Introduction and Overview of Therapeutic Apheresis

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CONVENTIONAL THERAPEUTIC APHERESIS: AN OVERVIEW

Apheresis is an extracorporeal therapy that plays a key role in the management of various renal, hematological, rheumatologic, and neurologic diseases. Conventional apheresis techniques include plasmapheresis (performed by online centrifugation or plasmafiltration) and cytapheresis (blood cell separation by online centrifugation). As first described in 1914 [1], plasmapheresis can also be performed manually, which is still done occasionally in pediatric practice or when no machine is available. Therapeutic cytapheresis procedures include red cell exchange (erythrocytapheresis), platelet reduction (thrombocytapheresis), and white cell removal (leukapheresis). Leukapheresis can be used to control extreme leukocytosis or to collect cells for subsequent therapeutic maneuvers. These conventional applications, and less-conventional techniques that require additional hardware, are depicted in Figure 1.

Indications for Plasmapheresis

The indications for plasmapheresis therapy have been repeatedly reviewed and updated [2,3]. The rationales include the removal of pathogenic antibodies, as well as the removal of other toxic plasma constituents, some still unidentified. The removed plasma is replaced typically by a combination of 5% albumin and 0.9% saline. Only in the treatment of thrombotic microangiopathies such as thrombotic thrombocytopenic purpura (TTP) is fresh-frozen plasma (FFP) used for the entire replacement volume; this repletes the deficient ADAMTS13 enzyme while simultaneously removing the autoantibody that causes the common form of this disease [4].

This and many other uses of plasmapheresis have been established empirically for more than a quarter of a century [2]. Since then, modern molecular biology has illuminated many of the pathogenetic mechanisms, revealing increasing complexity. For instance, myasthenia gravis was recognized in the 1970s as caused by autoantibody against the acetylcholine receptor, but some of the previously “seronegative” cases are now known to be due to autoantibody against the muscle-specific kinase, and other subsets are suspected [5]. Acute Guillain-Barré syndrome also has several subtypes: the Miller–Fisher variant has an antibody to the GQ1b ganglioside, other patients have autoantibodies to other neuronal epitopes, and many cases are precipitated by antibodies crossreactive with Campylobacter jejuni [6]. Hepatitis C can cause cryoglobulinemic vasculitis, a life-threatening complication that can be treated by plasmapheresis. It turns out that hepatitis C virus is not only hepatotropic but lymphotropic, deregulating B-cells and causing autoimmune events, including the production of rheumatoid factor (IgM anti-IgG), an essential component for mixed cryoglobulin formation [7]. A myriad other new insights have been forthcoming in diseases treated by plasmapheresis [3]. Some provide an opportunity to specifically remove the offending autoantibody, based on detailed knowledge of the epitope to which it binds. This approach was foreshadowed 30-years-ago when plasmaperfusion columns containing immobilized specific antigen were used to adsorb antiglomerular basement membrane antibody or antinuclear antibody [8]. However, these pioneering attempts were frustrated by the risk of antigen escaping...
from the column into the patient. This can now be overcome by constructing peptide ligands that mimic the antigenic site, and coupling them covalently to sepharose in the plasmaperfusion column. This has been used effectively in autoimmune dilated cardiomyopathy, which is due to autoantibodies with agonist-like effect on the β-1 adrenergic receptor and cross-reactivity with an antigen on cardiac myosin [9]. However, the advantage of being able to use the patient’s own purified plasma as the replacement solution may be outweighed by the finite shelf life of these costly columns. Also there cannot be certainty that every case will have an antibody against the same specific epitope. This serves as a reminder that conventional plasmapheresis can work equally well for this disease, and for any autoantibody disease.

Controlled clinical trials to prove the efficacy of plasmapheresis have been relatively few, and many initiatives are underway to correct this. The problem arose in part because conventional apheresis machines are not like new pharmaceuticals, where regulatory approval of the drug depends on proof of efficacy for specific indications. Manufacturers are rewarded mainly for making a safe and reliable machine, not for generating data for each candidate disease, so sources of funding for clinical trials are limited. Nevertheless, an impressive and expanding body of clinical evidence is now available [3].

