Vascular access for therapeutic plasma exchange

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Therapeutic plasma exchange is an apheresis modality in which plasma is separated from the blood cellular components ex vivo, discarded, and replaced with an isosmotic fluid (most commonly 5% albumin) to maintain appropriate oncotic pressure in the patient. Therapeutic plasma exchange is used in the treatment of many diseases and indications. The recent seventh edition of the American Society for Apheresis guidelines indicates approximately 72 diseases and 116 indications for which therapeutic plasma exchange may be effective. One of the critical aspects for the successful performance of therapeutic plasma exchange is appropriate vascular access to provide high blood flow for the collection and return phases of the procedure, especially because most patients who need therapeutic plasma exchange will require more than one treatment over days to weeks. This article provides an overview of the characteristics of therapeutic plasma exchange, the clinical diseases and indications that may be treated with therapeutic plasma exchange, and the different types of vascular access employed, with their advantages and disadvantages. The latter may include peripheral venous access and intravascular or implantable access devices, such as arteriovenous grafts and fistulas, central venous catheters, and central venous catheters tunneled with ports.

Current health care employs large numbers of invasive diagnostic and therapeutic procedures that depend on adequate vascular access, such as percutaneous coronary interventions and hemodialysis (HD), among the most common. A literature search on PubMed for review articles on "vascular access" retrieved almost 2900 articles in English alone from 1966 to the present. Such papers were published in the vascular surgery, interventional radiology, renal, neurologic, cardiac, gastrointestinal, emergency medicine, critical care, and oncologic literature and deal with a range of issues. There are also scientific journals dedicated to this topic, such as *The Journal of Vascular Access* and the *Journal of the Association for Vascular Access*.[1,2] However, a search for reviews dealing with vascular access in apheresis yielded only 29 citations, of which only 19 focused on vascular access for therapeutic plasma exchange (TPE). This is compared with HD, in which more than 1000 articles were published on vascular access risks, benefits, and alternatives to the various options. This is not surprising, because the estimated annual volume of TPE in the United States is 125,000 procedures (Dr R. Weinstein, University of Massachusetts Medical School, personal communication,

ABBREVIATIONS: AV = arteriovenous; CVC(s) = central venous catheter(s); HD = hemodialysis; IVAD(s) = intravascular or implantable access device(s); TA = therapeutic apheresis; TCVC(s) = tunneled central venous catheter(s); TPE = therapeutic plasma exchange; TTP = thrombotic thrombocytopenic purpura; WAA = World Apheresis Association.

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2017) compared with more than 73 million HD procedures based on the most recent US Renal Data System Annual Data Report for 2015, stating that 468,000 patients are dialysis-dependent and receive three sessions per week.

Among therapeutic apheresis (TA) modalities, such as red blood cell exchange, leukocytapheresis, and extracorporeal photopheresis, TPE is the most commonly performed procedure in most institutions, perhaps with the exception of cancer centers. At the University of Alabama at Birmingham, TPE comprised 70% of the total number of TA procedures performed by the apheresis service from 2003 to 2012.[3] More recently, the number of annual TPEs from 2012 to 2016 at the University of Alabama at Birmingham was approximately 1200 procedures, which is a substantial increase from 544 TPEs performed in 2003.[3] The New York Blood Center, which performs apheresis for 95 hospitals in the New York metropolitan area, performed 76.8% of their total procedures (N = 7193) for therapeutic reasons rather than donor apheresis during 2011 and 2012.[4] TPE comprised the majority of TA procedures at 81.9%. TPE can be defined as an extracorporeal separation of the patient's plasma from the cellular components of the blood with the goal of removing high-molecular-weight molecules, such as antibodies, implicated in diseases.[5] A useful guide to determine whether a patient will benefit from TPE includes the McLeod criteria: knowledge that the molecule causing the pathologic process is at least 15 KDa or greater, that it has a prolonged half-life (days to weeks), that it is distributed preferentially in the intravascular compartment, and that there is no other alternative to removing it from the body (such as with HD, which only filters small molecules). The McLeod criteria help the apheresis practitioner determine whether apheresis will be efficacious by: 1) understanding the disease pathogenesis, 2) determining that the abnormality will be corrected by the procedure, and 3) there is evidence that the patient improves. Many conditions treated with TPE are caused by immunoglobulin G (IgG) autoantibodies or alloantibodies (Table 1).[6] However, because the total body intravascular IgG load is approximately 45%, several TPEs are necessary to decrease the patient's total IgG significantly to produce a therapeutic effect, provided that the removal is not undermined by new antibody production. Indeed, once the IgG plasma level is decreased after each TPE, there is a postulated rebound in its synthesis in addition to re-equilibration of the antibody with the extravascular space. Unlike HD, which is lifelong unless a transplant occurs, most TPE treatment series are short and are based on clinical and/or laboratory parameters. For example, in a 10-year review of a single-institution experience, patients underwent a mean of seven TPE procedures.[3] Conversely, more TPEs were required for the treatment of thrombotic thrombocytopenic purpura (TTP); the number varied widely from four to 21, with an average of 13 TPEs, in a publication by the Thrombotic Microangiopathy Registry of North America.[7] Indeed, some patients may require up to 50 TPEs or more during a single hospitalization to achieve a hematologic response. Treatment of TTP with TPE contrasts from several other common diseases for which TPE is utilized, such as myasthenia gravis or chronic inflammatory demyelinating polyneuropathy, for which patients typically receive four to six TPEs during an acute exacerbation or crisis.

