Therapeutic PE in critically ill patients with kidney diseases

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STATE-OF-THE-ART REVIEW

Therapeutic apheresis in kidney diseases: an updated review

Yi-Yuan Chen*, Xin Sun*, Wei Huang, Fang-Fang He and Chun Zhang

Department of Nephrology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Besides conventional medical therapies, therapeutic apheresis has become an important adjunctive or alternative therapeutic option to immunosuppressive agents for primary or secondary kidney diseases and kidney transplantation.

The available therapeutic apheresis techniques used in kidney diseases, including **plasma exchange**, **double-filtration plasmapheresis**, **immunoadsorption**, and **low-density lipoprotein apheresis**.

Plasma exchange is still the leading extracorporeal therapy.

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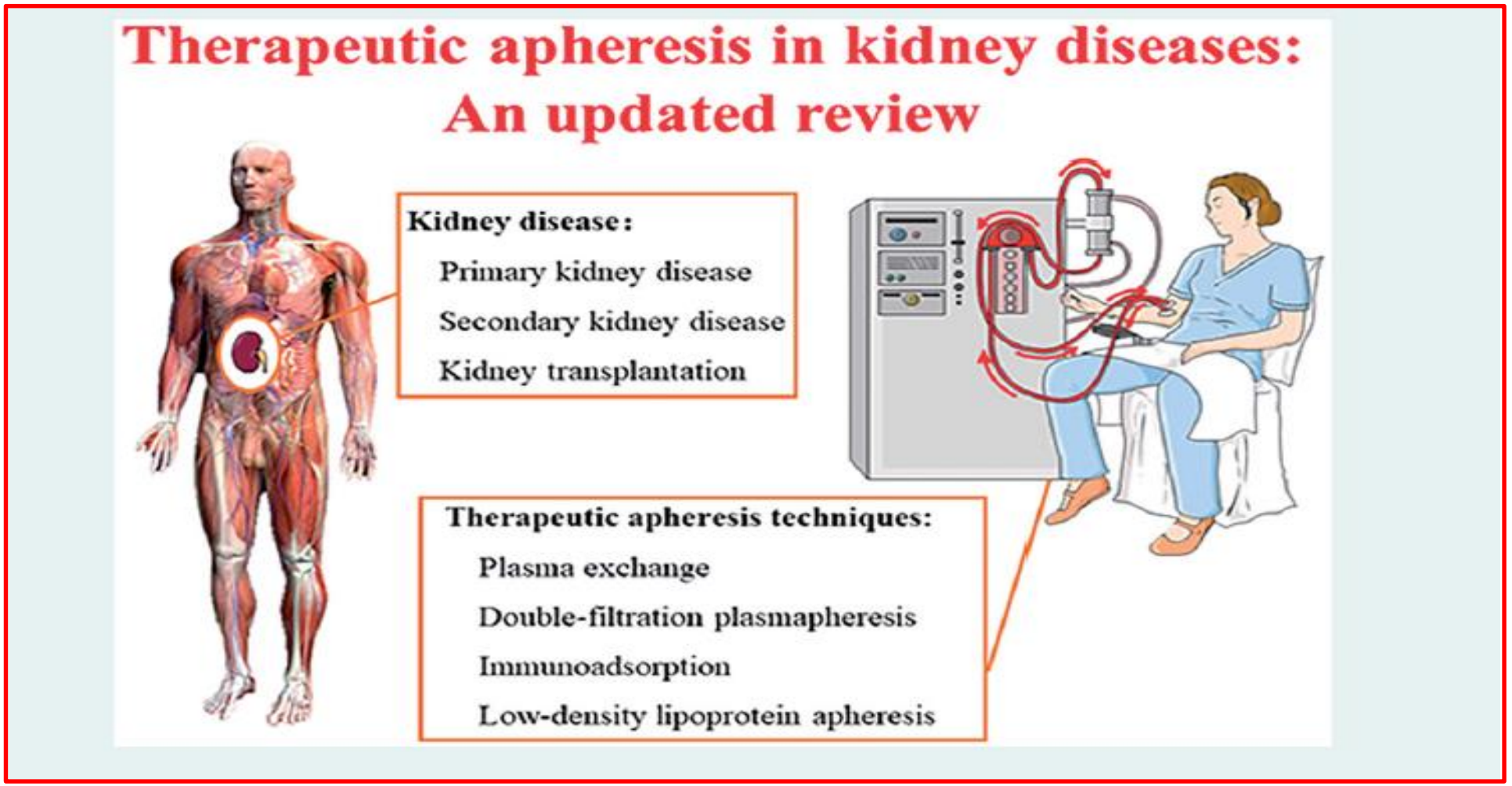


Table 1. Apheresis Modalities

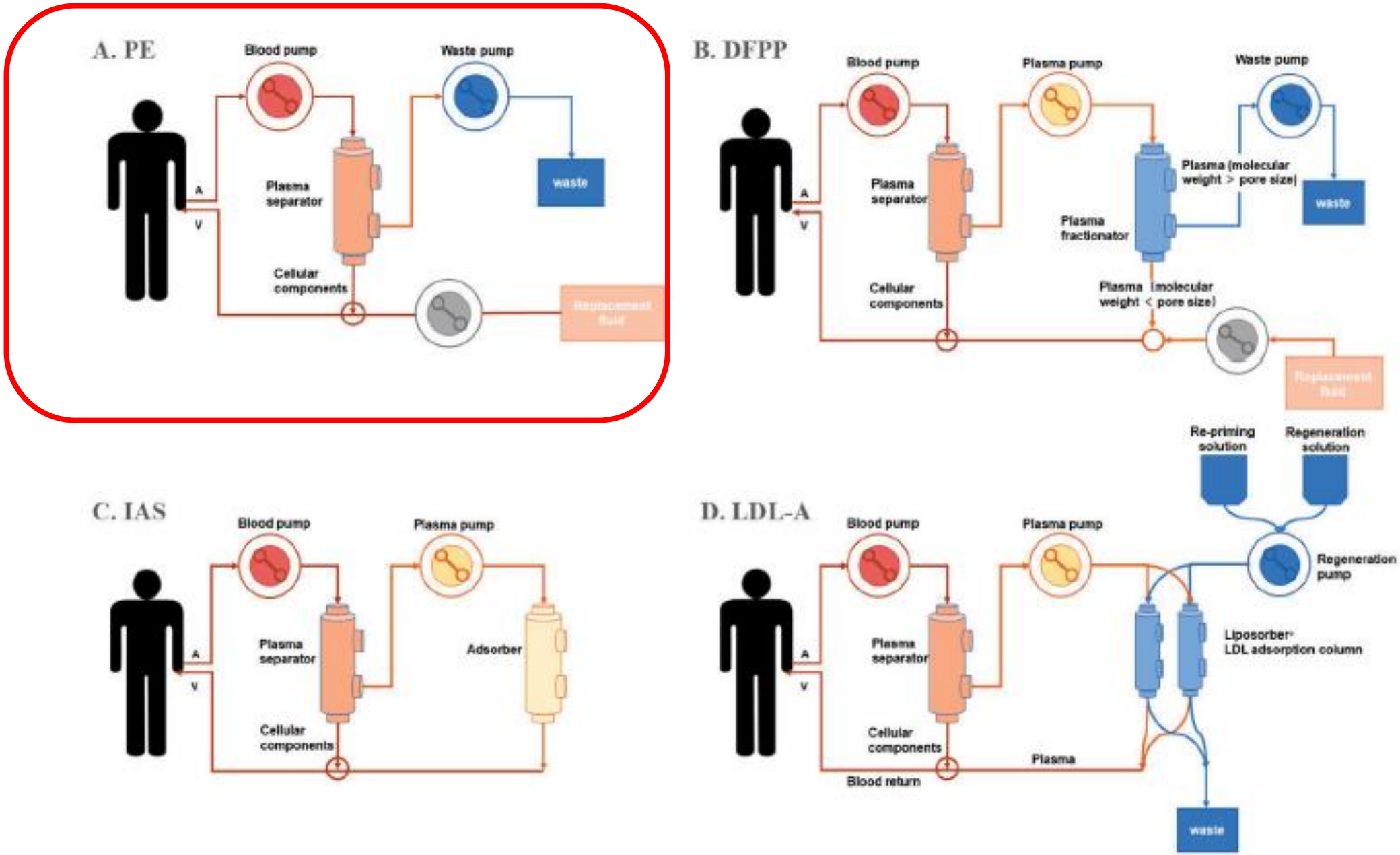
Procedure	Target Molecule
Adsorptive cytapheresis	Monocytes, granulocytes
$ß_2$-microglobulin column	$ß_2$-microglobulin
Double filtration plasmapheresis	Autoantibodies, immune complexes, lipoproteins
Erythrocytapheresis	Red blood cells
Extracorporeal photopheresis	Buffy coat (white blood cells and platelets)
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.

Plasma Separation by TPE

TPE is an extracorporeal blood purification technique designed for the removal of large molecular weight substances from the plasma.

A single plasma volume exchange will lower plasma macromolecules levels by 60% & an exchange equal to 1.5 times will lower plasma level by 75%.


A. PE
Blood pump
Waste pump
Plasma separator
waste
A
V
Cellular components
Replacement fluid
B. DFPP
Blood pump
Plasma pump
Waste pump
Plasma separator
Plasma fractionator
Plasma (molecular weight > pore size)
waste
A
V
Cellular components
Plasma (molecular weight < pore size)
Replacement fluid
Re-priming solution
Regeneration solution
C. IAS
Blood pump
Plasma pump
Plasma separator
Adsorber
A
V
Cellular components
D. LDL-A
Blood pump
Plasma pump
Regeneration pump
Plasma separator
Liposorber® LDL adsorption column
A
V
Cellular components
Plasma
Blood return
waste

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Core Curriculum in Nephrology

AJKD

Therapeutic Plasma Exchange: Core Curriculum 2023

C. Elena Cervantes, Evan M. Bloch, and C. John Sperati

Mechanisms of TPE

1-Removal of a pathogenic substance from the plasma

Removal of antibodies
Removal of immune complexes
Removal of cytokines and chemokines

