Therapeutic Plasma Exchange: Core Curriculum 2023

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From producing individual blood components for transfusion to the removal of pathogenic substances, apheresis is a cornerstone of modern medical therapies. The use of therapeutic plasma exchange (TPE), in which plasma and its soluble constituents are removed from the body in exchange for a replacement fluid, can be organ- and life-saving in many diseases. Given the notable similarities between TPE and hemodialysis, the nephrologist is often responsible for managing TPE. As such, one must be familiar with the technologies, approach to therapy, indications for use, and complications. TPE uses centrifugation or membrane separation technologies, with the latter able to be performed with certain hemodialysis machines familiar to the nephrologist. Furthermore, primary kidney diseases such as anti–glomerular basement membrane disease are frequently associated with autoantibodies, potentially making them ideal candidates for TPE. Nevertheless, the use of TPE in many kidney diseases is controversial because of the lack of supporting evidence. This review discusses TPE from the perspective of a nephrologist responsible for prescribing and managing TPE, as well as nephrologists engaged in the care of patients undergoing the procedure.

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Am J Kidney Dis. 81(4):475-492. Published online February 10, 2023.

doi: 10.1053/j.ajkd.2022.10.017

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

It has long been postulated that removal of pathogenic substances from the blood may be therapeutic or even curative for some diseases. Phlebotomy dates to ancient times, and, in the modern era, technology has evolved to enable separation of specific blood components. The term apheresis refers to the general technique of extracorporeal removal of a blood constituent. As the name suggests, plasmapheresis removes plasma from a patient, whereas therapeutic plasma exchange (TPE) entails removing plasma from the patient in exchange for replacement fluid. Table 1 describes different apheresis modalities based on target molecule.

TPE is an extracorporeal therapy performed using centrifugation or membrane filtration. Notably, the ideal characteristics of a substance to be removed by TPE include large molecular weight, distribution in the intravascular space, and prolonged half-life, among others. As the nephrologist is often responsible for managing TPE, one must understand the indications, how to write the prescription, selection of replacement fluid, appropriate use of anticoagulation, and monitoring for and treating procedural complications. With the exception of anti–glomerular basement membrane (GBM) disease, in which the evidence of benefit is acceptably clear, data supporting the use of TPE for many kidney diseases have been mixed.

Additional Reading

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Technique

Two technologies are available for the removal of plasma and its pathogenic substance(s): centrifugation and membrane filtration. Membrane filtration TPE can only separate plasma, whereas centrifugation TPE can fractionate any of the blood components (eg, erythrocytes, platelets, plasma). As such, centrifugation TPE is the apheresis modality employed when specific blood fractions are targeted. Both methods are similarly effective at removing plasma proteins, and each involves administration of replacement fluid at an equal or greater volume to what was removed. As shown in Table 2, however, membrane filtration TPE extracts a smaller fraction of plasma (30%) per unit of time than centrifugal systems (80%), requiring longer treatment times and higher blood flow rates. This can increase the risk for circuit clotting. Although clinical trials have largely used centrifugation, the specific modality used often varies by country. Most TPE sessions in the United States are centrifugation-based.

Centrifugation

The centrifuge is the functional unit of this continuous-flow extracorporeal circuit and does not require a blood-membrane interface. By spinning at 2,000-2,500 revolutions per minute, it separates the components of anticoagulated

Table 1. Apheresis Modalities

Procedure	Target Molecule
Adsorptive cytapheresis	Monocytes, granulocytes
ß$_2$microglobulin column	ß$_2$-microglobulin
Double filtration plasmapheresis	Autoantibodies, immune complexes, lipoproteins
Erythrocytapheresis	Red blood cells
Extracorporeal photopheresis	Buffy coat (white blood cells and platelets)
Immunoadsorption	Immunoglobulins
Leukocytapheresis	White blood cells
Lipoprotein apheresis	Lipoprotein particles
Red blood cell exchange	Red blood cells (exchanged for replacement fluid)
Rheopheresis	High-molecular-weight plasma components (fibrinogen, α_2-macroglobulin, low-density lipoprotein cholesterol, and IgM)
Therapeutic plasma exchange	Plasma (exchanged for replacement fluid)
Thrombocytapheresis	Platelets

Abbreviation: IgM, immunoglobulin M.

blood according to density. Consequently, the blood separates around the axis of rotation, with plasma in the innermost layer, then granulocytes (ie, buffy coat), monocytes, lymphocytes, platelets, and finally red blood cells in the outermost layer (Fig 1).

Centrifugation can pack red blood cells to a hematocrit level of ≥80%, allowing for removal of larger plasma volumes and shorter sessions. Furthermore, because lower blood flow rates are sufficient, peripheral vein access can be used for centrifugation TPE.

Membrane Filtration

Similar in concept to isolated ultrafiltration in dialysis, plasma constituents are nonselectively removed across a semipermeable membrane. The two membrane separation filters marketed in the United States are the Plasmaflo OP (polyethylene with γ-ray sterilization) and the Prismaflex TPE series (polypropylene with ethylene oxide sterilization), although other filters are available worldwide. Certain models of continuous kidney replacement therapy (CKRT) and intermittent hemodialysis machines are compatible with these filters. The separation efficiency depends on plasma filtration rates, membrane properties such as pore size and surface area, and the sieving coefficients. The latter is a measure of equilibration of a given solute between the filtrate and blood sides of the membrane, thereby indicating how effectively a molecule is moved across the filter. Sieving coefficients depend on molecule factors such as size, protein binding, and charge. Serum protein adsorption to the membrane will lead to filter clogging and decreased separation.

Similar to CKRT modalities that rely on convective clearance, high ultrafiltration rates lead to high filtration fractions, and red blood cell damage and/or filter clotting may occur as the hematocrit level increases. Therefore, membrane filtration TPE is limited to a filtration fraction of 30%-35% of the plasma, requiring longer treatment sessions and higher blood flow rates. Consequently, membrane filtration TPE requires central venous access.

Unlike hemodialysis or hemofiltration, which removes substances of low to medium molecular weight from serum, TPE targets larger-molecular-weight substances present in plasma (Table 2).

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Table 2. Apheresis Versus Hemodialysis

	Therapeutic Plasma Exchange		
Characteristic	Centrifugation	Membrane Filtration	Hemodialysis
Mechanism	Centrifugal force	Convection	Diffusion and/or convection
Blood flow, mL/min	10-150	150-200	Continuous: 100-300; intermittent: 200->400
Blood volume in circuit, mL	180	125	160-280
Plasma extraction, %	80	30	NA
Molecular weight cutoff, Da	>15,000	>15,000	<15,000
Vd, L/kg	Low (<0.3)	Low (<0.3)	Moderate (≤1.5-2)
Protein binding, %	>80	>80	<80
Anticoagulation	Citrate	Heparin	Heparin
Sterilization	γ-Irradiation; ethylene oxide	γ-Irradiation; ethylene oxide	Ethylene oxide; steam; electron beam; γ-irradiation

Abbreviations: NA, not applicable; Vd, volume of distribution.

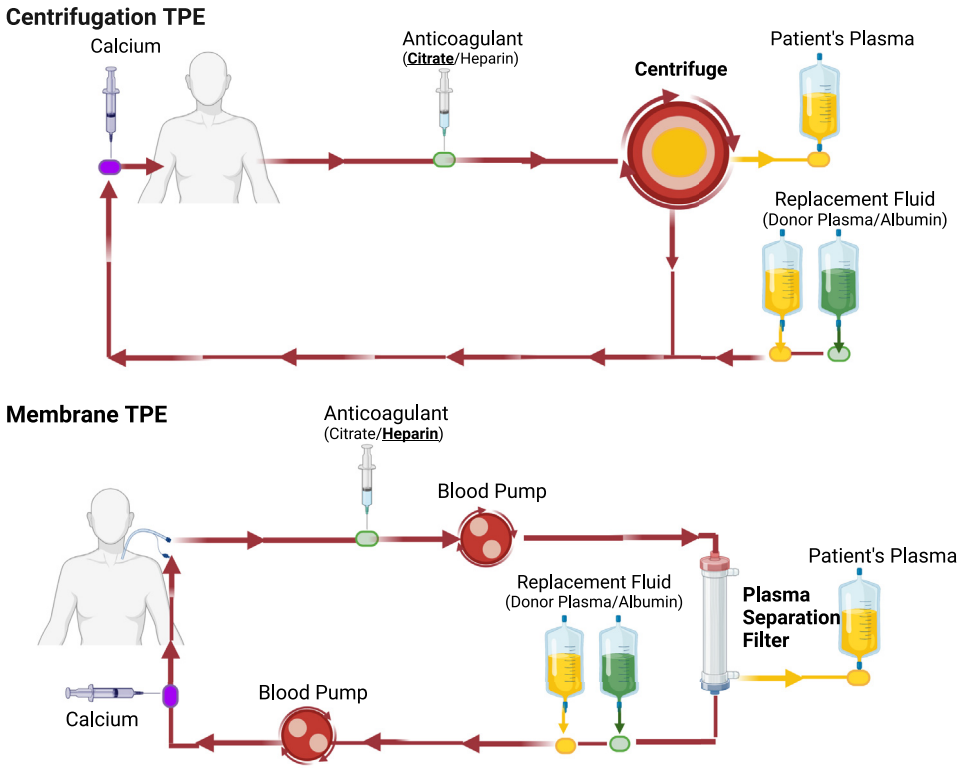

Figure 1. Comparison of centrifugation and membrane separation therapeutic plasma exchange (TPE). In centrifugation TPE, blood is removed from the patient and anticoagulated before centrifugation, and then plasma is separated. Replacement fluid is infused after centrifugation upon return to the patient. Membrane separation TPE is similar except that, instead of using centrifugal force, blood is perfused through a hollow fiber filter across which plasma is convectively transported. Replacement fluid is infused after filtration upon return to the patient. Figure created with Biorender.com.