To complete a TPE procedure, the apheresis practitioner connects the patient's vascular system to the apheresis device, which will separate the plasma ex vivo and replace it either with an oncotic solution such as 5% albumin, donor plasma, or a combination of colloid solutions or with a crystalloid solution (such as 0.9% saline). Plasma is used for specific diseases like TTP or for patient-specific needs (ongoing hemorrhage, high risk of bleeding, need to replace deficient proteins, such as antithrombin), due to its inherent risks of transfusion reactions and infectious disease transmission.

The first apheresis device was developed in 1963 and was based on continuous-flow centrifugation developed by Edward Cohn at Harvard Medical School in the 1950s. Although the initial instrument was replaced with a newer model in 1972 and with subsequent devices since, all TPE devices approved in the United States are centrifugation-based as opposed to the membrane-based devices used in other countries. Some of the membrane-based devices have dual functionality and can be used for TPE as well as dialysis. Centrifugation-based TPE separates blood components based on the specific gravity of plasma (range, 1.025-1.029), which is lower than that of red blood cells (range, 1078-1.114; most dense), leukocytes, and platelets, when the blood is exposed to an appropriate centrifugal force (G force). Because the blood flow from the patient into the device has to be steady and preferably faster than 50 mL/min, the site of vascular access has to withstand high negative pressure without collapsing. Furthermore, the line from the instrument returning the patient's cells admixed with the replacement fluid also has to be in a large blood vessel capable of tolerating high positive pressure.

Table 1 lists American Society for Apheresis indications for TPE separated by the presumed mechanism of action for each disease and condition.[6] These guidelines are published every 3 years and are based on published evidence for the use of TA. Each page is a fact sheet for a single diagnosis, and it contains sections, such as description of the disease, rationale for TA, and guidance on technical aspects like the total number of procedures to be performed. As mentioned above, most treatments are limited to days or weeks, and do not require long-term vascular access. However, in some patients who require ongoing TPEs, such as those who have myasthenia with frequent crises, it is a challenge to find adequate and safe vascular access.