2-Delivery of large amount of deficient plasma components

Replacement of missing plasma components

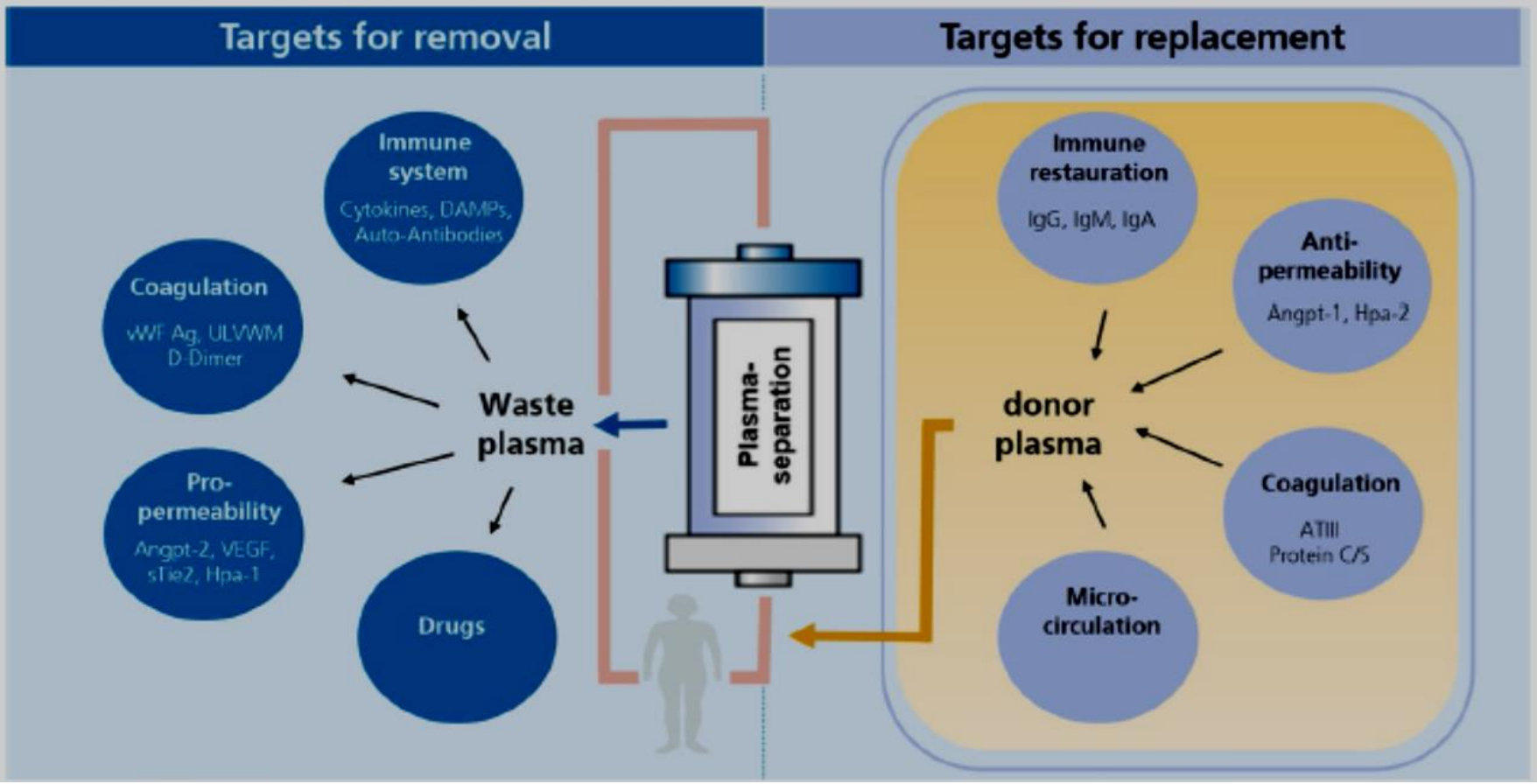

Targets for removal
Targets for replacement
Immune system
Cytokines, DAMPs, Auto-Antibodies
Coagulation
vWF Ag, ULVWM D-Dimer
Pro-permeability
Angpt-2, VEGF, sTie2, Hpa-1
Drugs
Waste plasma
Plasma-separation
Immune restauration
IgG, IgM, IgA
Anti-permeability
Angpt-1, Hpa-2
donor plasma
Coagulation
ATIII
Protein C/S
Micro-circulation

Table 2 Circulating factors that might be modulated by therapeutic plasma exchange

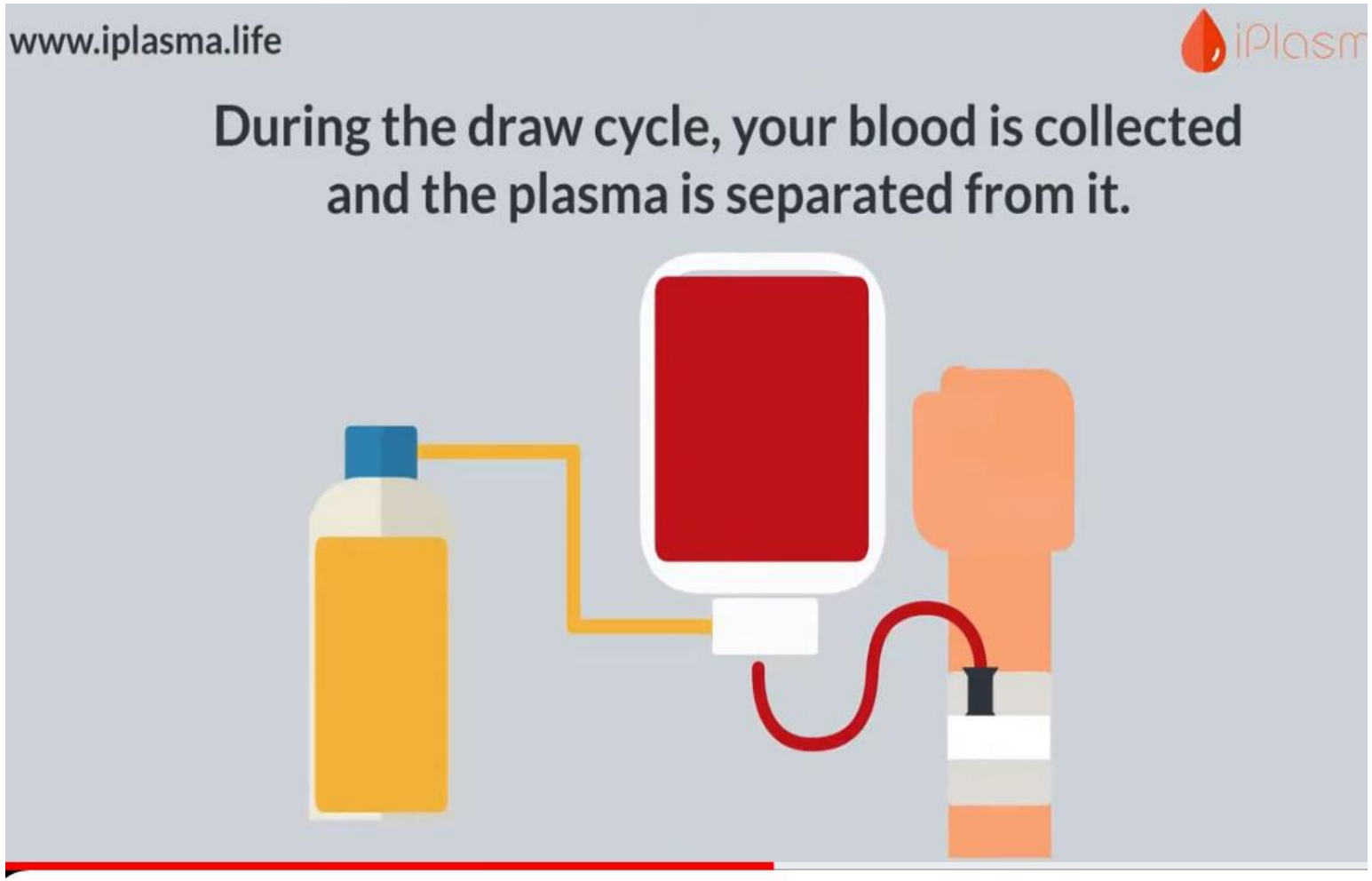
Removal

Potential target	Role	Disease	Available data
Cytokines	Inflammation	Sepsis, SIRS	Experimental
Autoantibodies (e.g. ANCA)	Autoimmune	vasculitis, Goodpasture's syndrome	SOC
Donor-specific antibodies	Rejection	Transplantation	SOC, expert opinion
Immunoglobulins	Hyperviscosity	Hyperviscosity syndrome	SOC
Angiopoietin-2	Permeability	ARDS, sepsis	OBS
vWF antigen	Coagulopathy	Sepsis, DIC	OBS
Heparanase-1	Glycocalyx shedding	Systemic inflammation, Covid-19	OBS
Active viral particles (HSV, EBV)	infectious diseases	Virus-induced acute liver failure	CR
Heparin/PF4 antibody	Coagulation	Heparin-induced thrombo-cytopenia	CS

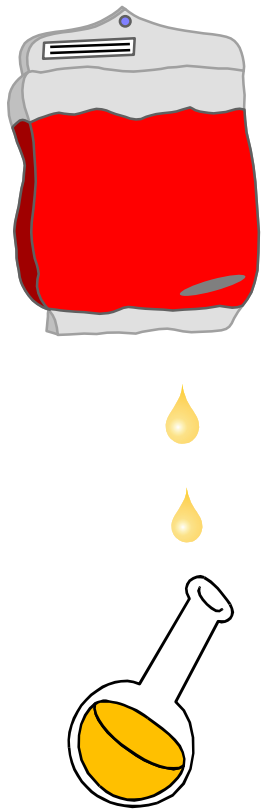
Replacement

Potential target	Role	Disease	Available data
ADAMTS13	vWF cleaving protease	TTP	RCT, SOC
Heparanase-2	Glycocalyx stabilisation	Systemic inflammation, Covid-19	OBS
Immunoglobulins	Ig deficiencies	Infection	OBS
Angiopoietin-1	Anti-permeability	Sepsis, systemic inflammation	OBS
Protein C	Coagulation, microcirculation	Sepsis, purpura fulminans	OBS
Coagulation factors	Coagulopathy/DIC	Investigated in acute liver failure	RCT

ANCA anti-neutrophil cytoplasmic antibody, *vWF* von Willebrand factor, *PF4* platelet factor4, *SIRS* systemic inflammatory response syndrome, *ARDS* acute respiratory distress syndrome, *DIC* disseminated intravascular coagulopathy, *HSV* herpes simplex virus, *EBV* Epstein–Barr virus, *ADAMTS13* A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member13; *TTP* thrombotic thrombocytopenic purpura, *SOC* standard of care, *OBS* observational study, *CR* case report, *CS* case series, *RCT* randomized controlled trial


www.iplasma.life
iPlasm
During the draw cycle, your blood is collected
and the plasma is separated from it.