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Basic Principles and General Considerations

When to Consider TPE

TPE is most commonly used to target a single pathogenic substance for removal from the plasma. The ideal characteristics of such substances include large molecular weight (>15,000 Da), slow rate of formation, prolonged half-life, higher-percentage intravascular distribution, and low turnover rate. Nevertheless, within specific diseases, TPE has not always demonstrated clinical benefit. Its use should be most strongly considered in those conditions for which there is evidence to support clinical benefit. Table 3 describes common plasma proteins and their characteristics.

Vascular Access

Most apheresis devices use centrifugation and require blood flow rates of 50-120 mL/min, compared with 150-200 mL/min in membrane filtration TPE (Table 2). The TPE procedure can be continuous, which requires access and return catheters, or discontinuous, which allows a single catheter to serve for access and return. A discontinuous setup requires longer procedure times.

Procedure-related factors (urgency, volume[s] exchanged, frequency), patient-related factors (underlying disease, mental status, and vascular anatomy), and institutional capabilities determine the ideal vascular access. Options include the following.

Large-Bore Peripheral Intravenous Access

In adults, 17-19–gauge needles are used; these are used to supply blood flow rates ranging from >80 to 60 mL/min. In children, 19-22–gauge needles are used. Routinely, blood is withdrawn from the basilic or cephalic vein and returned with replacement fluid to smaller veins in the hands.

Table 3. Distribution and Metabolism of Plasma Proteins

Protein	Plasma Concentration, mg/mL	Mass, kDa	Intravascular, %	Fractional Turnover, %/d	Half-Life, d
IgA	2.6	160	42	25	6
IgD	0.02	175	75	37	2.8
IgE	0.0001	190	41	94	2.5
IgG	12.1	150	45	6.7	22
IgM	0.9	950	78	19	5
Albumin	42	65	40	10	17
Fibrinogen	2-4	340	80	25	4.2
C3	1.5	240	63	56	2

Abbreviation: Ig, immunoglobulin.
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Central Venous Catheters for Dialysis

In adults, 11.5-F catheters provide consistent and reliable blood flow rates and are usually placed into the internal jugular or femoral veins.

Ports

Ports are subcutaneous chambers with a distal tip that terminates at the junction of the right atrium and the superior vena cava. Often, a single-lumen 9-F port is used for access (ie, blood draw) with blood and replacement fluid return via peripheral intravenous (IV) access. Dual-lumen ports typically have flow rates similar to large-bore peripheral IV accesses. Ports are associated with low infection rates and provide greater patient comfort. For central venous catheters (CVC) and port patency, heparin locks at 1,000 U/mL are often used.

Arteriovenous Fistulas or Grafts

Arteriovenous fistulas (AVFs) or arteriovenous grafts (AVGs) are excellent choices for patients undergoing ongoing, repetitive TPE because these accesses provide fast blood flow, low risk of infection, and excellent long-term patency. This is the access of choice particularly for hemodialysis recipients who need TPE. AVFs are used in only 2%-4% of apheresis procedures. Given the time needed for creation and maturation, they are not suitable for patients requiring urgent or short courses of therapy.

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Anticoagulation

Anticoagulation is used to prevent clotting in the extracorporeal circuit. The specific anticoagulant depends on the method of apheresis, comorbid processes (eg, cirrhosis, kidney failure, or thrombocytopenia), and the need for systemic anticoagulation for other indications (eg, extracorporeal membrane oxygenation [ECMO]). There are 2 standard anticoagulant agents used to maintain the patency of the circuit, citrate and heparin.

Citrate

Citrate is the preferred agent because of its regional effect, short half-life (30-60 min), and excellent safety profile. Citrate is infused in the circuit before the pump, where it chelates ionized calcium to prevent activation of the coagulation cascade. In centrifugation TPE, the risk of citrate toxicity is low because 80% is removed with the discarded plasma. Membrane filtration TPE, however, requires higher blood flow rates and clears only 20%-30% of the citrate. This increases the risk for citrate toxicity, particularly in patients with liver or kidney disease, and heparin is preferred with this modality. Calcium must be replaced orally or IV to avoid systemic hypocalcemia. The most commonly used commercial citrate solutions are Anticoagulant Citrate Dextrose Formula A (ACD-A), which is a hypertonic solution (sodium concentration of 252 mmol/L), and ACD-B, which is isotonic to plasma. Whole blood to anticoagulant ratios of 10:1-14:1 (expressed in milliliters) are commonly used. The ratio may be adjusted to deliver more anticoagulant agent if platelet clumping occurs, while monitoring for increased citrate reactions.

Heparin

Heparin is inexpensive, has a short half-life (23 minutes to 2.48 hours), and is almost entirely cleared during TPE. A bolus of 3,000-5,000 U is administered at the start of treatment, followed by 1,000 U/h if needed. Heparin is the preferred anticoagulant agent in membrane filtration TPE, and the clotting risk is low enough that initial treatment without anticoagulation can be considered with modern equipment.

There is considerable institutional variability in the management of patients already receiving anticoagulation. For patients receiving a heparin drip and undergoing centrifugation TPE, one approach is to discontinue the drip

1 hour before TPE with citrate infusion. Treatment of patients currently receiving warfarin, low-molecular-weight heparin, or direct oral anticoagulant agents may be challenging because of longer drug half-lives, less availability of reversal agents, and reduced ability to easily monitor the bleeding risk. TPE with albumin replacement is safe to perform in individuals receiving warfarin, although albumin replacement increases the anticoagulant effect through removal of clotting factors. At many institutions, TPE is performed in the standard fashion with citrate or heparin in patients receiving preexisting anticoagulation.

Finally, in patients with small blood volumes (eg, pediatric patients), many centers use a combination of ACD-A and heparin (eg, 500 mL ACD-A with 10,000 U heparin) to minimize the amount of citrate, although a whole blood to anticoagulant ratio of at least 26:1 is used.

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Replacement Fluids

The choice of replacement fluid depends on the indication for apheresis, as well as infection and bleeding risks. Replacement fluids consist of colloids, crystalloids, or a combination of the 2, although crystalloids are typically only used for hyperviscosity syndrome. Human albumin solution is used most frequently for its oncotic properties.

Albumin

Commercially available 5% albumin solutions contain approximately 145 mmol/L sodium and <2 mmol/L potassium. TPE followed by albumin replacement will result in a 50%-60% reduction in pro- and anticoagulant factors. Fortunately, rebound is biphasic, with an initial increase 4 hours after pheresis and almost complete recovery by 48 hours. Coagulation testing should not be performed for 8-12 hours after albumin replacement. If cost is a limitation, an 80:20 albumin–saline solution combination can be used, with a minimum ratio of 70:30. These diluted replacement fluids carry a higher risk for hypotension, and use is commonly limited to hyperviscosity syndrome. Because albumin is heat-inactivated, it has a lower risk than plasma of hypersensitivity reactions, transfusion-related acute lung injury, and transmission of infection.

Frozen Plasma

Plasma is primarily used to replenish ADAMTS13 in thrombotic thrombocytopenic purpura (TTP) and clotting factors in patients with bleeding (eg, diffuse alveolar hemorrhage [DAH]). Frozen plasma is typically fresh frozen plasma or 24-hour frozen plasma. Three or more sessions of daily TPE may require replacement with 2-4 U fresh frozen plasma (500-1,000 mL) to reduce the bleeding risk, although monitoring coagulation studies to guide this practice is preferred. Frozen plasma contains approximately 7 mmol citrate per unit, increasing the risk for citrate toxicity with large-volume infusions. Moreover, because unit size is 200-300 mL, a single plasma volume exchange of 3 L will require 10-15 U obtained from this many donors.

To prevent allergic reactions, patients are often pretreated with diphenhydramine despite data showing no benefit of preprocedure antihistamine. If there is a history of sensitivity to fresh frozen plasma, solvent detergent plasma (pathogen-inactivated blood product) or pretreatment with steroids, diphenhydramine, and ephedrine has been used successfully. Risks associated with donor plasma include transfusion reactions and citrate toxicity. There is a higher rate of infection transmission in low- and middle-income countries, whereas the risk is extremely low in high-income countries.