TABLE 1. Diseases and indications treated by TPE*

Disease	Category (grade)†
Rationale for therapeutic apheresis: Removal of autoantibodies	
Acute Disseminated Encephalomyelitis	II (2C) (Steroid-refractory)
Acute Inflammatory Demyelinating Polyradiculoneuropathy/Guillain-Barre Syndrome	I (1A) (Primary treatment) III (2C) (After IVIG)
ANCA-associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis); and Microscopic Polyangiitis	I (1A) (Dialysis-dependence) I (1C) (DAH) III (2C) (Dialysis-independence)
Anti-glomerular basement membrane disease (Goodpasture's syndrome)	III (2B) (Dialysis-dependence, no DAH) I (1C) (DAH) I (1B) (Dialysis- independence)
Autoimmune hemolytic anemia; warm autoimmune hemolytic anemia (WAIHA); cold agglutinin disease (CAD)	III (2C) (severe WAIHA) II (2C) (Severe CAD)
Aplastic anemia	III (2C)
Pure red cell aplasia	III (2C)
Cardiac neonatal lupus	III (2C)
Catastrophic antiphospholipid syndrome	II (2C)
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	I (1B)
Coagulation factor inhibitors	III (2C)
Complex regional pain syndrome	III (2C) (Chronic)
Dermatomyositis/polymyositis	IV(2B)
Dilated cardiomyopathy, idiopathic	III (2C) (NYHA II-IV)
Hashimoto's encephalopathy: Steroid-responsive encephalopathy associated with autoimmune thyroiditis	II (2C)
Immune thrombocytopenia, refractory	III (2C)
Lambert-Eaton myasthenic syndrome	II (2C)
Multiple sclerosis	II (1B) (Acute CNS inflammatory demyelinating) III (2B) (Chronic progressive)
Myasthenia gravis	I (1B) (Moderate-severe) I (1C) (Pre-thymectomy)
Neuromyelitis optica spectrum disorders	II(1B) (Acute) III (2C) (Maintenance)
N-methyl D-aspartate receptor antibody encephalitis	I (1C)
Paraneoplastic neurological syndromes	III (2C)
Paraproteinemic demyelinating neuropathies/ chronic acquired demyelinating polyneuropathies	III (1C) (Anti-MAG neuropathy) IV (1C) (Multifocal Motor Neuropathy) I (1B) (IgG/IgA) I (1C) (IgM) III (2C) (Multiple Myeloma)
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; Sydenham's chorea	II (1B) (PANDAS exacerbation) III (2B) (Sydenham's chorea, severe)
Pemphigus vulgaris	III (2B) (Severe)
Post transfusion purpura	III (2C)
Scleroderma (systemic sclerosis)	III (2C)
Stiff-person syndrome	III (2C)
Systemic lupus erythematosus	II (2C) (Severe) IV (1B) (Nephritis)
Vasculitis	II (2C) (HBV-PAN) IV (1B) (Idiopathic PAN) III (1B) (EGPA) III (2C) (Behcet's disease)
Voltage-gated potassium channel antibodies	II (2C)

Table 1: *Continued*

Disease	Category (grade)†
Rationale for therapeutic apheresis: Removal of alloantibodies	
Cardiac transplantation	II (1C) (Desensitization prior to transplant) III (2C) (Antibody-mediated rejection)
Coagulation factor inhibitors	IV (2C) (Alloantibodies)
Hematopoietic stem cell transplantation, ABO incompatible	II (1B) (Major HPC, marrow) II (2B) (Major HPC, apheresis)
Hematopoietic stem cell transplantation, HLA desensitization	III (2C)
Heparin-induced thrombocytopenia with thrombosis	III (2C) (Pre-cardiopulmonary bypass) III (2C) (Thrombosis)
Liver transplantation	I (1C) (Desensitization, ABOi living donor) III (2C) Desensitization, ABOi deceased donor) III (2C) (Antibody-mediated rejection (ABOi & HLA)
Lung transplantation	III (2C) (Antibody mediated rejection) III (2C) (Desensitization)
Red cell alloimmunization in pregnancy	III (2C) (Prior to intra-uterine transfusion availability)
Renal transplantation, ABO compatible	I (1B) (Antibody-mediated rejection, living donor) I (1B) (Desensitization, living donor) III (2C) (Desensitization, deceased donor)
Renal transplantation, ABO incompatible	I (1B) (Desensitization, living donor) II (IB) (Antibody-mediated rejection) IV (1B) (A_2/A_2B into B, deceased donor)
Rationale for therapeutic apheresis:Thrombotic microangiopathies	
Thrombotic microangiopathy, coagulation-mediated	III (2C) (THBD mutation)
Thrombotic microangiopathy, complement-mediated	III (2C) (Complement factor gene mutations) I (2C) (Factor H autoantibodies) III (1C) (MCP mutations)
Thrombotic microangiopathy, drug-associated	I (2B) (Ticlopidine) III (2B) (Clopidogrel) III (2C) (Calcineurin inhibitors) IV (2C) (Gemcitabine) IV (2C) (Quinine)
Thrombotic microangiopathy, hematopoietic stem cell transplantation-associated	III (2C)
Thrombotic microangiopathy, Shiga toxin-mediated	III (2C) (Severe neurological symptoms) III (2C) (*Streptococcus pneumoniae*) IV (1C) (Absence of neurological symptoms)
Thrombotic thrombocytopenic purpura (TTP)	I (1A)
Rationale for therapeutic apheresis: Removal of miscellaneous molecules	
Acute liver failure	III (2C) (Albumin-bound and unbound toxins)
Amyloidosis, systemic	IV (2C) (Interleukin 6)
Atopic (neuro-) dermatitis (atopic eczema), recalcitrant	III (2C) (IgE and immune complexes)
Burn shock resuscitation	III (2B) (Inflammatory or other substances)
Chronic focal encephalitis (Rasmussen Encephalitis)	III (2C) (Cytotoxic T cell-mediated neuronal damaged molecules/antibody)
Cryoglobulinemia, symptomatic/severe	II (2A)
Erythropoietic porphyria, liver disease	III (2C) (Protoporphyrin)
Familial hypercholesterolemia, homozygotes with small blood volume	II (1C)
Focal segmental glomerulosclerosis recurrent in transplanted kidney	I (1B) (Permeability factor)
HELLP syndrome, postpartum	III (2C) (protein-bound platelet aggregating and procoagulant factors)
HELLP syndrome, antepartum	IV (2C)
Hemophagocytic lymphohistiocytosis; Hemophagocytic syndrome; Macrophage activating syndrome	III (2C) (Cytokines)
Henoch-Schonlein purpura, crescentic or severe extra-renal disease	III (2C) (IgA-containing immune complexes or IgG autoantibodies)