The Plasmapheresis Prescription

The prescribed volume of each plasmapheresis procedure depends on the patient’s size (50 to 60 mL plasma removal/Kg body weight), whereas the number and frequency of treatments depends on the disease characteristics. For Waldenstrom macroglobulinemia or neuropathy due to IgM, one or two plasmaphereses will make a dramatic difference, because IgM is large (C24/970,000 Da) and 90% stays intravascular, from where it can be cleared efficiently. In contrast, most antibody-mediated diseases are due to IgG, which is smaller (C24/146,000 Da) and only 25 to 35% intravascular; thus the volume of distribution is much larger than the plasma compartment, and it will take 5 or 6 standard plasmapheresis procedures to reduce blood levels substantially. Plasmapheresis requirements will be affected also by the rate of resynthesis of the toxic molecule, which in many autoimmune diseases can be reduced by concomitant immunosuppressive drugs.

Plasmafiltration systems (semipermeable hollow fibers or membranes) usually use heparin anticoagulation. To get the same rate of plasma removal, they require a higher blood flow than centrifugal systems, because the blood cannot safely be concentrated to as high a hematocrit. Thus a central venous access catheter is necessary, whereas with a centrifugal system the lower blood flow rate may often be supported via bila-
eral arm vein needles, which carry a much lower risk of bacteremia. With centrifugal systems, citrate anticoagulation is usual, at a dose of ~14 mmol/hr (for a blood flow rate of 70 mL/min). This is usually well tolerated, although a return-line infusion of calcium at 8 mEq/hr will help guard against the symptomatic hypocalcemia of “citrate toxicity.” Citrate accumulation is more likely with FFP replacement, because each unit of FFP contains approximately 7 mmol of citrate (so FFP replacement at 30 mL/min adds citrate at 50 mmol/hr).

**Therapeutic Cytapheresis**

Cell separation by centrifugation depends on the specific gravity of cell types (Table I). Red cell apheresis is used sparingly for complications of sickle cell disease and other hemoglobinopathies, and rarely for severe complications of red cell infections such as malaria and babesiosis [3]. White cell and platelet separation on modern machines can be finely tuned such that a product can be obtained that contains only one cell type. However, for cerebral leukostasis syndrome during a myeloid blast crisis, for instance, it may be more important to run a high WBC collection rate, to maximize the quantity rather than purity of the cells removed, even if this creates a need for subsequent platelet or red cell transfusion [10].

**EVIDENCE AND DECISION MAKING IN APHERESIS MEDICINE**

According to the AMA/Specialty Society Relative Value Scale Update Committee database from Medicare [11], 40% of plasma exchange procedures billed to Medicare in 2007 were billed by clinical nephrologists and another 40% billed by pathologists. Hematologists/oncologists, internists, neurologists, hematologists, rheumatologists, and others accounted for the rest of the 20%. The thought process that precedes the use of apheresis for medical conditions has evolved over the years. In the 1970s and 80’s, the evidence for use of apheresis for management of clinical conditions were basically case reports. The physiology of apheresis and how it worked was in part theoretical and in part clinical assumptions. The focus was on serum markers of disease, with the assumption that clearing serum antibody markers of a disease successfully controlled the condition. Apheresis was often considered the last resort for exotic conditions. Unfortunately, there were few properly designed clinical trials to study the role of apheresis in specific diseases. Fortunately, the thought process preceding the use of therapeutic strategies including apheresis for specific diseases is different in this current era. This is the era of evidence based medicine, which is often strictly followed by the medical community, regulatory bodies and judicial system. The use of meta-analysis permits us to power similar studies to confidently produce evidence-based answers that would otherwise not be provided by smaller studies. The American Society for Apheresis (ASFA) has published indication categories for therapeutic apheresis. A proper clinical trial is now a requirement in most cases before adoption of a new apheresis technology or approval of a new indication for apheresis by the Food and Drug Administration (FDA). Hence the practice has shifted to a truly evidentiary basis for new indications.