Plasma Separation by TPE



In principle there are 2 methods how to separate plasma

Centrifugation

Separation of plasma by centrifugal power

Filtration

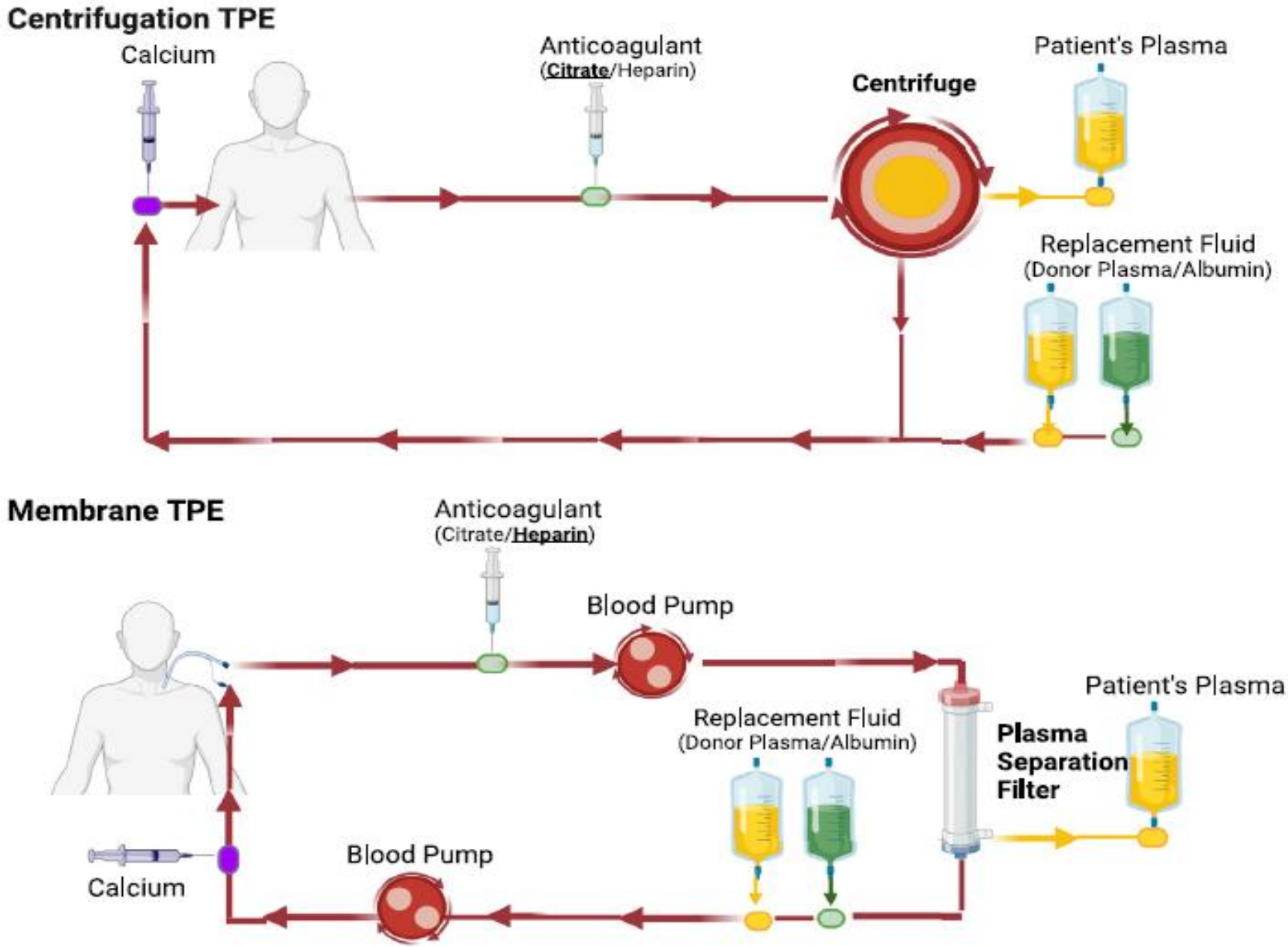
Separation of plasma by membrane filter

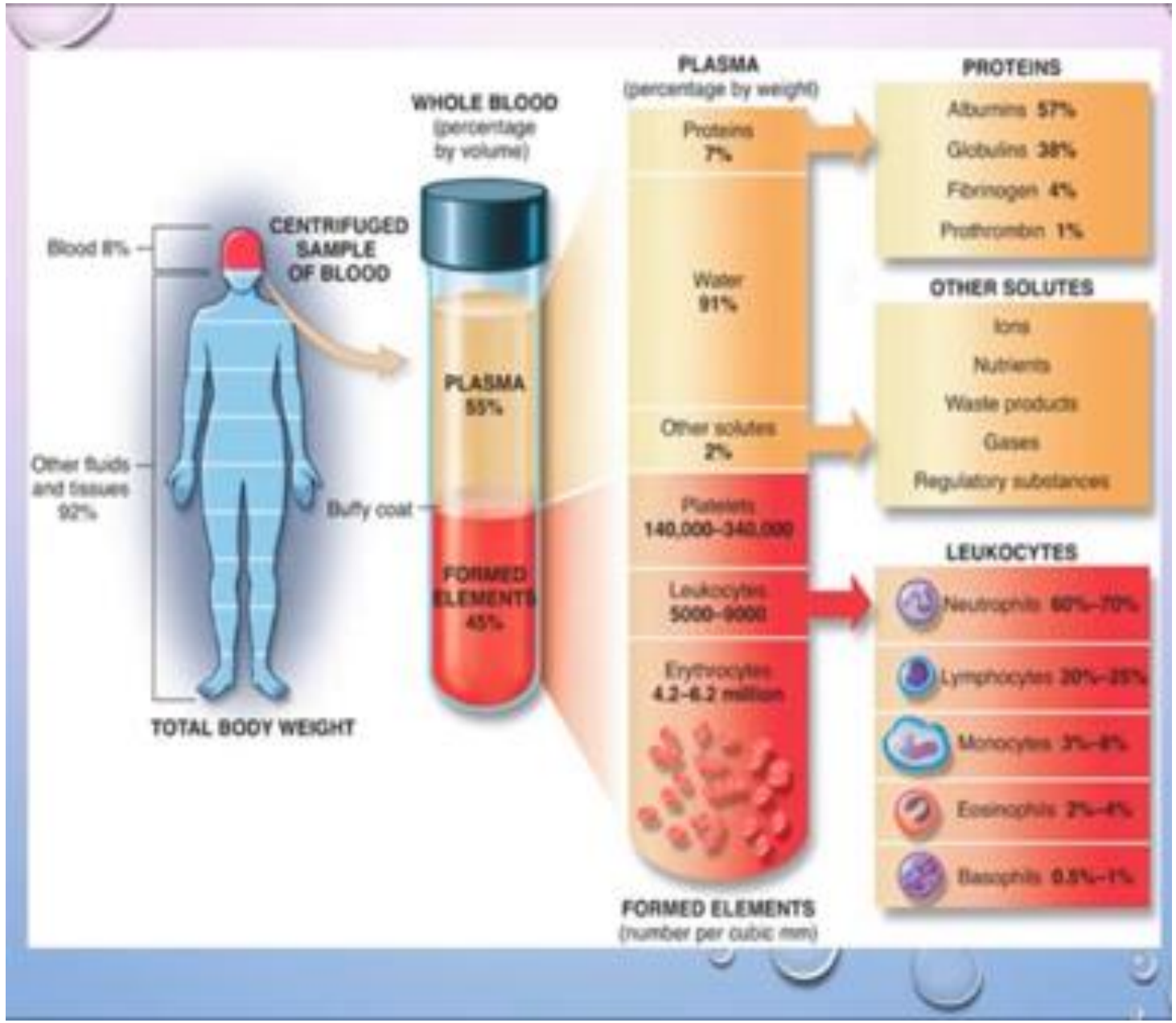
Machine

During TPE, the plasma can be separated from the corpuscular components of the blood by Centrifugation, Membrane filtration , or both.

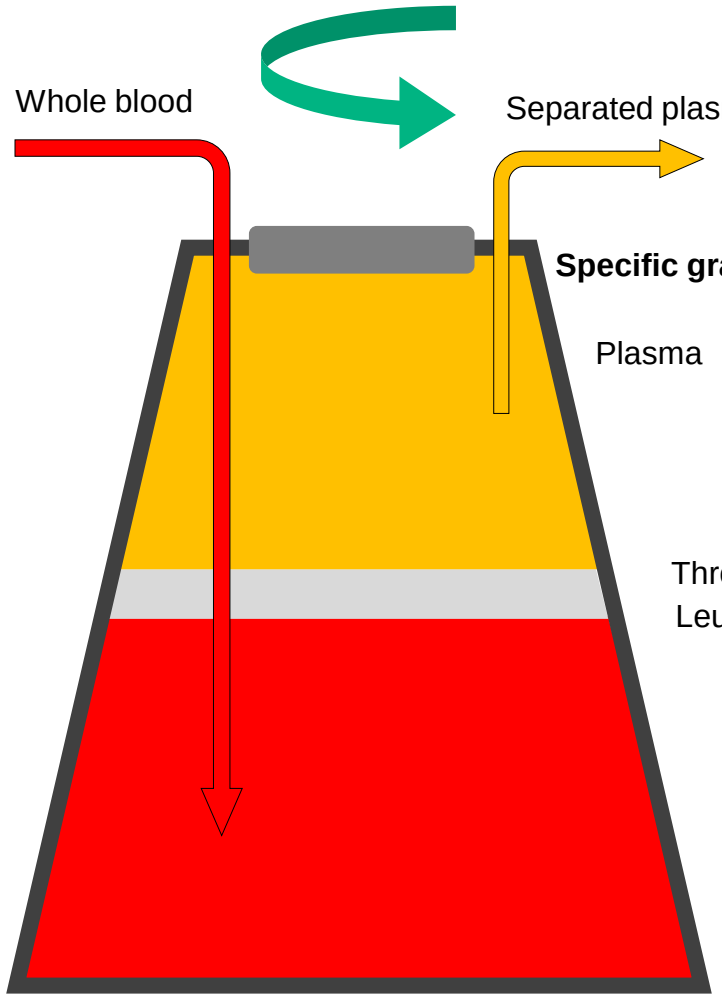
Centrifugation is based on the differences in density of the various blood components. cTPE is achieved using a rapidly rotating centrifuge which separates plasma from the rest of blood based on density & centrifugal force.
Centrifugation is the apheresis method employed when specific blood fractions are targeted.

Filtration takes advantage of differences in particular size to separate plasma. mTPE is achieved by a hollow fiber which separates plasma from the rest of blood based on pore size.
Plasma constituents are nonselectively removed across a semipermeable membrane.


Centrifugation TPE
Calcium
Anticoagulant
(Citrate/Heparin)
Centrifuge
Patient's Plasma
Replacement Fluid
(Donor Plasma/Albumin)
Membrane TPE
Anticoagulant
(Citrate/Heparin)
Blood Pump
Patient's Plasma
Replacement Fluid
(Donor Plasma/Albumin)
Plasma
Separation
Filter
Blood Pump
Calcium


WHOLE BLOOD
(percentage by volume)
CENTRIFUGED SAMPLE OF BLOOD
Blood 8%
Other fluids and tissues 92%
PLASMA 55%
Buffy coat
FORMED ELEMENTS 45%
TOTAL BODY WEIGHT
PLASMA
(percentage by weight)
Proteins 7%
Water 91%
Other solutes 2%
Platelets 140,000–340,000
Leukocytes 5000–9000
Erythrocytes 4.2–6.2 million
FORMED ELEMENTS
(number per cubic mm)
PROTEINS
Albumins 57%
Globulins 38%
Fibrinogen 4%
Prothrombin 1%
OTHER SOLUTES
Ions
Nutrients
Waste products
Gases
Regulatory substances
LEUKOCYTES
Neutrophils 60%–70%
Lymphocytes 20%–25%
Monocytes 3%–8%
Eosinophils 2%–4%
Basophils 0.5%–1%