Table 1: *Continued*

Disease	Category (grade)†
Hypertriglyceridemic pancreatitis	III (2C)
Hyperviscosity in monoclonal gammopathies	I (1B) Symptomatic I (1C) Prior to Rituximab
Immunoglobulin A nephropathy, crescentic	III (2B) (Pathologic IgA molecules and related immune complexes)
Immunoglobulin A nephropathy, chronic progressive	III (2C) (Pathologic IgA molecules and related immune complexes)
Myeloma cast nephropathy	II (2B) (Light chains)
Nephrogenic systemic fibrosis	III (2C) (Unknown)
Overdose, envenomation and poisoning	II (2C) (Mushroom poisoning) III (2C) (Envenomation) III (2C) Drug overdose/poisoning)
Phytanic acid storage disease (Refsum's disease)	II (2C)
Progressive multifocal leukoencephalopathy associated with natalizumab	I (1C) (Natalizumab)
Pruritus due to hepatobiliary diseases	III (1C) (Potential pruritogens)
Psoriasis	IV (2C)
Sepsis with multi-organ failure	III (2B) (Inflammatory and antifibrinolytic mediators)
Sudden sensorineural hearing loss	III (2C) (Fibrinogen and LDL cholesterol)
Thyroid storm	III (2C) (T3 and T4 bound to plasma proteins)
Toxic epidermal necrolysis	III (2B) (Drug/drug metabolites, cytokines, or other mediators of keratinocyte cytotoxicity)
Wilson's disease, fulminant	I (1C) (Copper)

* See Schwartz et al.[6]

† The American Society for Apheresis categories are as follows: Category I, disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment; Category II, disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment; Category III, optimum role of apheresis therapy is not established and decision making should be individualized; and Category IV, disorders in which published evidence demonstrates or suggests that apheresis is ineffective or harmful, and institutional review board approval is desirable if apheresis treatment is undertaken in these circumstances.

IVIG, intravenous immunoglobulin; DAH, diffuse alveolar hemorrhage; CNS, central nervous system; NYHA, New York Heart Association; MAG, myelin-associated glycoprotein; HBV-PAN, hepatitis B virus-associated polyarteritis nodosa; EGPA, eosinophilic granulomatosis with polyangitis; HPC, hematopoietic progenitor cells; THBD, thrombomodulin; MCP, membrane cofactor protein; HELLP syndrome, hemolysis, elevated liver enzyme levels, and low platelet levels; LDL, low-density lipoprotein.