The old paradigm in clinical thinking involved knowledge built from unsystematic observations. Clinical experience and expertise was assumed to be necessary and sufficient to adopt a particular modality of treatment. The new paradigm of evidence-based medicine holds that clinical experience is certainly necessary but not sufficient. Personal observations have to be supplemented with published literature. The most important dimension to evidence-based medical practice is that the literature should be interpreted with the individual patient in mind and how the patient compares with the subjects used for a given randomized, controlled study that may appear to be applicable to the patient’s management. In analyzing articles pertaining to new treatments, emphasis is now focused on enrollment criteria, randomization, similarity of study population to patient to receive the new treatment modality, and method of analysis as opposed to the former practice of scanning the introduction, results and discussion of such articles [12]. Although expert opinions and consensus conferences still may play a role in the development of clinical guidelines, critically evaluated published studies, and observations are the dominant foundation for clinical guideline development.

The Office of Technology Assessment created by the United States Congress to provide Congressional members and committees with objective analysis of complex scientific and technical issues published in 1983 a review of technological advances in apheresis medicine. The executive summary of their report concluded that apheresis was often carried out as a last resort in a wide range of diseases, was an effective acute therapy in only a few obscure diseases and its optimal role and treatment parameters were unknown.
The document also lamented that there were very few high quality studies that documented efficacy of apheresis in improving health and there was lack of convincing proof of clinical efficacy of apheresis in most diseases in which it was used. Shumak and Rock’s review article in 1984 paved the way for subsequent articles pertaining to apheresis medicine. They proposed criteria for assessment of plasma exchange as established therapy and published a list of conditions that were commonly treated with therapeutic plasma exchange [14].

The American Society for Apheresis (ASFA) and the American Medical Association’s Panel on Therapeutic Plasmapheresis independently attempted to organize and critique various indications for apheresis therapy and both came up with four categorizations of indications for therapeutic apheresis [15,16]. The ASFA indication categories for therapeutic apheresis as published every 7 years [17–19] in the special issues of Journal of Clinical Apheresis is quite familiar to physicians involved with therapeutic apheresis but does have some drawbacks.

Categorization of indications for apheresis therapy could be ambiguous depending on how one interprets the ASFA indication categories. Also, insurance companies tend to follow these guidelines with an arbitrary and, sometimes, inappropriate rigidity thus denying reimbursement for treatments where apheresis may have played a therapeutic role. The 2007 special issue on indications for therapeutic apheresis [19] was unique in that it was presented in a fact sheet format with a summary of the associated level of evidence for use of therapeutic apheresis.

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McLeod’s criteria for likelihood of benefit of apheresis therapy [20] are a suitable approach to determine when to use apheresis (Table II). The first criterion termed “plausible pathogenesis” suggests a secure understanding of the disease process which proposes a clear rationale for apheresis therapy. The second, “better blood” expects the abnormality that made apheresis plausible to be meaningfully corrected by apheresis therapy. The final criterion, “perkier patients” suggests that there should be a strong evidence that apheresis confers clinical benefit that is meaningful and not merely statistically significant. The utility of McLeod’s criteria may enhanced by applying certain corollary considerations (Table I): Is the problem reversible with apheresis therapy? Is there a first line or standard therapy other that apheresis and has it been tried? If apheresis is tried, is the goal of a therapeutic trial defined? A physician who goes through these corollary considerations before instituting apheresis therapy, is in a position to make a better judgment for use of therapeutic apheresis for a Category III condition as defined by the ASFA indication categories for therapeutic apheresis. A revision of the ASFA indication categories for therapeutic apheresis is scheduled to be released in 2010 and will obviate some of the ambiguities inherent in the current indication category definitions.

The three important tools that aid clinical decisions regarding apheresis therapy, McLeod’s criteria, the corollary considerations and the revised indication categories, if used efficiently with knowledge of available evidence will aid the physician in making rational apheresis decisions.

**Corollary Considerations**

- Is the problem reversible with apheresis therapy?
- Is there a 1st-line or standard therapy?
- Has it been tried?
- Outcome?
- If apheresis to be tried, is the goal of a therapeutic trial defined?