Prescribing Principles

Case 1: *A 50-kg, 42-year-old woman presents with fatigue and headache of 2 weeks' duration. In the emergency department, she is ill-appearing with heart rate of 115 beats/min and blood pressure 120/65 mm Hg. She has a petechial rash. Laboratory results include hematocrit level of 18%, platelet count of 12 × 10^3/μL, serum creatinine (Scr) level of 1.3 mg/dL (from a baseline of 0.8 mg/dL), lactate dehydrogenase level of 2,100 U/mL, and haptoglobin level of <6 mg/dL. A peripheral blood smear shows 15% schistocytes.*

Question 1: You decide to initiate TPE for treatment of likely TTP while awaiting results of ADAMTS13 activity. What is the estimated plasma volume (EPV) to be exchanged?

(a) 2.7 L
(b) 3.7 L
(c) 4.7 L
(d) 5.7 L

Question 2: Which one of the following is the most appropriate initial prescription?

(a) Two plasma volumes exchanged every other day
(b) Two plasma volumes exchanged daily
(c) One plasma volume exchanged every other day
(d) One plasma volume exchanged daily

Question 3: Which one of the following replacement fluids would be most appropriate?

(a) Frozen plasma
(b) Albumin
(c) Combination of albumin and frozen plasma
(d) 0.9% saline solution

For the answers to these questions, see the following text.

Writing the Prescription

The average blood volume in adults is 6.5% of body weight (~5 L), of which 60% is plasma (~3 L). EPV can be calculated from estimated blood volume (0.065 × weight in kilograms) and hematocrit as EPV = (0.065 × weight) × (1 − hematocrit).

There are numerous formulas and "rules of thumb" for this calculation, and apheresis machines use a modified formula that includes patient sex, height, and weight to estimate the exchange volume.

One plasma volume exchange removes a fixed proportion (approximately 65%-70%) of the targeted substance from the intravascular compartment. Equilibration across body fluid compartments determines the net clearance of the substance, represented by the equation $X_1 = X_0 - V_e/EPV$, where X_1 represents the final plasma concentration, X_0 the initial concentration, and V_e the volume exchanged.

As V_e/EPV increases, however, the incremental decrease in the initial concentration of the targeted substance also decreases (ie, the procedure becomes less efficient; Fig 2). For example, an exchange of 1.4 times the EPV decreases the pretreatment levels of a substance approximately 75%, with minimal additional clearance beyond 1.5 plasma volumes. In addition, the plasma concentration of the target substance decreases as a result of dilution by the replacement fluid. Thus, TPE sessions typically exchange 1 volume and virtually never more than 1.5.

The extracorporeal volume, which refers to the volume of blood outside the body during TPE, should be <15% of total blood volume to decrease the risk of complications related to hypovolemia. If necessary, a blood prime or transfusion may be required.

Number of Exchanges, Duration, and Discontinuation

A 70-kg adult with a hematocrit level of 34% will require approximately 3 L of replacement fluid for a single plasma volume exchange, which will last approximately 1.5-2 hours with centrifugation TPE and 3 hours with membrane filtration TPE. The frequency and number of TPE sessions depend on the characteristics of the pathogenic substance and the time required to reach the desired clinical improvement. The following factors are important determinants of the efficiency of TPE:

- Sieving coefficient: A measure of equilibration of a solute across a semipermeable membrane. A sieving coefficient of 1 indicates perfect equilibration across a membrane and a need for fewer TPE sessions, whereas a solute with a sieving coefficient of 0 does not cross at all.
- Plasma half-life (also expressed as $t_{1/2}$): Substances with a shorter half-life may be synthesized more rapidly, leading to faster rebound and need for more frequent TPE. Conversely, an exogenous substance with a short half-life will have faster clearance even in the absence of TPE.
- Extravascular concentration: Substances with large extravascular distribution will be removed more slowly because they must redistribute intravascularly for removal.
- Rate of synthesis: Faster synthesis may require more frequent TPE and/or additional therapies to decrease endogenous production.

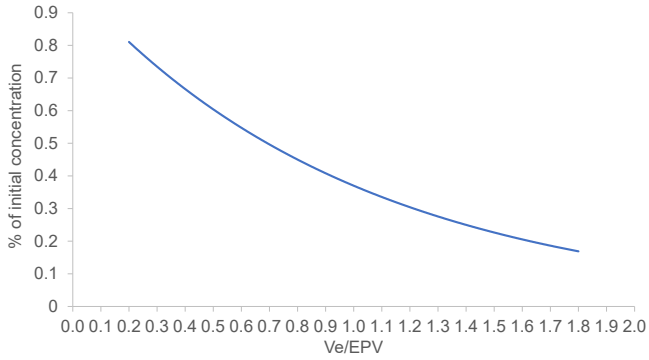

Figure 2. The relationship of percentage decrease in initial concentration for a given substance as a function of volume exchanged (Ve) relative to estimated plasma volume (EPV). Based on information in Kaplan, 1999 (*A Practical Guide to Therapeutic Plasma Exchange*; Blackwell Science).

Most immune complex diseases are related to the production of immunoglobulin G (IgG), a molecule with 45% extravascular distribution, long half-life (22 days), and low turnover per day (7%; Table 3). Therefore, several consecutive treatments each separated by 24-48 hours will be required to achieve meaningful clearance. In general, TPE performed every other day for 6 treatments will decrease circulating IgG levels to 16%-20% of the baseline level (Fig 3). Diseases with a high autoantibody production rate (eg, anti-GBM disease) require daily sessions with concomitant immunosuppression.

In contrast, IgM is a larger molecule with 80% intravascular distribution, shorter half-life (5 days), and higher daily turnover (17%). As such, one TPE will achieve significant clearance, but discontinuation of therapy will lead to faster rebound than for IgG.

Returning to question 1, option (a), 2.7 L, is the best answer. The estimated plasma volume can be calculated as (0.065 × 50 kg) × (1 − 0.18) = 2.7 L. For question 2, option (d), daily exchange of 1 plasma volume, is the best answer. TPE is the first-line therapy for TTP, reducing mortality from >90% to 5%-10%. TTP needs to be treated aggressively

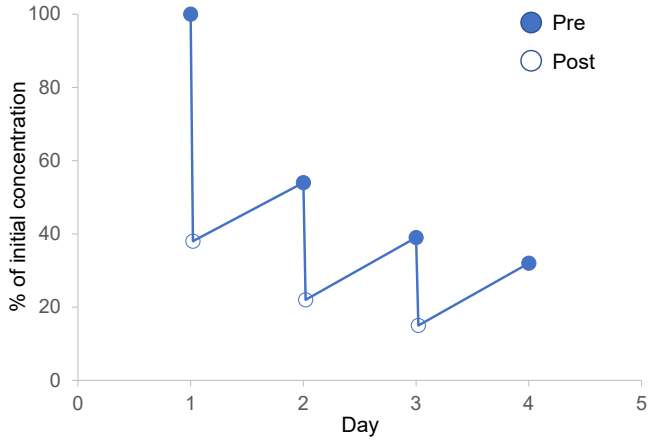

Figure 3. Immunoglobulin G removal from 1 plasma volume exchanged per day for 3 days. The intertreatment increase is a result of equilibration between the intra- and extravascular compartments, as well as new immunoglobulin G synthesis. Table 4 shows the reduction and subsequent rebound in common blood constituents achieved with a single plasma volume exchange. Based on information in Kaplan, 1999 (*A Practical Guide to Therapeutic Plasma Exchange*; Blackwell Science).

(daily TPE initially) with 1-1.5 plasma volume exchanges. For question 3, option (a), frozen plasma, is the best answer. Daily sessions with frozen plasma replacement fluid are lifesaving, as TPE removes autoantibodies against ADAMTS13 and frozen plasma provides functional ADAMTS13.

Laboratory Monitoring

Optimal laboratory testing for hemostasis in patients undergoing TPE is not defined, and there is significant practice variation across institutions. The American Society for Apheresis (ASFA) and Choosing Wisely do not recommend routine monitoring of coagulation tests during a course of TPE unless the procedure is performed daily. This includes TPE performed with nonfrozen plasma replacement fluids such as albumin. Red blood cell transfusion should be considered to maintain hematocrit level >22%, and ionized calcium should be measured if symptoms of hypocalcemia develop. The effect at 48 hours of 1 plasma volume exchange on different proteins is shown in Table 4.

Additional important treatment recommendations from Choosing Wisely include not placing a central venous catheter if peripheral vein access is safe, using frozen plasma replacement fluid only when clearly indicated, and establishing a defined course of apheresis.

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Indications

Case 2: *A 70-year-old man presents with fatigue, dyspnea, and hemoptysis. He appears ill, with tachycardia and blood pressure 84/55 mm Hg. He is intubated for hypoxemic respiratory failure. Laboratory testing reveals a hemoglobin level of 8 g/dL, platelet count of 76 × 10^3/μL, and Scr concentration of 3.2 mg/dL (from a baseline of 1.2 mg/dL). Urinalysis reveals microscopic hematuria with 10% acanthocytes on microscopy. Computed tomography of the chest is compatible with DAH. Empirical corticosteroids are initiated, and, based on preliminary results of a kidney biopsy consistent with anti-GBM disease, cyclophosphamide and TPE are started. Serum antibodies to myeloperoxidase and proteinase 3 (MPO and PR3) are not detected, and serum anti-GBM antibody is 52 U (normal is <1 U).*

Table 4. Effect of a Single Plasma Volume Exchange on the Removal and Rebound of Common Blood Constituents Using Albumin and/or Crystalloid Replacement Fluid

Constituent	Decrease vs Baseline, %	Rebound 48 h Post Apheresis, %
Antithrombin III	70	100
C3	63	60-100
Factor VIII	50-82	90-100
Fibrinogen	67	46-63
Prothrombin	49	48
Immunoglobulins	60	44
Liver enzymes	55-60	100
Platelets	25-30	75-100

Values are given as means.