VASCULAR ACCESS—BACKGROUND AND TRENDS

Vascular access is the conduit by which TPE is performed. Blood flow into the device enables the process of centrifugation or membrane filtration to occur. Without adequate blood flow, TPE can be performed, but with significant disadvantages. Suboptimal flow may result in a suboptimal procedure, including longer procedural times, decreased efficiency, and the need to abort it before the target plasma volume has been processed. Among the options to obtain vascular access in a patient undergoing a TA procedure, the options range from a large-bore needle to cannulate the patient's peripheral veins to the use of intravascular or implantable access devices (IVADs), such as arteriovenous (AV) shunts or AV fistulae; central venous catheters (CVCs); and CVCs tunneled with a port (port-CVCs). However, obtaining and maintaining adequate vascular access is a notable concern to an apheresis service, regardless of the country where the apheresis service is located. A review of vascular access around the world indicates that practice variation exists on the principal methods used.

International apheresis surveys have been conducted and reported since 1983.[8] These surveys show that peripheral venovenous access is the primary access method in Europe, whereas CVCs are the primary access method in North, Central, and South America. In Asia, there was a marked shift from the use of peripheral venovenous access to central venous access when one compares the survey performed in 1983 to that performed in 2010.[8,9] This shift in vascular access usage may be real, in that it shows the changing usage patterns in Asia, or it may be inaccurate, because the results may only reflect the experience of those centers participating in the surveys. For example, certain countries in Asia, such as Japan, which predominantly used peripheral venous access, did not

participate in the 2010 survey, suggesting potential sampling bias. The World Apheresis Association (WAA) registry indicated that European apheresis practitioners performed their TA procedures primarily through venovenous or peripheral access methods (2003, 63%; 2003-2007, 71%).[10,11]

The international apheresis surveys and registries described challenges and complications related to vascular access during TA; from 3% to 5% of total procedures were affected, ranging from the lack of securing access, to bleeding at the access site.[8,9] The prevalence of mild adverse events in the WAA registry was 130 in 10,000 procedures, and the prevalence of severe adverse events was two in 10,000 procedures.[12] A mild adverse event was defined as one that did not require medications and could be corrected easily, for example, by the reinsertion of a needle. A severe adverse event was defined as one that prevented the continuation of the procedure. Among the different TA modalities, TPE was most often affected by vascular access difficulties at 0.5%, with many procedures having to be discontinued.[13] This finding is not surprising, because TPE is one of the most commonly utilized TA procedures at many institutions, roughly comprising at least 70% of the total.[3]

PROCEDURAL AND PATIENT FACTORS IMPACTING VASCULAR ACCESS

Given the risks associated with vascular access and the importance of establishing a reliable access method, several procedural and patient-related factors should be considered before choosing an appropriate vascular option for TPE.

In the United States, all devices approved for TPE are based on centrifugation, which requires blood flow rates that range from 50 to 120 mL/min.[5,14] In contrast, membrane-based TPE requires a higher blood flow rate, ranging from 150 to 200 mL/min, because of the propulsion of blood through a hollow-fiber porous membrane.[15] In the United States, the TPE procedure also may be continuous or discontinuous (rare). When the procedure is performed continuously, access (withdrawal) and return lines have to be established and maintained throughout the procedure. However, when performed discontinuously, such as with the Optia device (Terumo BCT), a single line can serve as both the access and return, with the significant disadvantage of a longer procedural time, because the centrifuge bowl fills and empties with each cycle. Thus, the latter is only used when there is not an option for two vascular access sites. In addition, the urgency of the procedure, the total procedural time, the plasma volume(s) exchanged, the frequency of the procedure, and the duration of the treatment (days or months) also will impact the choice of vascular access.[15-17]

In addition to procedural factors, patient-related factors can determine the choice of vascular access. For example, the patient's underlying disease and mental status can impact their ability to produce tension, thus enabling blood to enter into the device if peripheral veins are being considered. Their vascular anatomy; body habitus; hygiene; hydration; status as an inpatient, outpatient, or critically ill patient; and prior medications also affect the decision. Furthermore, the availability of personnel and resources to obtain vascular access are often important determinants, especially when emergent TPE is needed.