**CLINICAL ADVERSE EVENTS DURING THERAPEUTIC APERESIS**

Apheresis is not an entirely risk free treatment but could be associated with minimal to potentially fatal adverse events. Most large registries report a relatively low incidence (5 to 12%) of complications associated with TA procedures, with the exception of two, relatively small, single center series [21–30] (Figure 2). Most adverse events are categorized as Grade 1: Mild (no intervention required, 1.5%) or Grade II: Moderate (intervention required but treatment completed, 2.5%)
of calcium homeostasis in TA, Silberstein by volume, is used as replacement colloid. In a study when fresh frozen plasma, which contains 14% citrate associated hypocalcemic toxicity may be potentiated ionized calcium and hypocalcemic toxicity. Citrate-mol/L. Citrate anticoagulation may result in reduced whereas Acid Citrate Dextrose A (3%) contains 0.113 Sodium citrate (4%) contains 0.136 mol/L of citrate, procedure type. Citrate is commonly used as an anticoagulant type, (4) underlying disease state, (5) TA anticoagulant type, (2) replacement fluid type, (3) vas-

diac or respiratory arrest, anaphylaxis, and catheter- patients. The causes of death in these patients were car-

bosis, and infection occur uncommonly, (<1%). Death is a rare complication of TA, reported in ~0.5% of patients. The causes of death in these patients were car-
diac or respiratory arrest, anaphylaxis, and catheter- associated sepsis [21,31].

Factors that impact on the complication rate are: (1) anticoagulant type, (2) replacement fluid type, (3) vascular access type, (4) underlying disease state, (5) TA procedure type. Citrate is commonly used as an anticoagulant, particularly in centrifugal apheresis procedures. Sodium citrate (4%) contains 0.136 mol/L of citrate, whereas Acid Citrate Dextrose A (3%) contains 0.113 mol/L. Citrate anticoagulation may result in reduced ionized calcium and hypocalcemic toxicity. Citrate-associated hypocalcemic toxicity may be potentiated when fresh frozen plasma, which contains 14% citrate by volume, is used as replacement colloid. In a study of calcium homeostasis in TA, Silberstein et al [32], reported an 18% reduction in ionized calcium and a net calcium loss of 150 mg. Most hypocalcemic symptoms are mild-moderate, and present as perioral and distal extremity paraesthesias, nausea, and twitching, however, serious complications have also been reported, namely seizures, chest tightening, and arrhythmia [33]. Prolongation of the QT interval may occur when the ionized calcium is lowered by 35%. Hypocalcemic toxicity may be prevented, or easily treated. Strategies for minimizing hypocalcemic symptoms include reducing the citrate delivery rate (0.25 to 1.8 mg/kg/min), and pro-

Adapted from Ref. [31].

[23]. The most commonly reported symptoms are due to anaphylactoid reactions that may present as urticaria and/or rigors, (0.7 to 12%); hypocalcemic symptoms such as paraesthesias, nausea/vomiting, lightheadedness, and twitching, (1.5 to 9%); and symptoms of hypovole-
mia which may manifest as hypotension, muscle cramps and/or headache, (0.3 to 5%) (Table III).

More serious adverse events occur rarely, and are categorized as either Grade III: Severe (procedure in-
terrupted or abandoned, 0.8%), and Grade IV: Fatal (≤0.5%) [21,23]. These include cardiovascular events, such as arrhythmias or ischemic events, (0.03 to 1.5%); pulmonary events, including pulmonary edema and pul-

Adapted from Ref. [31].

TABLE III. Common Adverse Symptoms in Therapeutic Plasma Exchange

<table>
<thead>
<tr>
<th>No.</th>
<th>Type</th>
<th>Symptoms</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hypocalcemia</td>
<td>Paraesthesias</td>
<td>1.5–9.0</td>
</tr>
<tr>
<td>2</td>
<td>Hypovolemia</td>
<td>Hypotension</td>
<td>0.4–4.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscle cramps</td>
<td>0.4–2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headaches</td>
<td>0.3–5.0</td>
</tr>
<tr>
<td>3</td>
<td>Anaphylactoid</td>
<td>Urticaria</td>
<td>0.7–12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rigors</td>
<td>1.1–8.8</td>
</tr>
</tbody>
</table>

Another, less common, complication of citrate anti-

Adverse events reported in association with heparin anticoagulation are hemorrhagic in nature, usually at the vascular access site of insertion (0.7%) [21,27,36]. There have been few case reports of heparin-induced thrombocytopenia (HIT) associated with TA procedures, these presented as thrombocytopenia, venous thrombosis, and pulmonary emboli [37]. The incidence of HIT in the hemodialysis population is between 1 to 4% [38]. More recently, there have been reports of severe anaphylactoid reactions (~800) and deaths (~81) caused by contaminated heparin originating from a fac-

tory in Changzhou, China [39]. The contaminant has been identified by the FDA as over-sulfated chondroitin sulfate, which is a less expensive, animal cartilage-
derived, alternative to raw heparin, which is not approved for medicinal use.