Table 5. ASFA Category and Grade Recommendations for Therapeutic Apheresis

Disease	Modality	Indication	Category	Grade
Acute disseminated encephalomyelitis	TPE	Steroid-refractory	II	2C
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)	TPE	Primary treatment	I	1A
	IA	Primary treatment	I	1B
Acute liver failure	TPE-HV	–	I	1A
	TPE	–	III	2B
Age-related macular degeneration, dry	Rheopheresis	High risk	II	2B
Amyloidosis, systemic	B2M column	Dialysis-related amyloidosis	II	2B
	TPE	Other causes	IV	2C
Anti-GBM disease (Goodpasture syndrome)	TPE	DAH	I	1C
	TPE	Not receiving dialysis at presentation	I	1B
	TPE	Receiving dialysis at presentation, no DAH	III	2B
Atopic (neuro-)dermatitis (atopic eczema), recalcitrant	ECP	–	III	2A
	IA	–	III	2C
	TPE/DFPP	–	III	2C
Autoimmune hemolytic anemia, severe	TPE	Severe cold agglutinin disease	II	2C
	TPE	Severe warm autoimmune	III	2C
Babesiosis	RBC exchange	Severe	II	2C
Burn shock resuscitation	TPE	–	III	2B
Cardiac neonatal lupus	TPE	–	III	2C
CAPS	TPE	–	I	2C
Chronic focal encephalitis (Rasmussen encephalitis)	TPE	–	III	2C
Chronic inflammatory demyelinating polyradiculoneuropathy	TPE/IA	–	I	1B
Coagulation factor inhibitors	TPE	–	III	2C
	IA	–	III	2B
Complex regional pain syndrome	TPE	Chronic	III	2C
Cryoglobulinemia	TPE	Severe/symptomatic	II	2A
	IA	Severe/symptomatic	II	2B
Cutaneous T-cell lymphoma; mycosis fungoides; Sézary syndrome	ECP	Erythrodermic	I	1B
	ECP	Nonerythrodermic	III	2C
Dilated cardiomyopathy, idiopathic	IA	NYHA II-IV	II	1B
	TPE	NYHA II-IV	III	2C
Erythropoietic protoporphyria, liver disease	TPE	–	III	2C
	RBC exchange	–	III	2C
Familial hypercholesterolemia	LA	Homozygotes	I	1A
	LA	Heterozygotes	II	1A
	TPE	Homozygotes/heterozygotes	II	1B
FSGS	TPE/IA	Recurrent in KTx	I	1B
	LA	Recurrent in KTx/steroid-resistant in native kidney	II	2C
	TPE	Steroid-resistant in native kidney	III	2C
Graft-vs-host disease	ECP	Acute	II	1C
	ECP	Chronic	II	1B
HELLP syndrome	TPE	Postpartum	III	2C
	TPE	Antepartum	IV	2C
Hemophagocytic lymphohistiocytosis; hemophagocytic syndrome; macrophage activating syndrome	TPE	–	III	2C
Heparin-induced thrombocytopenia and thrombosis	TPE	Pre-CPB	III	2C
	TPE	Thrombosis	III	2C
Hereditary hemochromatosis	Erythrocytapheresis	–	I	1B
Hyperleukocytosis	Leukocytapheresis	Symptomatic	II	2B
	Leukocytapheresis	Prophylactic or secondary	III	2C

(Continued)

Table 5 (Cont'd). ASFA Category and Grade Recommendations for Therapeutic Apheresis

Disease	Modality	Indication	Category	Grade
Hypertriglyceridemic pancreatitis	TPE/LA	Severe	III	1C
	TPE/LA	Prevention of relapse	III	2C
Hyperviscosity in hypergammaglobulinemia	TPE	Symptomatic	I	1B
	TPE	Prophylaxis for rituximab	I	1C
IgA nephropathy (Berger disease)	TPE	Crescentic	III	2B
	TPE	Chronic progressive	III	2C
Immune thrombocytopenia	TPE/IA	Refractory	III	2C
Inflammatory bowel disease	Adsorptive cytapheresis	Ulcerative colitis/Crohn disease	III	1B
	ECP	Crohn disease	III	2C
Lambert-Eaton myasthenic syndrome	TPE	–	II	2C
Lipoprotein(a) hyperlipoproteinemia	LA	Progressive atherosclerotic CVD	II	1B
Malaria	RBC exchange	Severe	III	2B
Multiple sclerosis	TPE	Acute attack/relapse	II	1A
	IA	Acute attack/relapse	II	1B
	TPE	Chronic	III	2B
	IA	Chronic	III	2B
Myasthenia gravis	TPE/IA	Short-term treatment	I	1B
	TPE/IA	Long-term treatment	II	2B
Myeloma cast nephropathy	TPE	–	II	2B
Nephrogenic systemic fibrosis	ECP/TPE	–	III	2C
Neuromyelitis optica spectrum disorders	TPE	Acute attack/relapse	II	1B
	IA	Acute attack/relapse	II	1C
	TPE	Maintenance	III	2C
N-methyl-D-aspartate receptor antibody encephalitis	TPE/IA	–	I	1C
Overdose, envenomation, and poisoning	TPE	Mushroom poisoning	II	2C
	TPE	Envenomation	III	2C
	TPE	Drug overdose/poisoning	III	2C
Paraneoplastic neurological syndromes	TPE/IA	–	III	2C
Paraproteinemic demyelinating neuropathies; chronic acquired demyelinating polyneuropathies	TPE	IgG/IgA/IgM	I	1B
	TPE	Anti-MAG neuropathy	III	1C
	TPE	Multiple myeloma	III	2C
	TPE	Multifocal motor neuropathy	IV	1C
PANDAS; Sydenham chorea	TPE	PANDAS, exacerbation	II	1B
	TPE	Sydenham chorea, severe	III	2B
Pemphigus vulgaris	TPE	Severe	III	2B
	ECP/IA	Severe	III	2C
Peripheral vascular diseases	LA	–	II	1B
Phytanic acid storage disease (Refsum disease)	TPE/LA	–	II	2C
Polycythemia vera; erythrocytosis	Erythrocytapheresis	Polycythemia vera	I	1B
	Erythrocytapheresis	Secondary erythrocytosis	III	1C
Posttransfusion purpura	TPE	–	III	2C
PML associated with natalizumab	TPE	–	III	1C
Pruritus due to hepatobiliary diseases	TPE	Treatment-resistant	III	1C
Psoriasis	ECP	Disseminated pustular	III	2B
	Adsorptive cytapheresis	Disseminated pustular	III	2C
	TPE	Disseminated pustular	IV	2C
Red cell alloimmunization, prevention and treatment	RBC exchange	Exposure to RhD+ RBCs	III	2C
	TPE	Pregnancy, GA <20 wk	III	2C
Scleroderma (systemic sclerosis)	TPE	–	III	2C
	ECP	–	III	2A

(Continued)

Table 5 (Cont'd). ASFA Category and Grade Recommendations for Therapeutic Apheresis

Disease	Modality	Indication	Category	Grade
Sepsis with multiorgan failure	TPE	–	III	2B
Sickle cell disease, acute	RBC exchange	Acute stroke	I	1C
	RBC exchange	Acute chest syndrome, severe	II	1C
	RBC exchange	Other complications	III	2C
Sickle cell disease, nonacute	RBC exchange	Stroke prophylaxis	I	1A
	RBC exchange	Pregnancy	II	2B
	RBC exchange	Recurrent vaso-occlusive pain crisis	II	2B
	RBC exchange	Preoperative management	III	2A
Steroid-responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto encephalopathy)	TPE	–	II	2C
Stiff-person syndrome	TPE	–	III	2C
Sudden sensorineural hearing loss	LA/rheopheresis/TPE	–	III	2A
SLE	TPE	Severe complications	II	2C
Thrombocytosis	Thrombocytapheresis	Symptomatic	II	2C
	Thrombocytapheresis	Prophylactic or secondary	III	2C
TMA, coagulation mediated	TPE	*THBD*, *DGKE*, and *PLG* gene variants	III	2C
TMA, complement mediated	TPE	CFH autoantibody	I	2C
	TPE	Complement factor gene variants	III	2C
TMA, drug associated	TPE	Ticlopidine	I	2B
	TPE	Clopidogrel	III	2B
	TPE	Gemcitabine/quinine	IV	2C
TMA, infection associated	TPE/IA	STEC-HUS, severe	III	2C
	TPE	Pediatric HUS	III	2C
TMA, TTP	TPE	–	I	1A
TMA, transplant associated	TPE	–	III	2C
Thyroid storm	TPE	–	II	2C
Toxic epidermal necrolysis	TPE	Refractory	III	2B
Transplant, cardiac	ECP	Cellular/recurrent rejection	II	1B
	ECP	Rejection prophylaxis	II	2A
	TPE	Desensitization	II	1C
	TPE	Antibody-mediated rejection	III	2C
Transplant, HSCT, ABOi	TPE	Major ABOi HPC(M)	II	1B
	TPE	Major ABOi HPC(A)	II	2B
	RBC exchange	Minor ABOi HPC(A)	III	2C
	TPE	Major/minor ABOi with pure RBC aplasia	III	2C
Transplant, HSCT, HLA desensitization	TPE	–	III	2C
Transplant, liver	TPE	Desensitization, ABOi living donor	I	1C
	TPE	Desensitization, ABOi deceased donor/AMR	III	2C
	ECP	Desensitization, ABOi	III	2C
	ECP	Acute rejection/immune suppression withdrawal	III	2B
Transplant, lung	ECP	Bronchiolitis obliterans syndrome	II	1C
	TPE	AMR/desensitization	III	2C
Transplant, kidney, ABO compatible	TPE/IA	AMR	I	1B
	TPE/IA	Desensitization, living donor	I	1B
	TPE/IA	Desensitization, deceased donor	III	2C
Transplant, kidney, ABOi	TPE/IA	Desensitization, living donor	I	1B
	TPE/IA	AMR	II	1B