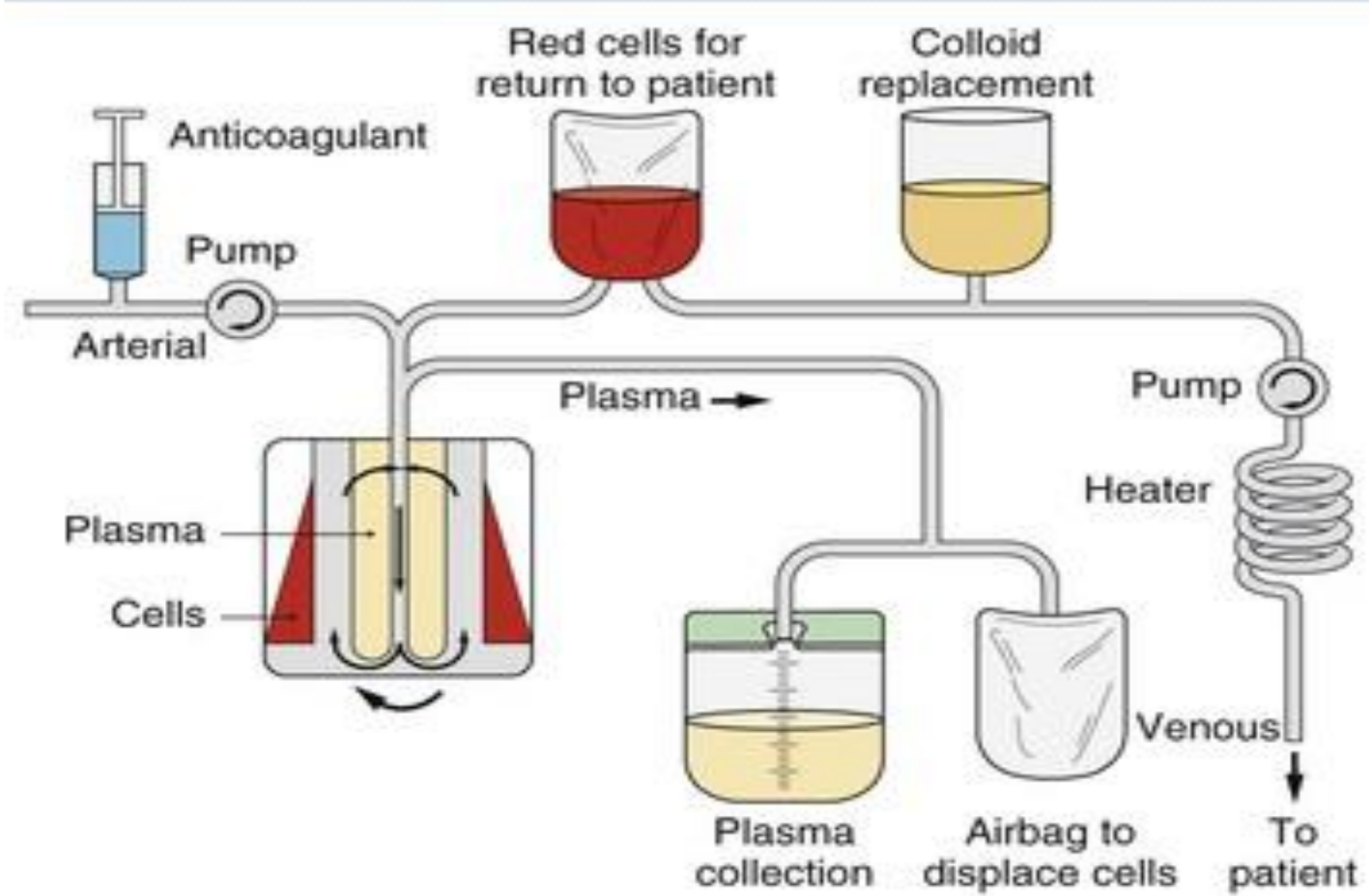
Plasma separation by Centrifuge



Specific gravity of blood components in g/ml ($kg/m^2 \cdot s^2$)

Plasma	1.025-1.029
Thrombocytes	1.040
Leucocytes	1.070-1.092
Erythrocytes	1.093-1.096