A second factor that impacts on type and frequency of adverse events in TA is the type of replacement colloid utilized. Anaphylactoid reactions have been reported commonly (~13%) with fresh frozen plasma (FFP). The incidence per unit of FFP is 1.48%, and is similar with cryo-supernatant. FFP-associated anaphy-
lactoid reactions present as fevers, rigors, urticaria, wheezing, pruritis, hypotension, and laryngeal edema. The risk may be increased by the concomitant use of angiotensin-converting enzyme inhibitors (ACE-I), due to inhibition of kinin degradation, therefore, it is rec-

Adapted from Ref. [31].

TABLE IV. Rare Symptoms in Therapeutic Plasma Exchange

<table>
<thead>
<tr>
<th>No.</th>
<th>Type</th>
<th>Symptoms</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cardiac</td>
<td>Myocardial ischemia/infarction/shock</td>
<td>0.03–1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arrhythmia</td>
<td>0.1–0.7</td>
</tr>
<tr>
<td>2</td>
<td>Pulmonary</td>
<td>Respiratory arrest/pulmonary edema</td>
<td>0.2–0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary embolism</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>Hematologic</td>
<td>Thrombosis/bleeding</td>
<td>0.2–0.7</td>
</tr>
<tr>
<td>4</td>
<td>Infectious</td>
<td>Hepatitis</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other infection</td>
<td>0.3</td>
</tr>
<tr>
<td>5</td>
<td>Neurologic</td>
<td>Seizure</td>
<td>0.03–0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNS ischemia</td>
<td>0.03–0.1</td>
</tr>
<tr>
<td>6</td>
<td>Pyrogenic</td>
<td>Hyper thermia</td>
<td>0.7–1.0</td>
</tr>
</tbody>
</table>

Adapted from Ref. [31].
at the bedside if needed [40]. As discussed previously, hypocalcemia and metabolic alkalosis may occur with FFP replacement colloid, due to the presence of citrate in FFP. Hypocalcemic toxicity occurs more frequently in procedures using FFP than with albumin, (4.8 vs. 1.8%) [41]. Overall, FFP is associated with a two-fold higher risk of total adverse events relative to albumin, but no difference in treatment interruption has been reported between replacement colloid types [25,27]. In TA procedures FFP is used predominantly for the treatment thrombotic thrombocytopenic purpura (TTP), and FFP replaces the depleted cleaving protease, ADAMTS-13. With respect to adverse event cause, it is difficult to isolate the contribution of the replacement colloid versus the underlying disease state. Lastly, although transmission of infectious agents is always a concern when administering FFP, the current risks of infections with test-negative FFP in the United States are very rare: HCV = 1/1.9 million, HIV = 1/2.1 million, respectively, HBV = 1/205,000 to 488,000, West Nile virus = 0 [42].

When TA is performed using albumin as the replacement colloid, depletion of clotting factors (–60%) and fibrinogen (–85%) may result in a coagulopathy and increase the bleeding risk, particularly after multiple consecutive treatments. The protime (PT) and partial thromboplastin time (PTT) are increase by 30 and 100%, respectively. The recovery time for PT is 24 hr and PTT is 4 hr. Hemorrhage can be prevented by administering 1–2 units of FFP at the end of the treatment, and may be particular beneficial if a venous catheter removal is intended postprocedure. Alternatively, the removal of circulating anticoagulants, such as antithrombin III (–50%), may increase the risk of thrombosis [31]. Albumin replacement colloid also results in immunoglobulin depletion (–60% after 1 treatment), which may be lowered by approximately 90% after three to four consecutive treatments. IgG levels may remain low for several weeks, as their half-life is 22 days. Infusion of immunoglobulins may be administered post-treatment in patients who have active infections or are immunosuppressed. Hypocalcemic symptoms may occur with albumin replacement, due to the fact that commercial albumin is stripped of calcium, thereby rendering it calcium-avid, but occurs less frequently than with FFP.