(Continued)

Table 5 (Cont'd). ASFA Category and Grade Recommendations for Therapeutic Apheresis

Disease	Modality	Indication	Category	Grade
AAV	TPE	MPA/GPA/RLV: RPGN, Scr ≥5.7 mg/dL	II[a]	1A
	TPE	MPA/GPA/RLV: RPGN, Scr <5.7 mg/dL	III	2C
	TPE	MPA/GPA/RLV: DAH	I	1C
	TPE	EGPA	III	2C
Vasculitis, IgA (Henoch-Schönlein purpura)	TPE	Crescentic RPGN	III	2C
	TPE	Severe extrarenal manifestations	III	2C
Vasculitis, other	TPE	Hepatitis B polyarteritis nodosa	II	2C
	TPE	Idiopathic polyarteritis nodosa	IV	1B
	Adsorptive cytapheresis	Behcet disease	II	1C
	TPE	Behcet disease	III	2C
VGKC antibody–related diseases	TPE/IA	–	II	1B
Wilson disease, fulminant	TPE	–	I	1C

Abbreviations: AAV, antineutrophil cytoplasmic antibody–associated vasculitis; ABOi, ABO incompatible; AMR, antibody-mediated rejection; ASFA, American Society for Apheresis; B2M, β_2-microglobulin; CAPS, catastrophic antiphospholipid syndrome; CFH, complement factor H; CPB, cardiopulmonary bypass; CVD, cardiovascular disease; DAH, diffuse alveolar hemorrhage; DFPP, double filtration plasmapheresis; DGKE, diacylglycerol kinase ε; ECP, extracorporeal photopheresis; EGPA, eosinophilic granulomatosis with polyangiitis; FSGS, focal segmental glomerulosclerosis; GA, gestational age; GBM, glomerular basement membrane; GPA, granulomatosis with polyangiitis; HELLP, hemolysis, elevated liver enzymes, and low platelets; HPC, hematopoietic progenitor cell; HSCT, hematopoietic stem cell; HUS, hemolytic uremic syndrome; IA, immunoadsorption; Ig, immunoglobulin; KTx, kidney transplant; LA, lipoprotein apheresis; MAG, myelin-associated glycoprotein; MPA, microscopic polyangiitis; NYHA, New York Heart Association [classification]; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PLG, plasminogen; PML, progressive multifocal leukoencephalopathy; RBC, red blood cell; RhD, rhesus factor D; RLV, renal-limited vasculitis; RPGN, rapidly progressive glomerulonephritis; SLE, systemic lupus erythematosus; STEC-HUS, Shiga toxin–producing *Escherichia coli* hemolytic uremic syndrome; TMA, thrombotic microangiopathy; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura; *THBD*, thrombomodulin; VGKC, voltage-gated potassium channel.
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[a]Changed to category II from category I in a 2020 update.

Question 4: Which one of the following best describes the duration of TPE for this patient?

(a) Because MPO and PR3 testing gives negative results, TPE should be discontinued
(b) TPE should be discontinued when serum anti-GBM antibody is undetectable
(c) TPE should be continued for a minimum of 3 sessions
(d) TPE should be continued for a minimum of 10-20 days and until resolution of active organ injury

For the answer to this question, see the following text.

General Recommendations for TPE

ASFA categorizes and grades 84 diseases and 157 indications for therapeutic apheresis. In category I, apheresis is first-line therapy. For category II, apheresis is second-line therapy with efficacy favored by available evidence but conventional therapy should be tried first. For category III, the role of apheresis has not been established, so the decision needs to be individualized. In category IV, the evidence suggests that apheresis is ineffective or harmful. In terms of ASFA grading, grade 1 is a strong recommendation, whereas grade 2 is weak. Quality of evidence is indicated by the letters A, B, and C, which represent high-quality, moderate-quality, and low-quality evidence, respectively (Table 5). These guidelines are updated approximately every 3 years, with the most recent version dated 2019.

Additional Readings

- Pham HP, Staley EM, Schwartz J. Therapeutic plasma exchange-a brief review of indications, urgency, schedule, and technical aspects. *Transfus Apher Sci.* 2019;58(3):237-246. https://doi.org/10.1016/j.transci.2019.04.006
- Padmanabhan A, Connelly-Smith L, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the eighth special issue. *J Clin Apher.* 2019;34(3):171-354. https://doi.org/10.1002/jca.21705 ★ESSENTIAL READING
- Sanchez AP, Balogun RA. Therapeutic plasma exchange in the critically ill patient: technology and indications. *Adv Chronic Kidney Dis.* 2021;28(1):59-73. https://doi.org/10.1053/j.ackd.2021.03.005

Nephrology-Specific Indications for TPE

Autoantibodies are frequently associated with primary kidney diseases and are ideal candidates for TPE. Nevertheless, few kidney diseases have evidence to support the use of TPE, and, in the 2021 KDIGO glomerular diseases guideline, the only recommendation for TPE is for anti-GBM disease (KDIGO grade 1C). Other conditions in which TPE may be beneficial are presented as practice points. The category I renal indications based on the ASFA guidelines are reviewed in the following sections.

Anti-GBM Disease

Anti-GBM disease (ie, Goodpasture syndrome) is an autoimmune disorder in which IgG antibodies directed against the α3 chain of type IV collagen result in glomerulonephritis and/or alveolar hemorrhage. Often a rapidly progressive glomerulonephritis, kidney failure develops in approximately 55% of patients despite treatment.

A single randomized controlled trial (RCT) of 17 patients showed favorable kidney outcomes and improved survival with TPE. In 2001, it was reported that patients receiving dialysis at presentation with 100% crescents on biopsy did not experience recovery of kidney function. In 2018, a retrospective analysis of 123 patients confirmed these findings and further determined that those with ≥50% global glomerulosclerosis had adverse kidney outcomes. Therefore, the KDIGO glomerular diseases guideline recommends TPE except in patients who require dialysis with (1) 100% crescents or (2) >50% global glomerulosclerosis and no pulmonary hemorrhage.

The current ASFA recommendations are as follows:

- Management: Therapy with corticosteroids, cyclophosphamide, and TPE
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - Frequency: Daily
  - Replacement fluid: Albumin or frozen plasma if DAH is present
  - Duration: Minimum of 10-20 days and until resolution of active glomerular and/or pulmonary injury; some providers continue until antibody testing is negative, although the necessity of this approach has not been established with certainty; if seronegative disease at presentation, minimum of 10-20 days and until resolution of active organ injury

Returning to question 4, the best answer is (d), TPE should be continued for a minimum of 10-20 days and until resolution of active organ injury.

Additional Readings

- Levy JB, Turner AN, Rees AJ, Pusey CD. Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. *Ann Intern Med*. 2001;134(11):1033-1042. https://doi.org/10.7326/0003-4819-134-11-200106050-00009 ★ESSENTIAL READING
- van Daalen EE, Jennette JC, McAdoo SP, et al. Predicting outcome in patients with anti-GBM glomerulonephritis. *Clin J Am Soc Nephrol*. 2018;13(1):63-72. https://doi.org/10.2215/CJN.04290417

Catastrophic Antiphospholipid Syndrome

Catastrophic antiphospholipid syndrome (CAPS) is defined by the presence of antiphospholipid antibodies and multiple thromboses in at least 3 organ systems in less than 1 week. It typically affects small vessels of the kidneys, lungs, brain, heart, and skin, although large vessels can also be involved. Approximately 65% of episodes have a precipitating event.