Many types of vascular access are used around the world to perform TPE, ranging from peripheral veins and arteries of the hands and arms, internal jugular veins, subclavian veins, femoral veins and arteries, and AV fistulae and grafts. In children, the radial artery or the dorsalis pedis artery also have been used internationally with success.[18,19]

OPTIONS FOR INTRAVASCULAR OR IMPLANTABLE ACCESS DEVICES

Intravascular arterial peripheral needles and catheters (arterial lines)

Peripheral access is performed through the placement of a dialysis-type steel needle that will support the flow rates needed to perform TPE. The gauge of the intravascular needle ranges from 17 to 19 in adults and from 19 to 22 in children. A 17-gauge needle allows for flow rates of 80 mL/min and greater, whereas a 19-gauge needle allows for flow rates less than 60 mL/min. The needles are usually placed in the antecubital fossa and other larger veins of the arms, such as the basilic or cephalic veins, for access (drawing whole blood) and in the smaller veins of the arms and hands for return of the patient's cells and replacement fluid. A single-institution experience demonstrated that peripheral venous access was obtained in 72% of total procedures.[20] However, only 29% of TPEs were performed peripherally at that institution.[20]

An arterial option for needle or peripheral catheter cannulation has also been noted in literature and is performed internationally, but not in the United States.[9,18,21] Institutions in Asia used arterial puncture as an access method for performing apheresis procedures, albeit rarely; approximately 0.4% (21 of 4334) of their total procedures were performed using arterial puncture.[9] In the pediatric population, cannulation of the radial artery using peripheral venous access or Broviac catheter provided consistent flow rates while being minimally invasive, safe, and cost effective.[18] In that study of pediatric patients undergoing leukapheresis procedures, 22-gauge needles were used, and the success rates of cannulation were similar, at greater than 97%, as reported previously in the literature.[18,19] Needle cannulation can be performed as needed, immediately before starting TPE, and has fewer complications compared with other intravascular devices. The risks of peripheral vascular access include hematoma formation, nerve damage, patient discomfort, and sclerosis of

veins or arteries.[11,15,16] In individuals with nonpalpable or difficult vascular anatomy, an ultrasound can aid in establishing peripheral vascular access.[22] Single-institutional experiences with ultrasound demonstrated that peripheral vein cannulations increased with a reduction in the placement of CVCs.[22,23]

Compared with the different types of access used in Europe, access problems due to peripheral cannulation were the second most common adverse events, affecting 148 of 10,000 procedures.[12]

CENTRAL VENOUS CATHETERS

CVCs that are dialysis-capable are the most common intravascular devices used for TPE, especially in the inpatient setting. They are surgically inserted into a vein in the neck or chest to terminate at the superior vena cava-right atrial junction and their diameter should be at least 11.5-French in adults. CVCs intended for short-term, temporary use, such as for a series of TPE during a myasthenia gravis exacerbation episode, are nontunneled CVCs. These catheters do not have a surgically created, cutaneous channel and are noncuffed, meaning that there is no polyester cuff located at the site of skin insertion. Thus, for most patients, they do not require any type of sedation and can be inserted at the bedside. Those for long-term use, during both inpatient and outpatient procedures, are tunneled catheters (TCVCs), which are cuffed, meaning that a polyester layer impregnated with an antimicrobial substance is present in the channel. This cuff allows for the growth of fibroblasts at the insertion site, increasing the stability of the catheter placement while reducing the risk of infection.[14] Because of the need to create a "pocket" under the skin for the insertion of a TCVC, patients are commonly under medium-conscious sedation with drugs like midazolam and fentanyl.