A rare complication of albumin replacement is the development of a pyrogenic reaction, presenting as rigors and fevers, however serious pyrogenic reactions are uncommon (1 in 30,000 infusions) [43]. These may be caused by the presence of altered albumin aggregates, Ig-albumin complexes, alloantibody production, the presence of nonalbumin proteins, such as IgA, or due to contamination with bacteria or endotoxin. Other uncommon complications of albumin are aluminum

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**Prophylactic calcium administration in TPE: Reduces symptoms**

1. **Constant IV infusion of 10% Ca++ Gluconate** 8.6%  
   **vs.**  
   Oral CaCO3 35.5%  
   Boluses of IV 10% Ca++ Gluconate 29.4%  

2. Calcium added to Albumin pre-infusion 2.7%  

3. **IV 10% Ca++ Gluconate prophylaxis** 1%  
   **vs.**  
   No calcium 9.1%  

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**Fig. 3.** Prophylactic calcium administration in TPE: Reduces symptoms.
toxicity, particularly in the setting of renal insufficiency, and hypokalemia, which can be rectified by intravenous administration during the procedure or by adding potassium to the replacement colloid. Hemolytic anemia has been reported in cases, in which albumin was improperly diluted with sterile water, instead of saline. Hypotension has been reported when albumin is rendered hypo-osmotic (3.3%) when diluted with saline, and may explain the high incidence of total adverse events in one of the single-center series [30]. Both can be avoided by using 5% albumin. An alternative way of minimizing adverse reactions caused by replacement colloid is to use a selective apheresis procedure. Plasma adsorption and double-filtration plasmapheresis can be performed without replacement colloid, in most cases. These selective procedures are advantageous, in that they are not associated with undesirable protein losses, and do not result in a depletion of coagulation factors or immunoglobulins.

A third factor that impacts on adverse events is the vascular access type. The incidence of total adverse events associated with the vascular access is low in most series, ~1%. Complications include infection, thrombosis, hemorrhage, pneumothorax, and mechanical complications [21,27,36]. In the International Apheresis Registry, however, vascular access complications were the most common type of adverse events, (38%). This may be due to the high prevalence of peripheral venous access in Europe (83%), and the association of “blood access difficulties” in 25% European patients. In North America, 68% of treatments were performed using a central vein catheter (CVC), and “difficulties” were reported in only 5% of patients. In this registry, there was no difference in treatment interruption between CVCs and peripheral venous access [24].

The main risks of peripheral vein access are scarring of veins and cannulation difficulties after multiple uses. Peripheral venous access is associated with an 80% lower risk of infection, relative to CVCs, and is the preferred access type. CVCs are associated with a higher total complication rate. These include infection (2 to 28%), thrombosis (0.2 to 11%), hemorrhage (2 to 14%), and venous stenosis (10 to 26%) with internal jugular catheters, up to 42% with subclavian vein catheters [44]. When a CVC is necessary for a limited (<2 week) course of TA, an antibiotic bonded nontunneled CVC should be considered, associated with a 44% lower infection risk compared to nonmedicated CVCs. For a longer duration (>2 weeks) of TA, a tunneled CVC is preferred over a nontunneled CVC, due to the 37% reduction in infection. The preferred venous site of CVC insertion is the internal jugular vein, and both ultrasound guidance and fluoroscopy have been shown to be associated with a lower rate of complications during insertion [45]. If long-term use is anticipated, creation of an arteriovenous fistula should be considered.

CVC dysfunction, characterized by poor blood flow or inability to aspirate, may be treated by patient repositioning or a forceful saline flush. Additional therapeutic options include the use of tissue plasminogen activator, which when instilled intra-luminally, is associated with relatively good short term success, but may fail with the need for repeated instillations [46,47]. CVC exchange over a guide-wire may preserve the vein site, although fibrin sheath disruption is necessary to optimize catheter function [48]. CVC infection can be avoided by implementing standard infection control measures. These include strict hand washing, use of clean gloves, and a mask worn by both the staff and patient during CVC accession. Routine CVC exit-site care should include the use of nonocclusive dressings, and approved cleansing solutions (chlorhexidine/isopropyl alcohol or povidone-iodine solution). More recently, the prophylactic use of topical or intralumenal antibiotics in CVCs used for hemodialysis has been shown to reduce the incidence of bacteremia by 3 to 4 fold, and should be implemented in CVCs used for TA [49]. When CVC exit site infections occur, treatment consists of either topical or oral antibiotics, however, when there is extension into the CVC tunnel tract intravenous antibiotics are necessary. Catheter-related bacteremia is a potentially life-threatening complication, and the risk of an infectious complications (endocarditis, osteomyelitis, etc.) and death is increased more than three-fold when *Staphylococcus aureus* is the isolate [50]. In addition to a minimum of 3 weeks of systemic antibiotics, the treatment of *S. aureus* catheter-related bacteremia should include removal of the catheter [45,50]. Intra-luminal antibiotic lock may be attempted when Gram-negative organisms or *Staphylococcus epidermidis* are isolated [44].