The current ASFA recommendations are based on 5 case series involving 192 patients, and are as follows:

- Management: Anticoagulation, steroids, and TPE and/or IV immunoglobulin
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - Frequency: Daily or every other day
  - Replacement fluid: Frozen plasma or frozen plasma/albumin
  - Duration: Minimum of 3 to 5 sessions with longer-term duration based on clinical response

Additional Readings

- Rodríguez-Pintó I, Moitinho M, Santacreu I, et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of 500 patients from the International CAPS Registry. *Autoimmun Rev*. 2016;15(12):1120-1124. https://doi.org/10.1016/j.autrev.2016.09.010
- Legault K, Schunemann H, Hillis C, et al. McMaster RARE-Best practices clinical practice guideline on diagnosis and management of the catastrophic antiphospholipid syndrome. *J Thromb Haemost*. Published online June 7, 2018. https://doi.org/10.1111/jth.14192

Focal Segmental Glomerulosclerosis Following Kidney Transplant

The etiology of this primary podocytopathy remains unknown, but a circulating factor has been postulated. Recently, anti-nephrin antibodies have been implicated in the pathogenesis and may represent a target of TPE in this disorder for some patients. After transplant, the risks of non-postadaptive recurrence of focal segmental glomerulosclerosis (FSGS) are generally 20%-50% in the first allograft and 80%-100% in subsequent allografts. Despite treatment, 30%-60% of patients experience progression to kidney failure within 3-7 years. FSGS may recur a few hours to 2 years after transplant.

The current ASFA recommendations, based on 50 case series involving 628 patients and 4 controlled trials, are as follows:

- Management: Steroids, rituximab, and TPE and/or IV immunoglobulin
- TPE prescription:
  - TPE, lipoprotein apheresis, or immunoadsorption with regenerative adsorbers can be used; for TPE, plasma volume of 1-1.5 EPV
  - Frequency: Daily or every other day
  - Replacement fluid: Albumin
  - Duration: Three daily TPEs followed by 6 more sessions in the following 2 weeks; for lipoprotein apheresis, 2 sessions per week for 3 weeks followed by 6 weekly treatments

Additional Readings

- Kashgary A, Sontrop JM, Li L, et al. The role of plasma exchange in treating post-transplant focal segmental glomerulosclerosis: a systematic review and meta-analysis of 77 case-reports and case-series. *BMC Nephrol.* 2016;17(1):104. https://doi.org/10.1186/s12882-016-0322-7
- Raina R, Wang J, Sharma A, Chakraborty R. Extracorporeal therapies in the treatment of focal segmental glomerulosclerosis. *Blood Purif.* 2020;49(5):513-523. https://doi.org/10.1159/000506277 ★ESSENTIAL READING

Thrombotic Microangiopathy: Factor H Autoantibody–Mediated

Activation of the alternative pathway of complement is a cause of thrombotic microangiopathy (TMA). Genetic variants in the alternative pathway are present in approximately 60% of patients, and an autoantibody inhibiting complement factor H function is present in <10%.

TPE in combination with immunosuppression can be an effective therapy, as is treatment with a complement C5 antagonist. The current ASFA recommendations, based on 5 case series involving a total of 126 patients, are as follows:

- Management: TPE and/or eculizumab with immunosuppression
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - Frequency: Daily
  - Replacement fluid: Frozen plasma or frozen plasma/albumin
  - Duration: Until adequate clinical response or antibody titer reduced to less than clinical threshold (similar to immune TTP)

Additional Readings

- Sinha A, Gulati A, Saini S, et al. Prompt plasma exchanges and immunosuppressive treatment improves the outcomes of anti-factor H autoantibody-associated hemolytic uremic syndrome in children. *Kidney Int.* 2014;85(5):1151-1160. https://doi.org/10.1038/ki.2013.373 ★ESSENTIAL READING
- Iorember F, Nayak A. Deficiency of CFHR plasma proteins and autoantibody positive hemolytic uremic syndrome: treatment rationale, outcomes, and monitoring. *Pediatr Nephrol.* 2021;36(6):1365-1375. https://doi.org/10.1007/s00467-020-04652-x

Thrombotic Microangiopathy: Ticlopidine-Associated

Drug-induced TMA has been associated with numerous drugs, including but not limited to ticlopidine, calcineurin inhibitors, and gemcitabine. Ticlopidine usually presents with severely diminished ADAMTS13 levels (<10%) within 2 weeks of drug exposure, often with an autoantibody directed against ADAMTS13.

Current ASFA recommendations, based on 5 case series with a total of 174 patients, are as follows:

- Management: Drug discontinuation plus TPE
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - Frequency: Daily or every other day
  - Replacement fluid: Frozen plasma
  - Duration: Daily until recovery of hematologic parameters (similar to immune TTP)

Thrombotic Microangiopathy: TTP

TTP is a systemic thrombotic illness of small vessels that has a 90% mortality rate if untreated. Clinical characteristics include thrombocytopenia and microangiopathic hemolytic anemia (MAHA) in combination with deficiency of plasma ADAMTS13 activity (<10%). Because the activity assay may not be readily available, the PLASMIC score may help triage patients for TPE who are at high risk for ADAMTS13 deficiency. In most patients, IgG autoantibodies against ADAMTS13 are present. TPE aims to remove anti-ADAMTS13 antibodies while replacing ADAMTS13 activity through frozen plasma.

Current ASFA recommendations, based on 7 RCTs involving 301 patients and 5 clinical trials with 270 patients, are as follows:

- Management: Steroids and TPE; adjunct therapies can be used in refractory cases; if rituximab is used, a 24-hour interval should be allowed between infusion and TPE; caplacizumab (a monoclonal antibody against von Willebrand factor) is also available
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - Frequency: Daily
  - Replacement fluid: Frozen plasma
  - Duration: Daily until platelet count is $>150 \times 10^3/\mu L$ and lactate dehydrogenase level is near normal for 2-3 consecutive days

Additional Readings

- Sarode R, Bandarenko N, Brecher ME, et al. Thrombotic thrombocytopenic purpura: 2012 American Society for Apheresis (ASFA) consensus conference on classification, diagnosis, management, and future research. *J Clin Apher.* 2014;29(3):148-167. https://doi.org/10.1002/jca.21302
- Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. *Lancet Haematol.* 2017;4(4):e157-e164. https://doi.org/10.1016/S2352-3026(17)30026-1 ★ESSENTIAL READING
- Zheng XL, Vesely SK, Cataland SR, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. *J Thromb Haemost.* 2020;18(10):2496-2502. https://doi.org/10.1111/jth.15010 ★ESSENTIAL READING

Living-Donor ABO-Compatible Kidney Transplant, Antibody-Mediated Rejection or Desensitization

Antibodies to donor HLA and non-HLA antigens may preclude living-donor transplant and result in antibody-mediated rejection (AMR) after transplant. To permit successful transplant via desensitization, conditioning regimens that include TPE may reduce circulating donor-specific antibodies to a level insufficient for cytotoxicity. Similarly, TPE is important in the management of acute AMR after transplant. Although TPE is a mainstay of AMR management, the optimal therapeutic approach remains unknown. The current ASFA recommendations are based on three RCTs involving 61 patients and 8 clinical trials with 342 patients (for desensitization from living donors, TPE is guided by 6 clinical trials [583 patients]) and are as follows:

- Management: AMR can be treated with TPE, double filtration plasmapheresis, and immunoadsorption, always in conjunction with other immunosuppressive drugs; desensitization regimens include IV immunoglobulin, rituximab, and optional additional immunosuppression
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - Frequency: Daily or every other day
  - Replacement fluid: Albumin or frozen plasma plus IV immunoglobulin 100-200 mg/kg
  - Duration: For AMR, TPE is usually daily or every other day for 5 or 6 sessions or based on clinical outcomes and decrease in donor-specific antibody titers; for those receiving TPE for desensitization, TPE is performed until cross-match is less than institution-dependent thresholds or postoperatively for a minimum of 3 procedures

Additional Readings

➢ Wan SS, Ying TD, Wyburn K, Roberts DM, Wyld M, Chadban SJ. The treatment of antibody-mediated rejection in kidney transplantation: an updated systematic review and meta-analysis. *Transplantation*. 2018;102(4):557-568. https://doi.org/10.1097/TP.0000000000002049 ★ESSENTIAL READING

➢ Simmons SC, Adamski J, Berg M, et al. The apheresis management of patients undergoing transplantation: a concise review. *Transfusion*. 2019;59(5):1863-1869. https://doi.org/10.1111/trf.15153

Living Donor ABO-Incompatible Kidney Transplant, Desensitization

If untreated, ABO-incompatible kidney transplants are at risk of hyperacute and acute AMR. The use of TPE in the peritransplant period has been proven to decrease anti-A and/or anti-B titers and facilitate graft survival. Short- and long-term outcomes are similar in ABO-incompatible and ABO-compatible transplants, although BK virus–associated nephropathy is a greater risk in ABO-incompatible kidney transplants. In living-donor kidney transplants, A2 donors are preferred over A1 because the risk for rejection is lower as a result of reduced expression of the A antigen on red blood cells and endothelium.