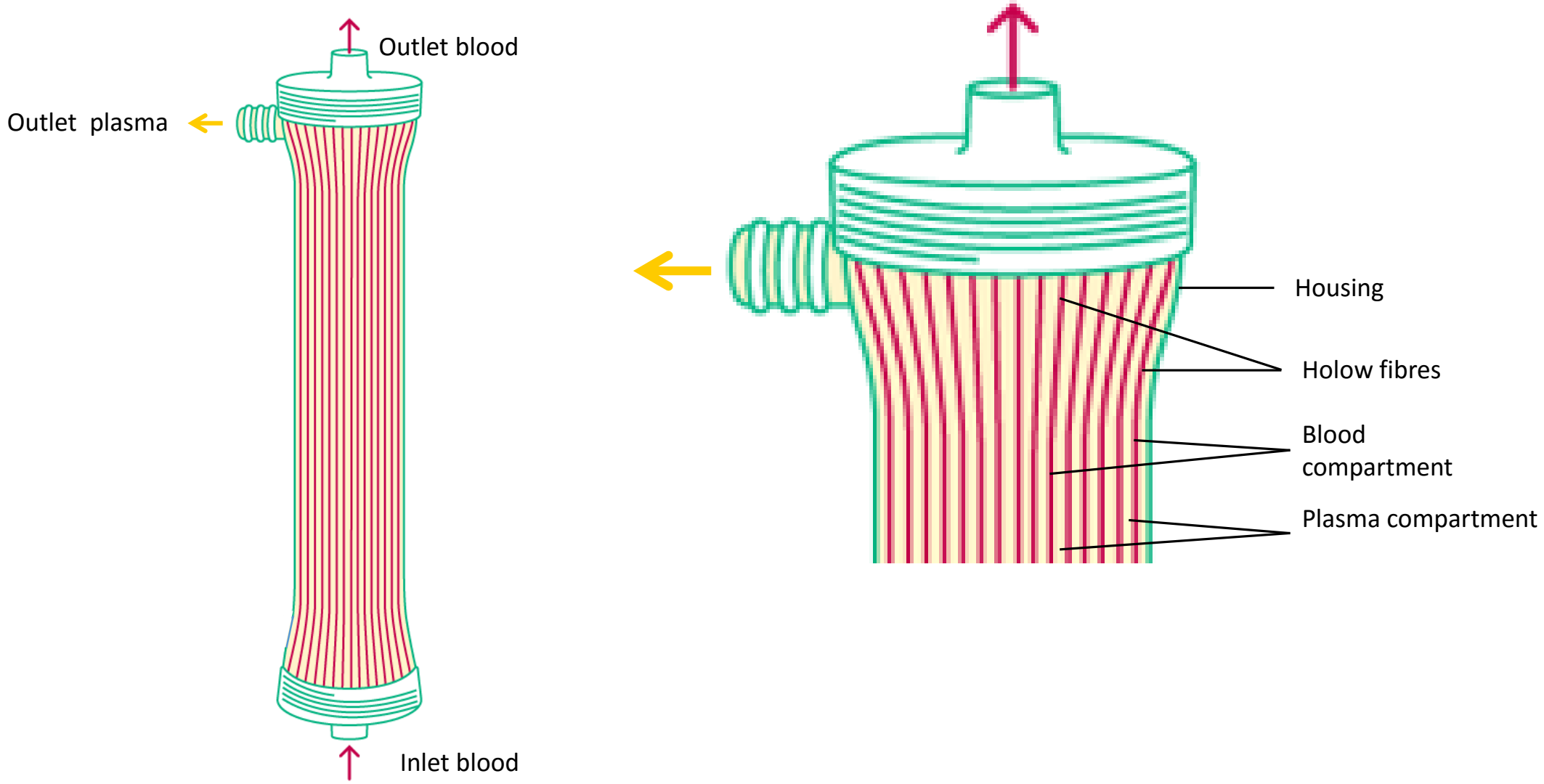
Centrifugal Cell Separation

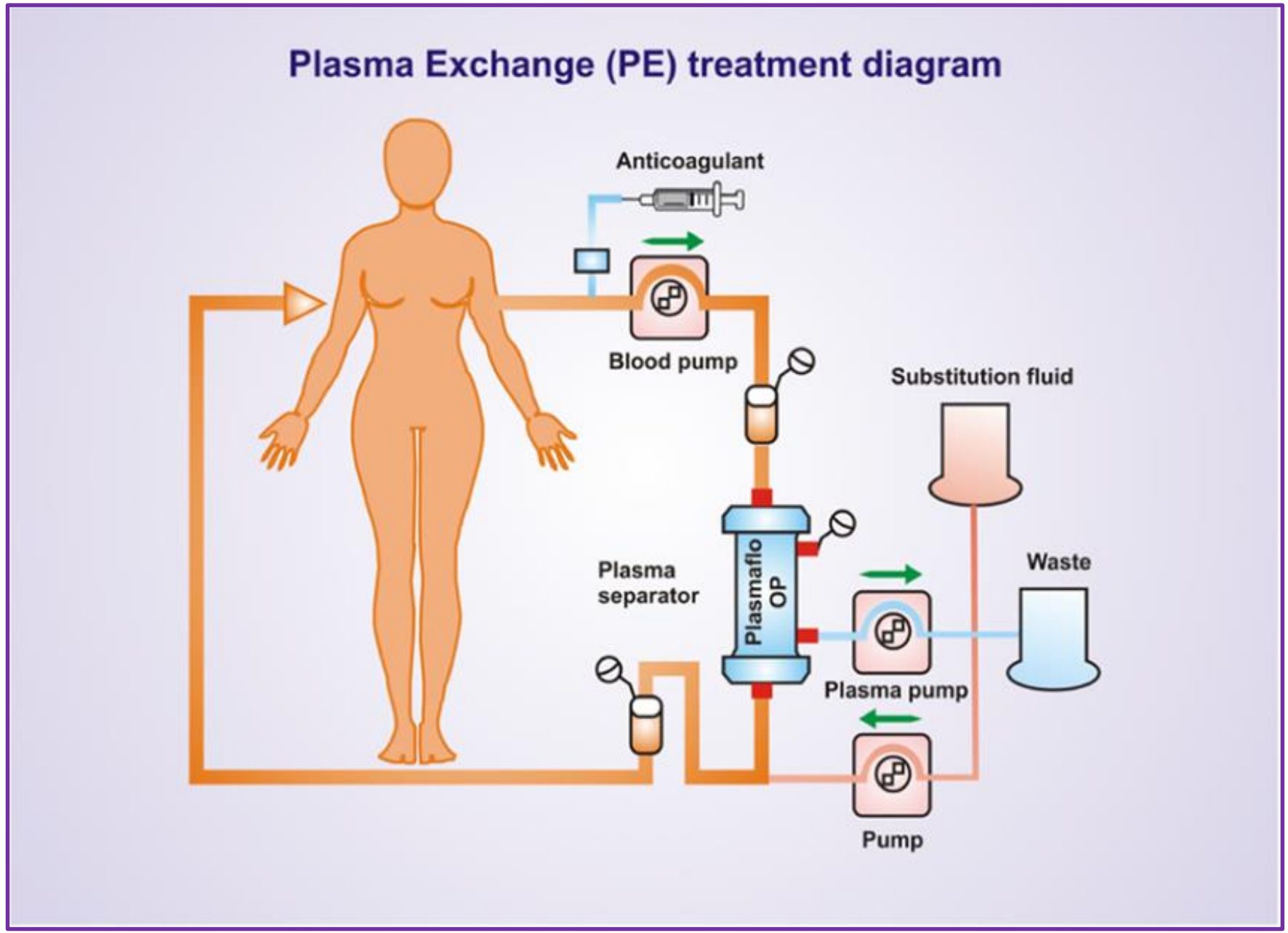


A

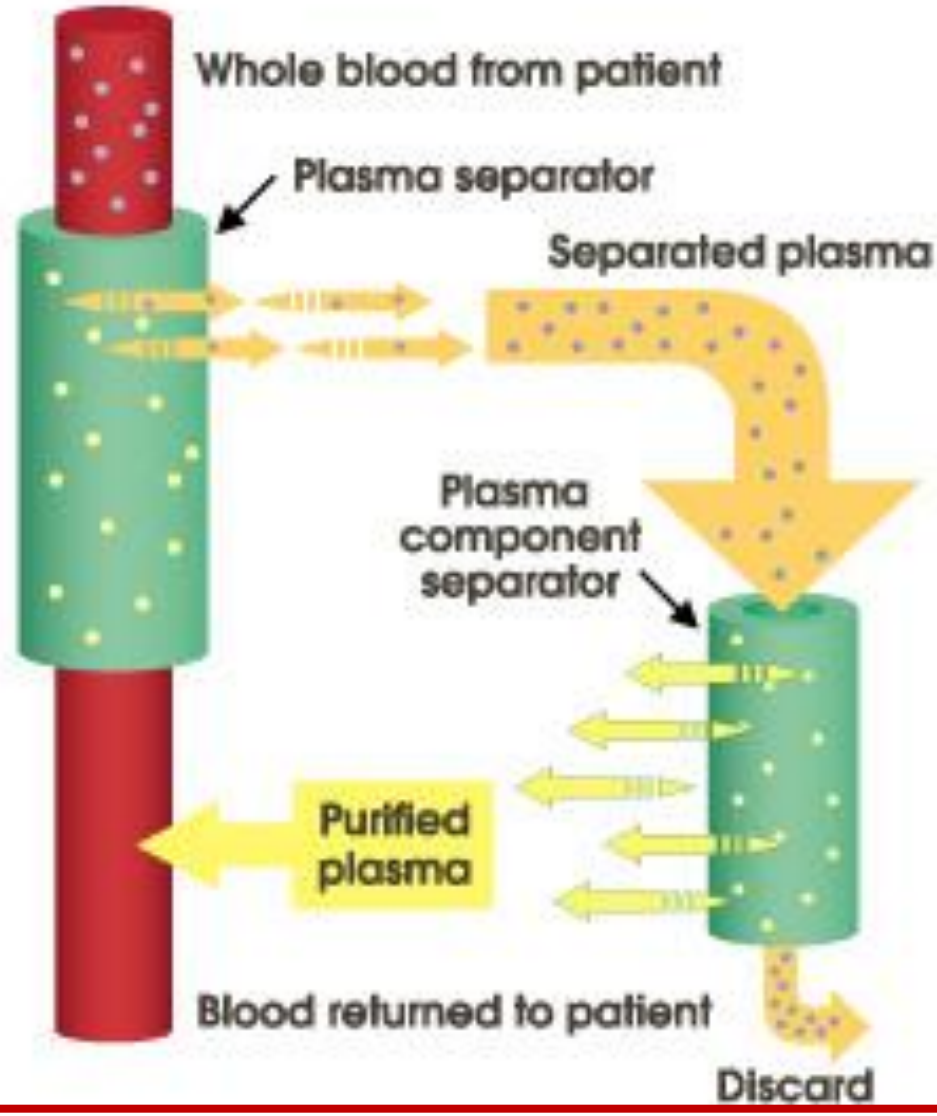
Plasma separation by filtration

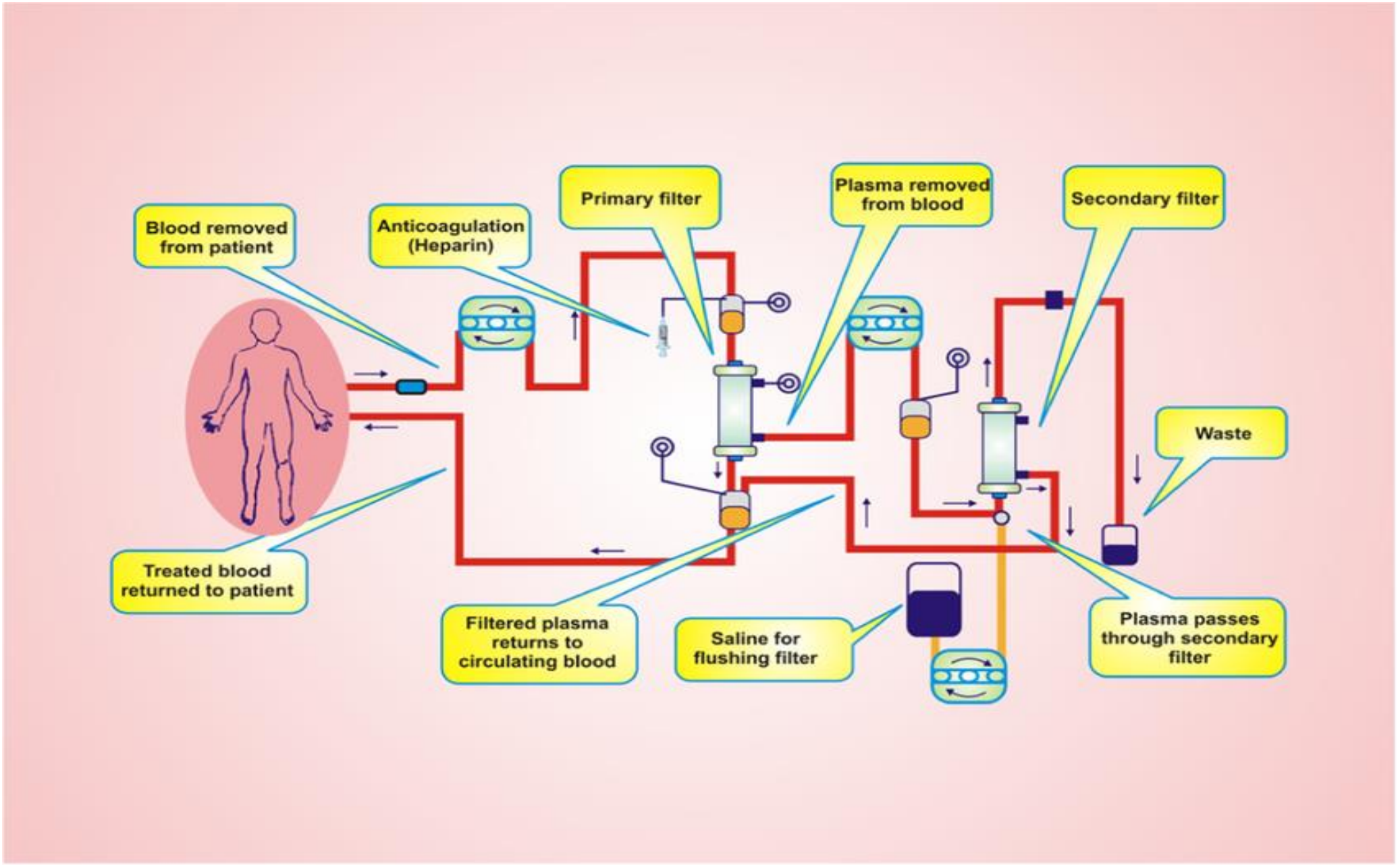
Structure of plasma filter




Plasma Exchange (PE) treatment diagram
Anticoagulant
Blood pump
Substitution fluid
Plasma separator
Plasmaflo OP
Waste
Plasma pump
Pump

Separation mechanism of DFPP




Blood removed from patient
Anticoagulation (Heparin)
Primary filter
Plasma removed from blood
Secondary filter
Waste
Treated blood returned to patient
Filtered plasma returns to circulating blood
Saline for flushing filter
Plasma passes through secondary filter

Basic Principles and Considerations of TPE

1-When to Consider
2- Vascular Access
3- Total Plasma Volume
4- Number of Sessions & Interval Between Sessions
5-Anticoagulation
6- Type of Replacement Fluid
7- Drug Dosing

Table 2. Apheresis Versus Hemodialysis

Characteristic	Therapeutic Plasma Exchange		Hemodialysis
	Centrifugation	Membrane Filtration	
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.

Table 1: Therapeutic plasma exchange procedure

Procedure	Centrifugal TPE				Membrane TPE
Plasma exchange volume	To be individualized, plasma exchange volume is 1-1.5 times patient's plasma volume (depending on condition and severity) Estimated plasma volume (L)=0.07 (set) × weight (kg) × (1−hematocrit) E.g., for a 70 kg patient with a hematocrit of 35% the calculation would be as follows (0.07 kg × 70 kg × 1 - 0.35)				
Apparatus	COM.TEC (Fresenius Kabi)/or Spectra Optia Apheresis system				Fresenius 4008/5008
Kit	Plastic disposable Kit PL1/Spectra Optia Exchange set				Plasma flux P2S/bloodlines
Investigations	Complete blood count, renal function tests, calcium, coagulation parameters, and fibrinogen				
Premedication	Hydrocortisone 100 mg IV (draw up with 10 ml of 0.9% saline) Phenergan 12.5 mg IV (draw up with 5 ml of 0.9% saline) Paracetamol 1 g orally				
Anticoagulation	AC; ensure maximum infusion rate does not exceed 0.9 ml/min/L TBV. The inlet: AC ratio defaults to 13:1 for all TPE procedures				Heparin: Bolus: 1000 units and maintenance: 500 units/h
Priming the circuit	Prime lines with 0.9% saline; draw and return lines of central venous catheter are connected to the tubing. Draw and return tubing is primed with packed red blood cells if the patient is weighing <20 kg				
Prophylaxis for citrate toxicity	10 ml of 10% calcium gluconate for every liter of plasma volume filtered				If citrate is used as an anticoagulant - for example, CRRT machines
Replacement fluid	Option 1		Option 2		Option 3
	HUS/TTP/following renal biopsy/renal transplant		For patients requiring frequent TPE or with depleting coagulation factors		Patients requiring infrequent exchanges and satisfactory coagulation parameters
Proportion of total volume	FFP 75%	HSA - 25%	FFP - 20%	HSA - 80%	HSA - 100%
E.g., 2 L	1.5 L	0.5 L	0.4 L	1.6 L	2 L
Disconnection	Disconnect after required plasma removal. Instill heparin into central venous catheter lumen. Check post-TPE fibrinogen if HSA is used as the replacement fluid				

TPE: Therapeutic plasma exchange, IV: Intravenous, AC: Acid citrate, CRRT: Continuous renal replacement therapy, HSA: Human serum albumin, FFP: Fresh frozen plasma, TTP: Thrombotic thrombocytopenic purpura, HUS: Hemolytic uremic syndrome, TBV: Total Blood Volume

Replacement Fluids

PE is a therapeutic procedure in which plasma is first separated from other components of blood and then discarded and replaced with substitute fluid.

PE non-selectively removes all substances, such as pathologic antibodies, immune complexes, inflammatory mediators, albumin, and other useful components in the plasma. Therefore, the fluid removed must be replaced to avoid significant hypovolemia.

Albumin, saline, or a combination of albumin and saline are the replacement fluids of choice. **FFP** should be used as the replacement fluids for TTP, TTP/HUS, or TMA.