Another factor that impacts on adverse events with TA is the underlying disease state. TA series in which there is a high prevalence of TTP are associated with a high complication rate, (approximately 66%). The types of adverse events reported in series of TA used for TTP were most commonly urticaria and respiratory distress, (96 and 4% of adverse events, respectively) [41]. Of the 14 deaths reported in the Canadian Apheresis registry, 10 occurred in TTP patients [26]. As discussed previously, the need for FFP or cryosupernatant is a confounding factor in these patients. Other disease states in which complications are relatively more common include Guillain-Barré syndrome (hypotension), systemic lupus erythematosi (infection), Goodpasture’s disease and vasculitis [23].

The last major factor that influences the adverse event rate in TA is the type of TA procedure. Plasma exchange may be performed using either centrifugation or a membrane-based technique. The total adverse event rate with centrifugal and membrane-based is similar, 1.5% to 25%, however serious adverse events (0.5 to 3.1%) and thrombocytopenia (up to 50%) have been reported more commonly with centrifugation. Double
filtration plasmapheresis, or cascade pheresis, is a selective form of plasma exchange that is associated with a higher risk of hemolysis possibly caused by high transmembrane pressures [51]. Selective, plasma adsorption procedures are associated with a lower risk of total adverse events and interrupted procedures, likely due to elimination of replacement colloid [23]. Adverse events attributable to the membrane in TA include anaphylactoid reactions, which may be ethyl-
ene-oxide antibody, mediated, or caused by membrane complement-activation. ACE-I interactions with specific membranes, namely the Prosorba column and dextran sulfate system, may also potentiate anaphylactoid reactions, and can be avoided by discontinuing ACE-
inhibitor use in advance of the procedure.

Many medications may be removed during TA procedures, particularly those characterized by a relative small volume of distribution, (<0.3 L/kg), and are highly protein bound, (>75%). Some commonly used drugs that may require supplementation include antibi-
otics, such as cephalosporins and vancomycin (~50%), antiseizure drugs such as phenytoin and valproate. Addition drugs that are removed by TA include glybur-
ide, heparin, thyroid, warfarin, propranolol, and fat soluble vitamins (vitamin B12, B6, A, C, E, β-carot-
ene) [31]. Of interest, cyclosporine is not significantly removed with TA [52]. In general, all drugs should be admin-
ister after the procedure.

In summary, anticipation of potential adverse reac-
tions that may occur with TA procedures can minimize their frequency. The administration of prophylactic cal-
cium is an important, simple, and inexpensive means of reducing hypocalcemic toxicity, an otherwise relatively common adverse event in TA procedures. Hemorrhage and infection, due to albumin replacement colloid, can be reduced by administering FFP or intravenous immunoglobulin at the end of the treatment. Anaphylactoid reactions can be reduced by administering prophylactic diphenhydramine, and by discontinuing an-
giotensin-converting enzyme inhibitor use in advance of the treatment. When possible, the preferred access type is a peripheral venous access, however, when CVC access is necessary, standard and novel infection control prac-
tices, and the use of antibiotic-coated nontunneled (short-
term use) or tunneled catheters or arteriovenous fistulas (long-term use) may reduce the risk of complications. TTP and Guillan-Barre’ are associated with a higher risk of adverse events, and a heightened awareness of poten-
tial complications can be anticipated and minimized. When possible, selective plasma adsorption procedures can reduce the risk of adverse events.