Current ASFA recommendations, based on 26 case series involving 911 patients, are as follows:

- Management: TPE, immunoadsorption
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - Frequency: Daily or every other day
  - Replacement fluid: Albumin or frozen plasma (should be compatible with recipient and donor ABO type); frozen plasma is used before and after surgery
  - Duration: Until cross-match is less than institution-dependent thresholds before transplant

Vasculitis, Antineutrophil Cytoplasmic Antibody–Associated

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) is a necrotizing small-vessel vasculitis in which few or no immune deposits are apparent in kidney biopsy specimens. The kidneys are involved in 70% of cases and the lungs in >50%. The most common kidney manifestation is rapidly progressive glomerulonephritis, and lung involvement can range from asymptomatic pulmonary lesions to life-threatening DAH. In its clinical presentation, the pulmonary-renal syndrome associated with ANCA may have similarities to anti-GBM disease. In cases in which ANCA and anti-GBM are present, the initial therapy should follow guidelines for management of anti-GBM disease. An induction regimen with steroids and cyclophosphamide or rituximab leads to remission in as many as 90% at 6 months. Maintenance therapy can include rituximab, azathioprine, or mycophenolate mofetil, sometimes in combination with low-dose steroids.

In 2007, results were reported from the MEPEX trial of 137 patients with AAV randomized to receive standard care (oral steroids and cyclophosphamide) plus IV methylprednisolone or TPE. MEPEX enrolled patients with severe kidney injury based on Scr concentration >5.8 mg/dL or dialysis treatment. In patients receiving TPE, there were 22% and 24% lower risks of kidney failure at 3 and 12 months, respectively. In 2020, the PEXIVAS trial randomized 704 patients with an estimated glomerular filtration rate <50 mL/min/1.73 m^2 or pulmonary hemorrhage to receive 0 or 7 sessions of TPE in combination with induction pulse methylprednisolone and cyclophosphamide or rituximab. The median Scr concentration was 3.8 mg/dL, 20% were receiving dialysis, and 41% had pulmonary involvement. There was no difference in the primary outcome by 12 months. In subgroup analysis, however, TPE appeared favorable in those with pulmonary hemorrhage or severe kidney disease (Scr >5.7 mg/dL), although this was

Table 6. Characteristics of Common Drugs Removed by TPE

Drug	Protein Binding, %	Volume of Distribution, L/kg
Acetaminophen	<3	0.1
Acetylsalicylic acid[a]	80-90	0.1-0.2
Azathioprine	30	0.6
Cefazolin[a]	80	0.13-0.22
Ceftriaxone[a]	90	0.12-0.18
Cyclosporine	90-98	13
Cyclophosphamide	23	0.8
Digoxin	20-30	5-8
Eculizumab	NA	5-8
Glyburide[a]	99	0.16-0.3
Heparin[a]	>90	0.06-0.1
Ibuprofen[a]	99	0.15-0.17
Levothyroxine[a]	90	0.1-0.2
Prednisone-prednisolone	90-95	0.6-0.7
Rituximab	NA	3.1-4.5
Valproic acid[a]	90	0.19-0.23
Tobramycin	10	0.25
Vancomycin	70	0.39
Verapamil[a]	90	NA
Warfarin[a]	97-99	0.11-0.15

Abbreviations: NA, not applicable; TPE, therapeutic plasma exchange.
Based on information in Ibrahim & Balogun, 2012 (*Semin Dial;* https://doi.org/10.1111/j.1525-139x.2011.01030.x) and Mahmoud et al, 2021 (*Neurocrit Care;* https://doi.org/10.1007/s12028-020-00989-1).
[a]Drugs that are particularly amenable to removal by TPE.

not statistically significant. In 2020, the ASFA guidelines were updated to maintain the category I indication for DAH, even though Scr concentration ≥5.7 mg/dL or dialysis was changed to category II. The current ASFA recommendations are based on 10 RCTs involving 1,091 patients and 5 clinical trials with 345 patients (before the publication of PEXIVAS) and are as follows:

- Management: Induction with pulsed methylprednisolone and rituximab or cyclophosphamide with or without TPE
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - Frequency: Daily or every other day
  - Replacement fluid: Albumin or frozen plasma if DAH present
  - Duration: Seven sessions over a median period of 14 days (as many as 12 sessions have been reported)

Additional Readings

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➢ Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe anca-associated vasculitis. *N Engl J Med.* 2020;382(7):622-631. https://doi.org/10.1056/NEJMoa1803537 ★ESSENTIAL READING

➢ Balogun RA, Sanchez AP, Klingel R, et al. Update to the ASFA guidelines on the use of therapeutic apheresis in ANCA-associated vasculitis. *J Clin Apher.* 2020;35(5):493-499. https://doi.org/10.1002/jca.21820

Special Considerations

Concomitant Use of Angiotensin-Converting Enzyme Inhibitors

Because angiotensin-converting enzyme inhibitors block the degradation of bradykinins, hypotension can occur if kinins are activated during apheresis in patients taking these medications. This was reported most commonly with the use of hydrophilic, electronegative membranes such as the polyacrylonitrile AN69 filter. Dextran sulfate systems, albumin replacement fluids, and the Plasmaflo OP filter (polyethylene) have also been linked to this reaction. Many practitioners continue to hold angiotensin-converting enzyme inhibitors 24-48 hours before TPE, particularly if albumin replacement or membrane filtration TPE is used.

Drug Removal

Plasma exchange may affect drug concentrations through direct removal or via removal of metabolizing enzymes. This is important for drug dosing and determining whether extracorporeal therapy can be beneficial in treating intoxications. In general, all daily drug dosing should be administered after the TPE session. TPE is most likely to remove drugs with a very low volume of distribution (<0.2 L/kg) and high protein binding (>80%). Glyburide intoxication, for example, would be more amenable to treatment with TPE than cyclosporine (Table 6).

Specific immunosuppressants are worth discussing in more detail. Prednisone is converted to prednisolone, which is highly protein-bound with a moderately low volume of distribution. TPE removes only 1% of prednisolone, and additional doses are not required after TPE. Cyclosporine and tacrolimus are predominantly intracellular and not affected by plasma exchange. Cyclophosphamide is unlikely to be removed by TPE. Rituximab has limited data, although 47%-54% may be removed when TPE is performed 24-72 hours after administration. Most of the effect occurs in 12-24 hours, so a dose can be administered after a TPE session with delay of the next session for 24-48 hours.

There are limited data on the effect of TPE on many old and new drugs. Factors such as endogenous clearance and extravascular distribution influence their clearance with TPE but may not be widely available. According to some studies, additional doses of aspirin, phenytoin, propranolol, and thyroxine may be needed after TPE.

Additional Readings

➢ Ibrahim RB, Balogun RA. Medications in patients treated with therapeutic plasma exchange: prescription dosage,

timing, and drug overdose. *Semin Dial*. 2012;25(2):176-189. https://doi.org/10.1111/j.1525-139X.2011.01030.x

➢ Puisset F, White-Koning M, Kamar N, et al. Population pharmacokinetics of rituximab with or without plasmapheresis in kidney patients with antibody-mediated disease. *Br J Clin Pharmacol*. 2013;76(5):734-740. https://doi.org/10.1111/bcp.12098

➢ Mahmoud SH, Buhler J, Chu E, Chen SA, Human T. Drug dosing in patients undergoing therapeutic plasma exchange. *Neurocrit Care*. 2021;34(1):301-311. https://doi.org/10.1007/s12028-020-00989-1 ★ESSENTIAL READING

Intoxications

Case 3: *A 50-kg 35-year-old man with history of hypothyroidism is found unresponsive. In the emergency department, he is diaphoretic and lethargic with a temperature of 101 °F, rapid atrial fibrillation with heart rate of 170 beats/min, and blood pressure 94/60 mm Hg. He is given lactated Ringer solution, IV amiodarone, and IV metoprolol. The patient experiences cardiac arrest with return of spontaneous circulation after 2 rounds of cardiopulmonary resuscitation. Bedside echocardiogram shows severe global dysfunction. Hematocrit level is 38%, and thyroid function tests reveal an undetectable thyroid-stimulating hormone level, free thyroxine level >60 ng/dL (reference range, 0.8-1.8 ng/dL), and free triiodothyronine level >50 pg/mL (reference range, 2-4.9 pg/mL). Emergent TPE is planned to treat thyroid storm with cardiogenic shock thought to have resulted from levothyroxine intoxication.*

Question 5: Which one of the following characteristics of levothyroxine make it amenable to removal by TPE?

(a) Volume of distribution >1 L/kg
(b) Large intracellular concentration
(c) Protein binding of 90%
(d) Slow release from tissue

For the answer to the question, see the following text.

In addition to low volume of distribution (<0.2 L/kg) and high protein binding (>80%), the time between drug/toxin administration and TPE initiation determines removal by apheresis. Routinely, albumin is used as the replacement fluid to facilitate binding and trapping of the substance in the blood compartment for elimination. However, there are some substances that may preferentially bind to plasma proteins other than albumin. Examples include dipyridamole, quinidine, imipramine, propranolol, and chlorpromazine, which have strong affinities for α-1-acid glycoprotein. Some venoms may cause coagulopathy and microangiopathy, and frozen plasma can restore ADAMTS13 and coagulation factors. In these examples, frozen plasma is preferred. TPE of 1-2 plasma volumes daily continues until clinical symptoms abate and there is cessation of delayed toxin release from tissues.

For question 5, option (c), protein binding of 90%, is the best answer. The volume of distribution of levothyroxine is 0.1-0.2 L/kg, with 90% protein-bound (Table 6), both of which are favorable characteristics for removal by TPE.