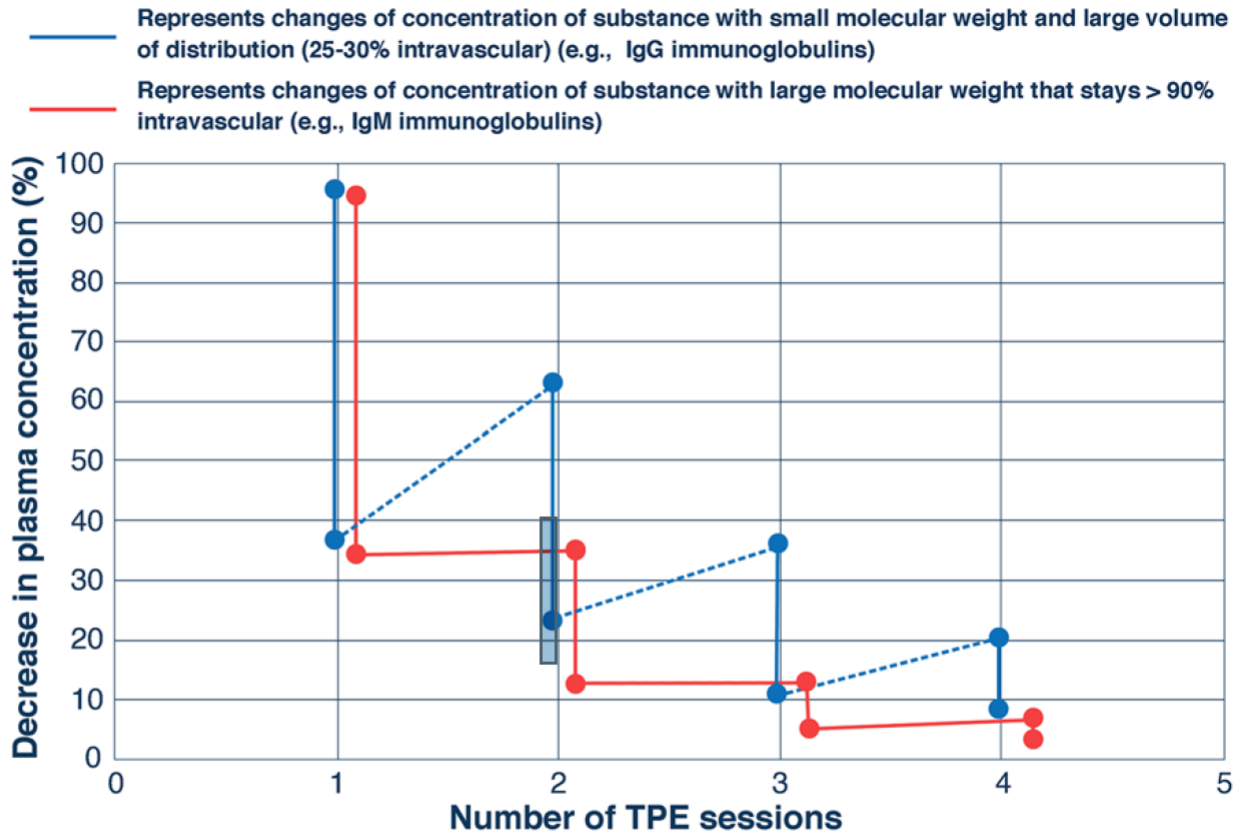


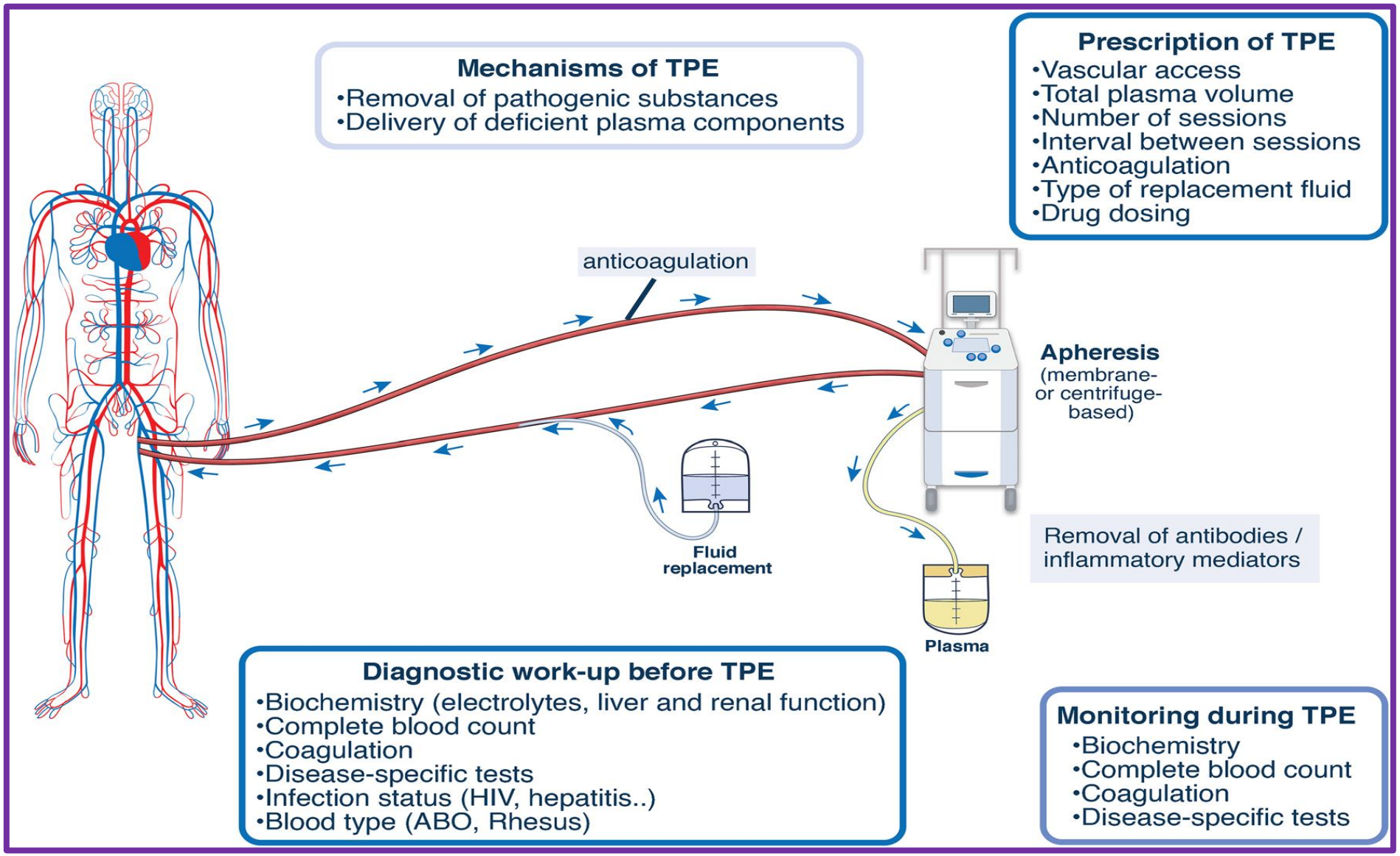
Fig. 2 Progressive decrease in plasma concentration of substance following four consecutive TPE treatments equaling 1.2 plasma volume each. *TPE* therapeutic plasma exchange

Table 2 Disease-specific workup for the most common indications

Disease	Specific laboratory tests	Diagnostic imaging	Special diagnostic tests
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome)	Serum IgG antibodies to GQ1b	Spinal MRI	Lumbar puncture (elevated CSF protein) Electrodiagnostic studies (i.e., EMG and nerve conduction studies)
Anti-glomerular basement membrane disease (Goodpasture syndrome)	Urine analysis (hematuria, proteinuria, cellular casts) Renal function (creatinine) Anti-GBM antibodies (serum, kidney) ANCAs (MPO, PR3)	Chest CT	Kidney biopsy
Hyper-viscosity syndrome (in hyper-gammaglobulinemia, especially Waldenström macroglobulinemia)	M component quantification Viscosity measurement	Eye fundus examination	
Catastrophic antiphospholipid syndrome	Lupus anticoagulant IgG and IgM anticardiolipin antibodies by ELISA Anti-beta2-GP I antibodies; IgG and IgM by ELISA Testing for DIC, HIT II, TMA	CT to rule out malignancy	
Myasthenia gravis	Acetylcholine receptor antibodies Receptor-associated protein, MuSK-Ab Low-density LRP4 antibodies	CT or MRI of the mediastinum	Repetitive nerve stimulation test
N-methyl-D-aspartate receptor antibody encephalitis	Antibodies in serum and CSF (IgG antibodies to GluN1)	MRI	CSF EEG Rule out malignancy
Thrombotic thrombocytopenic purpura	Blood smear ADAMTS13 activity and inhibitor Hemolytic parameters Stool tests (cultures and Shiga toxin) Troponins	CT and MRI	ECG Echocardiography
Thyroid storm	TSH, T4, and T3 Thyrotropin receptor antibodies	Echocardiography Thyroid ultrasound	ECG
Acute liver failure	Liver enzymes Coagulation profile (including prothrombin time, INR and fibrinogen and TEG or equivalent, consider ADAMTS13 if pregnancy related and concern re TTP/aHUS) Complete blood counts and renal biochemistry Urine toxicology screen and serum paracetamol level Viral hepatitis screen + viral PCR if clinically pertinent (CMV, HSV, EBV) Pregnancy test Autoimmune markers Caeruloplasmin level Arterial ammonia Arterial blood gas and lactate Ferritin, triglycerides if HLH considered as a cause of ALF	Abdominal Doppler ultrasonography Alternative: abdominal CT	Liver biopsy (e.g., malignancy) Echocardiography (hepato-pulmonary syndrome)
ANCA-associated vasculitis/anti-GBM disease	ANCAs (MPO, PR3) Anti-GBM antibodies Antinuclear antibodies C3 and C4 Cryoglobulins Urinary sediment Tuberculosis screen	CT (head, orbits, mastoids, neck, thorax)	Biopsy of an affected organ BAL

MRI magnetic resonance imaging, *CSF* cerebrospinal fluid, *EMG* electromyogram, *ANCA* antineutrophil cytoplasmic antibody, *MPO* myeloperoxidase, *GBM* glomerular basement membrane, *CT* computed tomography, *DIC* disseminated intravascular coagulation, *HIT* heparin-induced thrombocytopenia, *TMA* thrombotic microangiopathy, *ELISA* enzyme-linked immunosorbent assay, *MuSK-Ab* antibodies to muscle-specific kinase, *EEG* electroencephalogram, *TSH* thyroid-stimulating hormone, *T4* thyroxine, *T3* triiodothyronine, *ECG* electrocardiogram, *BAL* bronchoalveolar lavage, *INR* International Normalized Ratio, *PR3* proteinase 3, *ALF* acute liver failure, *HLH* hemophagocytic lymphohistiocytosis, *TTP* thrombotic thrombocytopenic purpura, *TEG* thromboelastography, *aHUS* atypical hemolytic uremic syndrome

Therapeutic plasma exchange: overview



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Department of Nephrology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Therapeutic apheresis has become an important adjunctive or alternative therapeutic option to immunosuppressive agents for primary or secondary kidney diseases and kidney transplantation.

Table 2. Indications for therapeutic apheresis in diseases involved kidney and their pathogenic factors.

Medical disciplines	Diseases	Pathogenic factors
Primary kidney diseases	FSGS	Circulatory permeability factors
	MN	PLA2R Ab and THSD7A Ab
	Anti-GBM glomerulonephritis (Goodpasture's syndrome)	Anti-GBM Ab
Secondary kidney diseases	ANCA-associated vessel vasculitis	Anti-MPO or anti-PR3 Ab
	TTP	ADAMTS-13 Ab, ICs
	aHUS	Complement regulatory components or autoantibodies
	SLE	Anti-dsDNA Ab, anti-nuclear Ab, ICs
KT	ABO-incompatible KT	Blood group isoagglutinins
	HLA-incompatible KT	HLA and non-HLA alloantibodies
	Ab-mediated allograft rejection	HLA and non-HLA alloantibodies

FSGS: Focal segmental glomerulosclerosis; MN: membranous nephropathy; PLA2R: M-type phospholipase A2 receptor; THSD7A: thrombospondin type 1 domain-containing protein 7 A, Ab: antibody; GBM: glomerular basement membrane; ANCA: antineutrophil cytoplasmic antibodies; MPO: myeloperoxidase; PR3: proteinase 3; TTP: thrombotic thrombocytopenic purpura; ADAMTS-13: a disintegrin-like and metalloprotease with thrombospondin type 1 motifs-13; ICs: immune complexes; aHUS: atypical hemolytic uremic syndrome; SLE: systemic lupus erythematosus; KT: kidney transplantation; HLA: anti-human leukocyte antigen.