Non-TCVCs are made of rigid biomaterial, usually polyurethane, and are placed in the internal jugular or femoral vein. These catheters, which are either straight or precurved, are used for less than 1 month (usually 2 weeks in the case of femoral line placement).[24] The precurved, nontunneled format minimizes the risk of kinking and obstructed blood flow. TCVCs are made of silicone and are softer and more flexible. However, the newer TCVCs are made from a mixture of polyurethane/polycarbonate material.[24] This composition allows for greater flexibility, increased strength, and resistance to breakdown by chemicals like iodine, peroxide, and alcohols. These catheters are placed in the subclavian vein under fluoroscopy and conscious sedation. Both CVCs and TCVCs also may have an antimicrobial coating to prevent or reduce infection and bacteremia, but each model has a distinctive design; for example, the Mahurkar catheter (a TCVC) has a double-D or modified double-D design, whereas the Power-Trialysis catheter has a double-barrel lumen design. Despite the differences in CVC designs, an advantage of CVCs is that they allow for consistent and adequate flow rates required for apheresis.[25,26] The Hickman, a TCVC that is also dialysis-capable, has three equally sized lumens that can be used to perform efficient apheresis.[27] Other TCVCs include the Broviac, Groshong, PermCath, and Neostar devices, which can have two or three lumens, some of which are used in the pediatric population.[28] The triple-lumen CVC that can be used for HD has the advantage of having two lumens capable of performing TPE and a smaller lumen (19-gauge) that can be used for medication infusion (such as calcium supplementation) or blood sampling during TPE. Radiographic examination of proper positioning must be performed before TPE for CVCs placed in the internal jugular and subclavian veins.

The benefits of CVCs include reliable blood flow and reduced resistance to withstand the high negative pressure needed to draw blood into the apheresis device. Complications include catheter occlusion due to thrombosis, infections (localized and systemic), catheter breakage, and embolism. A study evaluating the rate of complications from CVC placement for apheresis procedures in the intensive care unit demonstrated that insertion of CVCs was associated with early and late complications, such as pneumothorax, arterial puncture, and air embolism.[29] Access problems secondary to CVC placement in the jugular, femoral, or subclavian veins were uncommon, affecting 11 in 10,000, 36 in 10,000, and 18 in 10,000 procedures, respectively.[12] The complications associated with CVCs also depend on the location of the catheter. A study of 82 patients with 332 catheters demonstrated that subclavian placement of a CVC was associated with the most complications (60%) compared with jugular placement (20%) and femoral placement (57%).[30] For the period between TPEs, the patency of CVCs must be maintained with the instillation of heparin locks, often at high concentration, such as 1000 units/mL.

Peripherally inserted central catheters, which are CVCs placed into a vein in the arm, are not suitable for performing TPE because of the narrow catheter gauge, which collapses with the negative pressures exerted by apheresis devices.[28] There are other disadvantages, including catheter occlusion, thrombus formation, and higher failure rates compared with TCVCs.[28,31]

AV FISTULAE

AV fistulae are surgically created by direct anastomosis of an artery and a vein and are an appropriate choice for patients who undergo chronic TPE procedures. Common sites for AV fistulae include the radiocephalic or brachiocephalic anastomosis. AV fistulae, which have been used predominantly in HD, are increasingly being utilized in apheresis. However, according to the WAA and an international registry report, among the different IVADs, AV

fistulae were the least commonly used in apheresis, ranging from 2% to 4% of procedures.[11,32] The advantages of AV fistulae are that they can be used for months to years, provide good blood flow, and have a lower risk of infection. However, the disadvantage is that they cannot be used for patients who require urgent TPE procedures, because they require long-term planning for the surgical procedure and time for the fistula to mature. The skill of the surgeon is also paramount to creating a functioning, long-term AV fistula. Other complications include thrombosis and lack of fistula maturation. In a study on AV fistulae for HD, thrombosis occurred in 12% to 20% within 6 weeks of their creation.[33] In another study, among patients with renal diseases, more than one-half of AV fistulae (60%) did not mature sufficiently to be used.[34] Access issues also have plagued AV fistulae as the most common adverse events, occurring in 148 of 10,000 TA procedures.[12] Furthermore, many apheresis practitioners are not knowledgeable or proficient on the appropriate method for accessing an AV fistula, because it is uncommon in apheresis. Therefore, education on proper access, maintenance, and safety is needed with regard to AV fistulae unless dialysis nurses are available to properly access them. In our experience, AV fistulae are often used as the vascular access of choice in patients on HD who also require TPE, such as those undergoing desensitization before a renal transplant or those who experience humoral rejection post transplant. Also, at our institutions, we have often worked with the dialysis staff to obtain access if our apheresis practitioners were not proficient with AV fistulae or AV grafts.

