma is associated with low fibrinogen and increased risk of bleeding.

LDH is a sensitive indicator of response to therapy. Most authorities will advocate treating until LDH and platelet counts are normal. Schistocyte clearance may be delayed. It is important to follow these patients closely as ~20% often relapse. There is no clear benefit to tapering plasma exchange. Immunosuppressive therapy in TTP is less likely to help in the management of acute episode. Steroids may help to modulate production and effect of autoantibodies to ADAMTS-13 while more aggressive immunosuppressive therapy (vincristine and cyclophosphamide) are reserved for refractory or relapsing disease. Rituximab has been shown to decrease antibodies and induce a durable remission in small case series [130]. Its role as adjuvant or salvage therapy is unclear. The research in TTP is aimed at development of replacement of ADAMTS-13 and other drugs designed to block vWF interaction with platelets.

CONCURRENT THERAPEUTIC ApherESIS AND OTHER EXTRACORPOREAL THERAPIES

Occasionally, situations present whereby apheresis is indicated in patients receiving other extracorporeal therapies such as cardiac bypass, extracorporeal membrane oxygenation (ECMO), hemodialysis, or ventricular assist devices. Indication for two extracorporeal therapies simultaneously are rare but can be considered potentially lifesaving. As disconnecting the patient from a life-supporting device to perform apheresis is not an option, apheresis must be performed concurrently with extracorporeal devices. Literature in such situations is scant. Larson et al. [131] treated presensitized cardiac transplant patients with intraoperative plasmapheresis coupled to the cardiopulmonary bypass system to remove cytotoxic antibodies and reduce incidence of heart transplant rejection. Tsau et al. [132] also showed promising results when intraoperative plasmapheresis was used during cardiopulmonary bypass at the time of transplantation in a patient with high panel-reactive antibody titers. This is often the case with patients who are on ECMO. A few cases have been documented in the literature where concurrent plasmapheresis and ECMO therapy were well tolerated in these patients [133,134]. Apheresis in conjunction with ECMO has safely been performed in children with weight ≤10 kg [135].

Although plasmapheresis during cardiac bypass may appear a complex undertaking, it is actually a manageable process. Plasmapheresis during cardiopulmonary bypass is however more cumbersome when compared with conventional plasmapheresis as it often requires more time to set up and entails all precautions associated with working in the sterile environment of an operating room. Currently, there is no formal process for performing such seemingly complex procedures. Experience gained at certain centers (Mayo Clinic in Arizona) connects the apheresis machine in parallel with the bypass pump via tubing to a low-flow area of the
cardiopulmonary bypass pump. Whole blood is taken from existing access points on the bypass system and returned to a reservoir in the pump circuit through one of the many ports available on that device.

Citrate anticoagulation for apheresis during bypass is not necessary once the patient has been placed on bypass, as the patient is receiving high doses of heparin (30,000–50,000 U) during the course of surgery. The patient is also continuously monitored by anesthesia and tests include continuous online electrolytes, gasometry thromboelastography, periodic activated clotting time, and periodic coagulation profiles. The entire process of apheresis during the heart transplant is transparent to the surgeon. Of interest, plasma removed from a patient who is undergoing apheresis during bypass shows various tinges of pink. Although this may appear alarming at first, it is common and is attributed to hemolysis caused by very large roller pumps used in bypass instrument.

Caution must be exercised during connections to the bypass pump to prevent air embolism due to the high flow rates in some part of the extracorporeal circuit. Connecting to high flow rate areas of the bypass tubing is not recommended, as it may result in Venturi effect and creation of air bubbles in the circuit.

One and a half to two plasma volumes should be processed during the procedure for the purpose of antibody removal. This may have to be followed by additional plasmapheresis pre-transplant according to previously established protocols. Blood inlet flow in the apheresis instrument can be set at high rates (130–150 mL/min) without concern for fluid shifts, as the blood is not being returned directly to the patient. The exchange is actually being performed on the cardiac bypass pump. The choice of replacement fluids for plasmapheresis during cardiac bypass is important and needs to be discussed with the surgeon, anesthesia and perfusion before the onset of plasma exchange. It is also important to alert anesthesia team to the possibility of removal of medications during plasmapheresis. Usually, 5% human albumin is used at least as part of the replacement volume; some FFP is often added to replace coagulation factors. Care must be taken when using FFP because it contains citrate in addition to clotting factors. Therefore, when FFP is used, ionized calcium and magnesium levels should be closely monitored. The chelation effect on these ions can have a profound effect on cardiac function.

Plasmapheresis during ECMO presents a somewhat different set of challenges. As ECMO circuits are not standardized, there is no specific place to which apheresis connections can be made. Additionally, ECMO circuits run almost entirely with high flow rates (>4 L/min). The best place to connect to the ECMO circuit, if available, has to be a low flow line. If such connection is not available, a separate catheter needs to be placed for exclusive use of plasmapheresis. Care must be taken that the catheter placed for apheresis is not in close proximity to the high-flow catheters of the ECMO circuit. Connecting to high flow lines, including existing draw and return catheters for the ECMO circuit, is discouraged as the high flow in these catheters will result in a Venturi effect and possible air embolism. Because of the potential risks associated with plasmapheresis during ECMO therapy, the apheresis physician must have a complete understanding of flow dynamics on both ECMO and apheresis circuits. Ideally, the physician in charge of apheresis should be physically present throughout the entire duration of the procedure to quickly address unanticipated problems.

The above described approaches to apheresis during extracorporeal procedures make the entire process predictable and safe to perform.

Apheresis during dialysis has few advantages except for time saving. Undergoing both procedures in sequence results in a very long day process for the patient. It is this authors’ view that there is no strong or compelling evidence or medical reason to justify such elaborate connections for the sake of saving time by concomitantly performing apheresis and dialysis. Fortunately, apheresis and dialysis can usually be scheduled on different days. Although dialysis is usually a chronic process, apheresis is usually not. Nevertheless, if such an approach is contemplated, the apheresis and dialysis circuits should both be connected in parallel. Citrate anticoagulation should still be used by apheresis.

In conclusion, the use of plasmapheresis during extracorporeal therapies is feasible, effective, safe, and can potentially have life-saving benefits. Nevertheless, these procedures present their own sets of challenges, and therefore risk-benefit analysis of performing such procedures concomitantly need to be weighed.

REFERENCES

262 Balogun et al.