Table 1 Category I–II ASFA indications for therapeutic plasma exchange.

	Category I ASFA: Indications for therapeutic plasma exchange (first-line therapy)
	Acute inflammatory demyelinating polyradiculoneuropathy/Guillain–Barre syndrome
**	ANCA-associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis; and microscopic polyangiitis)
**	Anti-glomerular basement membrane disease (Goodpasture's syndrome)
	Chronic inflammatory demyelinating polyradiculoneuropathy
	Focal segmental glomerulosclerosis (Recurrent in transplanted kidney)
	Hyperviscosity in monoclonal gammopathies (Symptomatic/Prophylaxis for rituximab)
	Liver transplantation (Desensitization, ABOi LD)
	Myasthenia gravis (Moderate-severe/Pre-thymectomy)
	N-methyl-D-aspartate receptor antibody encephalitis
	Progressive multifocal leukoencephalopathy associated with natalizumab
	Renal transplantation, ABO compatible (Antibody-mediated rejection/Desensitization, LD)
	Renal transplantation, ABO incompatible (Desensitization, LD)
	Thrombotic microangiopathy, complement mediated (Factor H autoantibodies)
	Thrombotic microangiopathy (ticlopidine drug associated)
**	Thrombotic thrombocytopenic purpura
	Wilson's disease (Fulminant)
	Category II ASFA: indications for therapeutic plasma exchange (established second-line therapy)
	Acute disseminated encephalomyelitis
	Autoimmune hemolytic anemia (severe cold agglutinin disease)
	Cardiac transplantation (desensitization)
**	Catastrophic antiphospholipid syndrome
**	Cryoglobulinemia (symptomatic/severe)
	Familial hypercholesterolemia (homozygotes with small blood volume)
	Hashimoto's encephalopathy: Steroid-responsive encephalopathy associated with autoimmune thyroiditis
	Hematopoietic stem cell transplantation, ABO Incompatible (Major HPC, Marrow/Major HPC, Apheresis)
	Lambert–Eaton myasthenic syndrome
	Multiple sclerosis (acute CNS inflammatory demyelinating)
**	Myeloma cast nephropathy
	Neuromyelitis optica spectrum disorders (Acute)
	Mushroom poisoning
	Paraproteinemic demyelinating neuropathies/chronic acquired demyelinating polyneuropathies (IgG/IgA; IgM)
	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (exacerbation)
**	Renal transplantation, ABO incompatible (antibody medicated rejection)
**	Systemic lupus erythematosus (severe)
	Vasculitis (HBV-PAN)
	Voltage-gated potassium channel antibodies

ASFA, American Society for Apheresis; CNS, central nervous system; HBV-PAN, hepatitis B-polyarteritis nodasa; LD, living donor; HPC, hematopoietic progenitor cells.

Intensive Care Med (2022) 48:1382–1396
https://doi.org/10.1007/s00134-022-06793-z

REVIEW

Plasma exchange in the intensive care unit: a narrative review

Philippe R. Bauer[2*], Marlies Ostermann[12], Lene Russell[15], Chiara Robba[14], Sascha David[6], Bruno L. Ferreyro[7], Joan Cid[5], Pedro Castro[4], Nicole P. Juffermans[8], Luca Montini[10], Tasneem Pirani[13], Andry Van De Louw[17], Nathan Nielsen[11], Julia Wendon[18], Anne C. Brignier[3], Miet Schetz[16], Jan T. Kielstein[9], Jeffrey L. Winters[19], Elie Azoulay[1] on behalf of the Nine-I Investigators

Table 1 Indications for therapeutic plasma exchange (TPE) in the ICU: absolute (likely or less likely be used), relative, and rescue therapy

Disease	Rationale	Replacement fluid	Adjunct therapeutic options	Strategy[a] and Endpoints	Parameters to monitor	Additional comments
Absolute indications: disorders for which TPE is a recognized first-line treatment [2]						
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)	Removal of antibodies	Albumin or plasma	MG	1–1.5 TPV, 5–6 sessions over 10–14 days *until* clinical improvement	Clinical response	Consider TPE if failed to respond to IVIG and/or impending respiratory failure
Anti-glomerular basement membrane disease (Goodpasture syndrome)	Removal of pathogenic autoantibodies (including anti-GBM antibodies)	Albumin; plasma if bleeding	Corticosteroids, cyclophosphamide, rituximab	1–1.5 TPV daily or on alternate days over 10–20 days *until* disease control	Renal function Clinical response	Anti-GBM antibodies may fall to undetectable levels within 2 weeks; TPE course should be ≥ 10–20 days and should continue until resolution of glomerular or pulmonary injury The presence or absence of antibody should not guide decisions to initiate or end TPE
Hyper-viscosity syndrome (in hypergammaglobulinemia, especially Waldenström macroglobulinemia)	Removal of paraproteins, thereby reducing the plasma viscosity	Albumin or Albumin/saline	Systemic chemotherapy or immunotherapy	1–1.5 TPV daily *until* symptoms subside, most often 1–3 procedures	Clinical response M component (mainly IgM levels)	Symptoms are more reliable than concrete values of viscosity or immunoglobulins to guide therapy
Catastrophic antiphospholipid syndrome	Removal of antibodies (including antiphospholipid antibodies), cytokines, and complement factors; administration of coagulation factors	Plasma (± albumin)	Anticoagulation, corticosteroids, IVIG, rituximab or eculizumab	1–1.5 TPV daily or alternate days; *until* clinical response	Clinical response	
Myasthenia gravis	Removal of autoantibodies (including antiacetylcholine receptor antibodies) and immunomodulation	Albumin	Cholinesterase inhibitors, corticosteroids, immunosuppression, IVIG, thymectomy, eculizumab	1–1.5 TPV; 3–6 sessions over 10–14 days, *until* disease control	Clinical response	More effective if initiated during myasthenic crisis, especially with bulbar or severe generalized response; more effective than IVIG in patients with MuSK-Ab
N-Methyl-D-aspartate receptor antibody encephalitis	Removal of antibodies (including anti-neuronal autoantibodies)	Albumin	High dose corticosteroids, IVIG, occasionally rituximab or cyclophosphamide Tumor resection (when tumor is present)	1–1.5 TPV; 5–12 sessions over 1–3 weeks *until* clinical response	Clinical response	Check for ovarian tumors and other tumors (germ cell tumors, carcinoma, teratoma, lymphoma)

Table 1 (continued)

Disease	Rationale	Replacement fluid	Adjunct therapeutic options	Strategy[a] and Endpoints	Parameters to monitor	Additional comments
Thrombotic thrombocytopenic purpura	Administration of ADAMTS13 protease and removal of anti-ADAMTS13 autoantibodies	Plasma	Corticosteroids, rituximab, Caplacizumab (recombinant ADAMTS13?)	Daily *until* platelet count > 150 × 10^9/L, LDH approaching normal and resolution of non-fixed neurologic symptoms then Continue for 2 more sessions then stop	Platelet count, LDH, ADAMTS13 activity	Recovery of ADAMTS13 activity to > 10% within 7 days is associated with clinical response
Acute liver failure[a]	Removal of albumin-bound and water-soluble toxins Replacement of plasma proteins including clotting factors Immunomodulation Reduction of proinflammatory response	Plasma	Multiorgan support	High-volume TPE if possible (target 8–12 L); otherwise, 1–1.5 TPV daily *until* clinical improvement or transplantation	Clinical response Supportive care as a bridge to liver transplantation	Always consider TTP in the differential in specific scenarios (e.g., pregnancy and acute liver failure) Supportive care may improve nontransplant outcome Support care may stabilize while awaiting liver transplant
Relative indications: Disorders for which TPE is a recognized second-line treatment (alone or combined)						
Thyroid storm (refractory)	Removal of autoantibodies, catecholamines, and cytokines	Plasma, albumin	Propylthiouracil, corticosteroids, ß-blockers, cholestyramine, organ support	Daily to every 3 days, *until* control of systemic response	Clinical response	Although a category II per 8th ASFA guidelines, TPE could be considered in refractory cases
ANCA-associated vasculitis with diffuse alveolar hemorrhage	Removal of autoantibodies and inflammatory mediators	Plasma	Corticosteroids, rituximab, cyclophosphamide	1–1.5 TPV daily or every other day *until* disease control	Clinical response (resolution of pulmonary hemorrhage)	PEXIVAS trial suggested no benefit on death or end stage kidney disease Now category II per recent ASFA update [73]
Acute disseminated encephalomyelitis	Removal of presumedly pathogenic autoantibodies	Albumin	Corticosteroids, IVIG	1–1.5 TPV every other day *until* disease control	Clinical response	
Thrombotic microangiopathy-complement-mediated (formerly known as atypical hemolytic syndrome (aHUS))	Recommended while investigations for TTP and other forms of TMA are in progress or if eculizumab is not available	Plasma	Eculizumab	1–1.5 TPV daily *until* TTP ruled out	Platelet count	
Autoimmune hemolytic anemia	Removal of pathogenic immune complexes, autoantibodies and complement components	Albumin	Corticosteroids, rituximab, IVIG, immunosuppression, monoclonal antibody therapy, splenectomy	TPV 1–1.5 daily *until* disease control	Clinical response	

Table 1 (continued)

Disease	Rationale	Replacement fluid	Adjunct therapeutic options	Strategy[a] and Endpoints	Parameters to monitor	Additional comments
Chronic acquired demyelinating polyneuropathies (IgA- and IgG-associated polyneuropathy)	Removal of autoantibodies	Albumin	IVIG and rituximab	5–6 treatments over 10–14 days *until* improvement or stabilization of neurological response	Clinical response Nerve conduction studies; IgG and IgM titers	Frequency: 2–3/week until improvement, then tapered, e.g., weekly, or monthly
Lambert–Eaton myasthenic syndrome	Removal of autoantibodies	Albumin	Aminopyridines, possibly cholinesterase inhibitors; immunosuppression if symptomatic treatment is insufficient	1–1.5 TPV daily or on alternate days *until* clinical response	Clinical response	
Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) or Hashimoto's encephalopathy	Removal of autoantibodies	Albumin	Corticosteroids, IVIG, azathioprine, cyclophosphamide, potentially monoclonal antibody therapy	1–1.5 TPV daily or on alternate days; 3–9 procedures *until* Clinical response	Clinical response	Utilized in patients who have failed to respond to first-line therapy with corticosteroids
Rescue indications: disorders for which TPE may be used in the ICU as rescue therapy despite lack of strong evidence about efficacy						
HIT with progressive thrombosis	Removal of platelet-activating HIT antibodies	albumin, plasma	Non-heparin anticoagulation	1–1.5 TPV daily or on alternate days *until* clinical response	Clinical response; HIT antibody levels	
Cryoglobulinemia vasculitis	Removal of cryoglobulins	Albumin	Corticosteroids, cyclophosphamide, rituximab	1–1.5 TPV every 1–3 days; 3–8 sessions *until* disease control	Clinical response	
Pancreatitis with severe hypertriglyceridemia	Decrease of triglyceride levels, removal of inflammatory cytokines, and potential replacement of deficient lipoprotein lipase	Albumin, plasma	Dietary restriction, lipid-lowering drugs, insulin, heparin	TPV 1–1.5 daily for 1–3 days *until* clinical response and triglyceride levels	Clinical response; triglyceride levels	
Paraneoplastic neurological syndromes	Removal of autoantibodies	Albumin	Antitumor therapy, immunosuppression (corticosteroids, IVIG)	1–1.5 TPV daily or on alternate days; 5–6 procedures up to 2 weeks *until* clinical response	Clinical response	
Specific types of poisoning	Removal of toxic substances with high protein-binding capacity and low distribution volume	Albumin, plasma	Gastric lavage, activated charcoal (depending on toxic substance); multiorgan support	1–2 TPV daily *until* clinical response	Clinical response	