Additional Reading

➢ King JD, Kern MH, Jaar BG. Extracorporeal removal of poisons and toxins. *Clin J Am Soc Nephrol*. 2019;14(9):1408-1415. https://doi.org/10.2215/CJN.02560319 ★ESSENTIAL READING

Simultaneous Extracorporeal Therapies

Patients who require TPE may also need other extracorporeal therapies such as kidney replacement therapy or ECMO. When the procedures are continuous, they can be performed independently through separate vascular accesses or in parallel through the same access. Potential limitations of the latter approach include access pressure alarms, circuit clotting, and risk for air embolism.

In patients receiving intermittent hemodialysis for kidney failure, alkalemia may result from repeated apheresis treatments when frozen plasma is the primary replacement fluid. Therefore, if TPE and dialysis are required on the same day, TPE should be performed first to allow subsequent dialysis to correct the blood pH or hypervolemia resulting from TPE. Importantly, TPE should not be used as an ultrafiltration procedure by intentionally replacing less than the exchanged volume.

In ECMO, inflow to the TPE circuit can originate before or after the oxygenator. Plasma, heparin, and calcium gluconate infusions may be attached to this port via a stopcock. Return from the TPE circuit connects before the oxygenator to prevent air embolism. If the returning blood enters before the centrifugal pump, resistance tubing may be needed to maintain adequate return pressures. Because the ECMO circuit is anticoagulated with heparin, citrate is not used, and frozen plasma is the preferred replacement fluid. High circuit pressures may be a limitation, and lower ECMO blood flow rates can help run both circuits simultaneously.

Additional Readings

➢ Laverdure F, Masson L, Tachon G, Guihaire J, Stephan F. Connection of a renal replacement therapy or plasmapheresis device to the ECMO circuit. *ASAIO J*. 2018;64(1):122-125. https://doi.org/10.1097/MAT.0000000000000621

➢ Manuel L, Fong LS, Lahanas A, Grant P. How to do it: Plasmapheresis via venoarterial extracorporeal

Table 7. Complications Associated With TPE

Complication	Mechanism	Frequency
Access-related		
Peripheral access	Hematomas, nerve damage, sclerosis of veins/arteries	1.48%
CVC	Thrombosis, infections, pneumothorax, arterial puncture, air embolism	0.11%-0.36% (more complications in subclavian [60%] vs jugular [20%] CVCs)
Ports	Early: pneumothorax, hematomas, arrhythmia, arterial puncture; late: thrombosis, port-pocket infection, pinch-off syndrome	18%
AVF/AVG	Thrombosis	12%-20%
	Inadequate maturation	60%
Anticoagulation-related		
Hypomagnesemia	Citrate chelation	NA
Thrombocytopenia	Heparin-induced thrombocytopenia	1%-5% (not specific to TPE)
Procedure-related		
Anemia	Hematocrit may decrease 10% due to intravascular expansion with hyperoncotic fluids; hemolysis if hypo-oncotic priming solutions used	NA
Hypotension, dyspnea, chest pain	Complement-mediated membrane bioincompatibility; ethylene oxide hypersensitivity	0.4%-15%
Thrombocytopenia	Loss of platelets in the discarded plasma, circuit clotting, or dilutional effect by replacement fluid	NA
Vitamin deficiencies	Depletion of protein-bound vitamins (A, B_6, B_{12}, C, and E and β-carotene) of 24%-48% with rebound to pretreatment levels within 24 h	NA
Replacement fluid–related		
Anaphylactoid reactions	Transfusion of IgA in donor plasma to patients with selective IgA deficiency; contamination with bacteria, endotoxins, pyrogens; presence of prekallikrein activator and bradykinin (ACEI); antibodies to polymerized albumin (rare)	0.02%-0.07%
Coagulopathy	Depletion of coagulation factors and its inhibitors related to albumin replacement alone (Table 4)	0.06%-0.14% for thrombosis, 0.06% for bleeding
Electrolyte/acid base abnormalities	Hypokalemia (albumin), hypocalcemia (frozen plasma), hypomagnesemia (frozen plasma), metabolic alkalosis (frozen plasma)	9%-19.6% for hypocalcemia, 0.03% for alkalosis
Infection	Hypogammaglobulinemia (albumin), viral transmission (frozen plasma)	NA
Transfusion-related lung injury	Transfusion of donor antibodies (frozen plasma)	NA
Hypervolemia	Administration of replacement fluid	NA

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AVF, arteriovenous fistula; AVG, arteriovenous graft; CVC, central venous catheter; IgA, immunoglobulin A; NA, not applicable; TPE, therapeutic plasma exchange.

membrane oxygenation circuit for thyroid storm. *Ann Med Surg (Lond)*. 2021;67:102485. https://doi.org/10.1016/j.amsu.2021.102485

Complications

Case 4: *A 22-year-old woman with kidney failure caused by primary FSGS is seen 3 days after deceased-donor kidney transplant. She has persistent sanguineous drainage from Jackson-Pratt drains. Immunosuppression includes tacrolimus twice daily, mycophenolate mofetil 1,000 mg twice daily, and prednisone 10 mg/d. Laboratory testing demonstrates an increase in urinary protein-creatinine ratio (from 0.2 to 3.9 g/g) with worsening allograft function. You suspect recurrence of FSGS and initiate membrane filtration TPE with a Prismaflex TPE-2000 filter and frozen plasma replacement while awaiting results of allograft biopsy.*

Question 6: Eighty minutes into her TPE session, the patient reports muscle cramps and paresthesia. Which one of the following is the most likely cause of her symptoms?

a. Citrate-induced electrolyte abnormalities
b. Bradykinin generation caused by interaction of tacrolimus with the filter

c. Ethylene oxide hypersensitivity
d. IgA-induced anaphylactoid reaction

For the answer to the question, see the following text.

TPE is generally a safe procedure, but the practitioner must be vigilant for numerous potential complications (Table 7). Hypocalcemia is the most common complication and is more frequent with frozen plasma (20%) than albumin (9%). Patients with reduced renal or liver excretion of citrate are more susceptible to the development of citrate toxicity. Different interventions such as the addition of IV calcium to albumin bottles, slowing the citrate infusion, or using ACD-B have been reported, but most practices provide intermittent IV calcium or a continuous IV calcium infusion with the returning blood. Hypokalemia can result from the approximately 25% reduction in blood potassium concentration seen with albumin replacement. Similar to calcium, the addition of potassium to the albumin bottle can be helpful in preventing this. Hypotension has been reported in 0.4%-15% of treatments and is more common with combination albumin–saline solution replacement. Potential mechanisms include delayed or inadequate volume replacement, vasovagal episodes, low oncotic fluid replacement, anaphylaxis, transfusion-associated lung injury, arrhythmia, bradykinin reactions, bleeding from vascular access, and cardiovascular collapse. If an 80:20 ratio of albumin to saline solution is used, one approach to minimize hypotension is to replace at 110% of the volume exchanged. The mortality rate associated with apheresis is low, ranging from 0.03% to 0.05%, and is primarily related to the underlying disease(s).

For question 6, answer (a), citrate-induced electrolyte abnormalities, is the best answer. Frozen plasma is 14% citrate, and the risk for citrate-induced hypocalcemia and hypomagnesemia is higher in membrane filtration TPE than in centrifugation TPE. Bradykinin generation was most common with older polyacrylonitrile membranes in the setting of angiotensin-converting enzyme inhibitor use (not tacrolimus), although some albumin lots can also have increased concentrations of prekallikrein-activating factor activity. Ethylene oxide from membrane sterilization or transfusion of IgA present in frozen plasma into patients with selective IgA deficiency can result in anaphylactoid reactions. Paresthesia, however, is more commonly a result of hypocalcemia.

Additional Readings

- Kaplan A. Complications of apheresis. *Semin Dial*. 2012;25(2):152-158. https://doi.org/10.1111/j.1525-139X.2011.01026.x ★ESSENTIAL READING
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- Coirier V, Lesouhaitier M, Reizine F, et al. Tolerance and complications of therapeutic plasma exchange by centrifugation: a single center experience. *J Clin Apher*. 2022;37(1):54-64. https://doi.org/10.1002/jca.21950

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Support: None.

Financial Disclosure: Dr Sperati reports membership in the American Board of Internal Medicine (ABIM) Nephrology Longitudinal Knowledge Assessment Approval Committee and receipt of honoraria from Alexion Pharmaceuticals for serving on data safety monitoring boards. Dr Bloch reports personal fees and nonfinancial support from Terumo BCT and Abbott Laboratories outside of the submitted work and membership in the US Food and Drug Administration (FDA) Blood Products Advisory Committee. Dr Cervantes declares that she has no relevant financial interests.

Disclaimer: No ABIM examination questions are shared or otherwise disclosed in this article. Any views or opinions that are expressed in this manuscript are those of the authors, based on their own scientific expertise and professional judgment; they do not necessarily represent the views of either the Blood Products Advisory Committee or the formal position of the FDA, and also do not bind or otherwise obligate or commit either Advisory Committee or the Agency to the views expressed.

Peer Review: Received August 10, 2022, in response to an invitation from the journal. Evaluated by 3 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form October 19, 2022.