AV GRAFTS

AV grafts are created by interposing a prosthetic graft between an artery and a vein. The interposed material is made with expanded polytetrafluoroethylene. Compared with AV fistulae, AV grafts are prone to more complications, such as venous anastomotic stenosis, as the most common.[35] There is no data on the use of AV grafts in the apheresis patient population, although they would offer the advantage of earlier access than AV fistulae after placement, usually within 10-14 days.[15] AV grafts were noted to function better initially than AV fistulae. However, they are more prone to thrombosis and infections in comparison to AV fistulae.

Port-CVCs

Ports are tunneled chambers that are implanted under the skin, usually in the subcutaneous tissue of the anterior chest wall, with the distal tip of the attached tubing terminating at the junction of the right atrium and the superior vena cava. This vascular access option should be considered for patients who require long-term TPE procedures. The tubing is made of silicone or polyurethane, and the chamber (cylindrical or funnel-shaped) can be single or double and may be made of titanium, plastic, silicone, or a combination of these materials.[36] In the cylindrical port, the dome is made of silicone, which is punctured with noncoring needles to perform TPE. Some of the ports that are available for use in the United States are the Port-A-Cath (Smiths Medical), SportPort (Norfolk Medical Products, Inc.), Vortex Port (AngioDynamics, Inc.), SmartPort (AngioDynmanics, Inc.), TidalPort (Norfolk Medical Products, Inc.), and PowerFlow (Bard Peripheral Vascular, Inc.) devices. Most of the ports in use are not approved by the US Food and Drug Administration for apheresis, with the exception of the PowerFlow. Ports used in apheresis, compared with those used to infuse medications (such as chemotherapy), differ in the size of the attached catheter lumen. Apheresis flow rates are determined by the size of the catheter. The common catheter sizes for a single-lumen port are 9-French and 12-French for a dual-lumen catheter attached to the port. Similar to other vascular options, ports are capable of handling flows as high as 150 mL/min. According to the WAA report published more than 10 years ago, ports were used in 4% of apheresis procedures around the world.[11] It is unknown whether their usage differs now, because more ports are available, and the apheresis staff is more knowledgeable about these types of IVADs.

The advantages of "ports" are the low rates of infection, potential long-term use, and patient comfort and increased quality of life, because they are able to participate in different types of physical activity, including swimming.[36] Unlike CVCs, which are immediately available for use, most ports need a few weeks for the skin over them to heal. Furthermore, they require medium conscious sedation for insertion. Accessing a port before completion of the healing process is very uncomfortable and can be painful; thus, early access should be avoided if possible. Depending on the port, careful planning is required in anticipation of long-term TA needs. The PowerFlow port is the notable exception, because it can be used immediately for apheresis procedures after its placement. Several options can be considered when placing a port in a patient: two-port placement, with one serving as the access and the other for return; single-port placement, serving as the access and using peripheral cannulation for return; or placement of a dual-lumen port with both access and return capabilities. Ports are relatively easy to maintain after their placements, usually with periodic flushing. In a study of 700 port placements in the surgical literature, 18% had complications.[37] The most common early complications included pneumothorax, hematoma, cardiac arrhythmia, and arterial puncture.[37] The most common late complications included catheter-associated venous thrombosis, port pocket infection, and pinch-off syndrome. In many institutions that use ports, tissue

plasminogen activator is instilled for 30 to 45 minutes before performing TA when sluggish flow is observed or suspected from previous procedures. In children, similar complications were noted in a small study of eight pediatric patients.[38] Access difficulties (3%), treatment delays (4%), bleeding, and bruising were common complications of port use in this group. There was also a port pocket infection that necessitated port removal. Similar to CVCs, ports are kept patent for days to years by infusing heparin at high concentration (such as 1000 units/mL) for the length of the tubing at the end of each TPE or other procedure.

CONCLUSION

TPE requires adequate vascular access for its successful completion, and appropriate vascular access can be accomplished in many different ways. The type of access used for TPE depends on careful consideration of patient and procedural variables as well as the availability of IVADs at the institution and the skill set of the apheresis team. Appropriate placement of the best vascular access option should be a joint and collaborative decision with the primary care team, the apheresis group, interventional radiology, and/or surgery.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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