**BASIC CONCEPTS IN TRANSFUSION IMMUNOLOGY**

Blood transfusion is an immunologic event. Expos-
ure to foreign red cell antigens can have potentially life-threatening consequences in patients who have pre-existing antibodies to those antigens. Transfusion immunology has developed methods for detecting pre-
existing antibodies to red cell antigens so that transfu-
sions can be performed with a comfortable assurance of safety.

The mainstay of antibody detection is the agglutina-
tion reaction. Red cells suspended in solution can be made to agglutinate in the presence of antibodies to cognate antigens present on the red cell. Manipulating the testing parameters permits the detection of specific antigens on the patient’s red cells, (ABO and Rh anti-
gens) and can also detect the presence of antibodies to foreign red cell antigens in the patient’s plasma. These latter antibodies can be made if the patient has been exposed to foreign red cell antigens either through transfusion or pregnancy.

IgM red cell antibodies have a 35-nm diameter and five separate binding sites for antigens. A single IgM antibody is large enough to bind to cognate antigen on two different red cells and can cause agglutination when red cells are brought into close proximity by centrifugation without the addition of other reagents. IgG red cell antibodies, which have only a 14-nm diameter and two binding sites, can bind to cognate antigens, but generally are not large enough to crosslink red cells. To demon-
strate the presence of IgG bound to red cell antigens, an antihuman IgG (Coombs reagent) is added. This second antibody will crosslink antibody coated red cells via its specificity for the Fc portion of human IgG. Upon cen-
trifugation to bring the antibody-coated red cells in close proximity, agglutination will occur.

Two tests using Coombs reagents are performed in the blood bank. The direct antiglobulin test detects antibodies bound to the patient’s red cells in vivo. An aliquot of patient’s red cells is washed and Coombs re-
agent is added. If a red cell antibody is present on the patient’s red cells, the specimen will demonstrate agglutination after centrifugation. The indirect antiglob-
ulin test detects antibodies to red cell antigens present in the patient’s plasma. Test red cells of known pheno-
type are incubated with an aliquot of patient’s plasma. After washing, Coombs reagent is added, and if anti-
body has bound during incubation agglutination should be present after centrifugation.

Basic blood bank testing comprises the blood type, the antibody screen and the crossmatch. The blood type determines the ABO and Rh antigens present on the patient’s red cells. These two antigen systems in contrast to other red cell antigen systems will routinely evoke an immune response in a patient. Most other antigens will not provoke an immune response in most people even after repeated exposures. Correct determination of the patient’s ABO blood type before transfusion is especially critical to ensure a safe transfusion because virtually all humans have antibodies to those ABO antigens not pres-
ent on their own red cells. A transfusion of an ABO incompatible unit, therefore, generally results in immediate severe transfusion reaction, and approximately 10% of ABO incompatible transfusions result in death. Rh testing is important because the Rh antigen is highly immunogenic, and patients having the Rh negative phenotype have a very high likelihood of making an Rh antibody if exposed to blood containing the Rh antigen. Determination of ABO/Rh type is determined by reacting patient cells against monoclonal IgM reagents. Agglutination indicates that the antigens are present. In the case of ABO, a built in confirmatory test is present, because as previously noted, most humans have antibodies to those ABO antigens that they themselves lack. Consequently, the patient plasma is tested against reagent red cells to determine which ABO antibodies are present. A patient with specific ABO antigens present on red cells must have the reciprocal antibodies present in his plasma or further investigation is warranted.

Only a minority of patients (<5%) will have antibodies to other red cell antigens. A screening test for antibodies using the indirect antiglobulin test is performed to determine whether other red cell antibodies are present. If an antibody is present, definitive testing to determine the specificity of the antibody is performed, and blood that does not contain the antigen to which the patient has made an antibody is selected for transfusion. The crossmatch is the final check of compatibility. In this test, cells from the actual unit to be transfused are reacted with patient plasma to determine whether there is serologic incompatibility. The complete crossmatch utilizes the indirect antiglobulin test. More simple permutations look for ABO incompatibility only.

**SUMMARY**

This review addressed important concepts in conventional therapeutic apheresis, explained the evidence and decision making issue surrounding apheresis medicine, reviewed the basic concepts in immunology and transfusion medicine and also addressed thrombotic microangiopathies and clinical adverse events associated with therapeutic apheresis.

**REFERENCES**