ble 1 (continued)

ease	Rationale	Replacement fluid	Adjunct therapeutic options	Strategy[a] and Endpoints	Parameters to monitor	Additional comments
ystemic lupus erythematosus with severe vasculitic complications including lupus cerebritis and pneumonitis	Removal of autoantibodies	Albumin, plasma	Immunosuppression	1–1.5 TPV daily or every other day, 3–6 sessions *until* clinical response	Clinical response	TPE is not indicated for the treatment of lupus nephritis

therapeutic plasma exchange, *ICU* intensive care unit, *ANCA* antineutrophil cytoplasmic antibody, *HIT* heparin-induced thrombocytopenia, *IVIG* intravenous immunoglobulins, *GBM* glomerular basement membrane, 'total plasma volume, *TTP* thrombotic thrombocytopenic purpura, *TMA* thrombotic microangiopathy

ot widely used yet and limited to a few specialized centers but strong evidence base in acute liver failure (especially hyperacute) in improving transplant free survival in patients who meet transplant criteria but are ıer ineligible for transplant or do not have access to timely transplant. TPE may also be used as a bridge to transplant in acute liver failure with multiple organ failure [75]

Plasmapheresis for the treatment of kidney diseases

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Kidney International (2016) **90,** 974–984

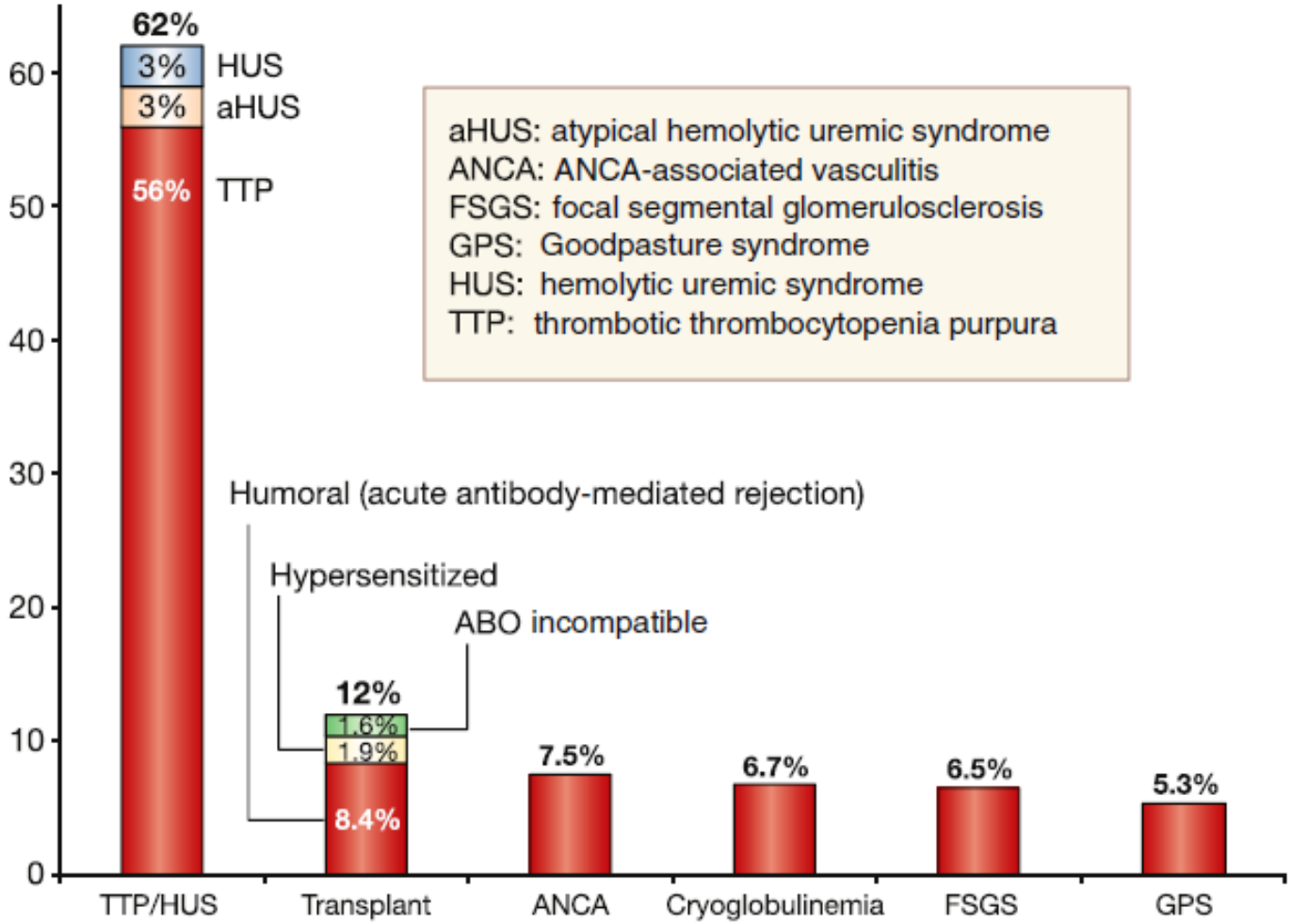

Table 1 | Plasma exchange for TMA—excluding disseminated intravascular coagulation[14,20,47–50,54,134,135]

TMA classification	Subclassification	Proportion of TMA cases[a]	Pathophysiologic features	Response to plasma exchange[a]
Primary TMA	Acquired TTP	29%–41%	Unexplained microangiopathic hemolytic anemia and thrombocytopenia (no predisposing condition). Severe ADAMTS13 deficiency <10% (present in 40% to 100% of patients).	80%–90%
	Hereditary/congenital TTP (Upshaw-Shulman)	1%–2%	Severe ADAMTS13 deficiency (<10%). No ADAMTS13 autoantibody inhibitor.	>90%
Secondary TMA	Autoimmune disease[b]	45%–50%	Endothelial injury (mediated by various insults). Variable ADAMTS13 activity.	50%–70%
	Drug-mediated[c]			80%–90%[d]
	Infection[e]			50%–70%[f]
	Pregnancy/postpartum			50%–70%
	Pancreatitis			50%–70%
	Malignancy			No response
	Malignant hypertension			No response
	Stem cell transplantation			No response
Shiga toxin-mediated TMA (STEC HUS)	STEC HUS	9%–10%	Shiga-toxin-mediated endothelial injury renal failure. Preserved ADAMTS13 activity.	Inconclusive
Complement-mediated TMA (atypical HUS)	Familial Sporadic	<2%	Patients have mutations in *CFH*, *CFHR1/3*, *CFI*, *C3*, *MCP* [*CD46*], *THBD*, or *CFB*, or carry anti-CFH antibodies. Preserved ADAMTS13 activity.	30%–70%[g]

High dose MEthylprednisolone or Plasma EXchange as adjuvant therapy for severe renal vasculitis – which is better? Asks MEPEX

STUDY POPULATION

28 European hospitals

03/1995 to 10/2002

Biopsy proven pauci-immune, ANCA associated glomerulo-nephritis

N = 137

COHORTS and INTERVENTION

N = 137

All patients

oral cyclophosphamide for 6 months

+

oral prednisolone taper over 12 months

→ N = 67

Steroid group

1 g/d IV Methyl-prednisolone for 3 days

↘ N = 70

Plex group

Plasma Exchange

7 sessions within 14 days

PRIMARY OUTCOME

Renal Recovery (dialysis independence) at 3 months

Steroid group

33/67 (49%)

Plex group

48/70 (69%)

95% CI: 18 to 35%; P 0.02

Conclusions: Plasma exchange increased the rate of renal recovery in ANCA-associated vasculitis presenting with renal failure, compared to high dose methylprednisolone. There was no difference in survival or renal function at 12 months. Also, patients with alveolar hemorrhage were excluded

Reference: Jayne D, Gaskin G, Rasmussen N, Abramowicz D. Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis. J Am Soc Nephrol 18: 2180 –2188, 2007

@madmagicdoc

PEXIVAS

Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis

#NephJC

Design

Open label
16 countries

ANCA - vasculitis

+

eGFR < 50

*Bx non-mandatory

or

Hemorrhage

n = 704

Randomization

All: CYC or Rituximab

PLEX x 7
n = 352

No PLEX
n = 352

Standard steroids
n = 351

Reduced steroids
n = 353

Median follow up: 3 years

Primary outcome: death + ESKD

28 % = CI = 0.6, 1.1 = 31 %

25 % = CI = -3.4, 8 = 28 %

Severe infections

33 % > CI = 0.52, 0.93 > 27 %

Conclusions: Among patients with severe ANCA-associated vasculitis, PLEX did not reduce the incidence of death or ESKD. A reduced-dose regimen of steroids was noninferior to a standard-dose regimen with respect to death or ESKD.

M. Walsh, P.A. Merkel, C.-A. Peh et. al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. NEJM 2020;382:622-31.

@NephroGuy

We should still give TPE for some cases of AAV esp for pts who are RPGN & pts with really “bad” DAH

TTP

TMA is the most common indication of PE.

Clinical characteristics include thrombocytopenia and microangiopathic hemolytic anemia (MAHA) in combination with deficiency of plasma ADAMTS13 activity (<10%).

In most patients, IgG autoantibodies against ADAMTS13 are present. TPE aims to remove anti-ADAMTS13 antibodies while replacing ADAMTS13 activity through frozen plasma.

TPE prescription:

- **Plasma volume: 1-1.5 EPV**
- **Frequency: Daily**
- **Replacement fluid: Frozen plasma**
- **Duration: Daily until platelet count is >150 × 103/µL and lactate dehydrogenase level is near normal for 2-3 consecutive days**

Anti-GBM Disease

In several nonrandomized trials, PE was Found to be effective in reducing antiGBM abs, improving renal function and DAH. 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.

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**

ANCA associated Vasculitis

For patients with severe clinical symptoms such as DAH or RPGN, PE is used as the first-line therapy.

MEPEX study: 137 patients with severe renal disease/ higher rate of renal recovery & dialysis independence in PE group

PEXIVAS study: 704 patients with kidney dysfunction or DAH / showed a transient benefit but did not reduce mortality or incidence of ESRD in long term

KDIGO: PE can be considered in patients with Cr> 5.7 and in patients with DAH / hypoxemia.

ANCA associated Vasculitis

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)

Transplantation

1- Desensitization in ABO incompatible

2- Desensitization in HLA incompatible

3-ABMR

4- Recurrence of FSGS after kidney transplantation

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.

David *et al.*
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Intensive Care Medicine
Experimental

REVIEWS Open Access

Research priorities for therapeutic plasma exchange in critically ill patients

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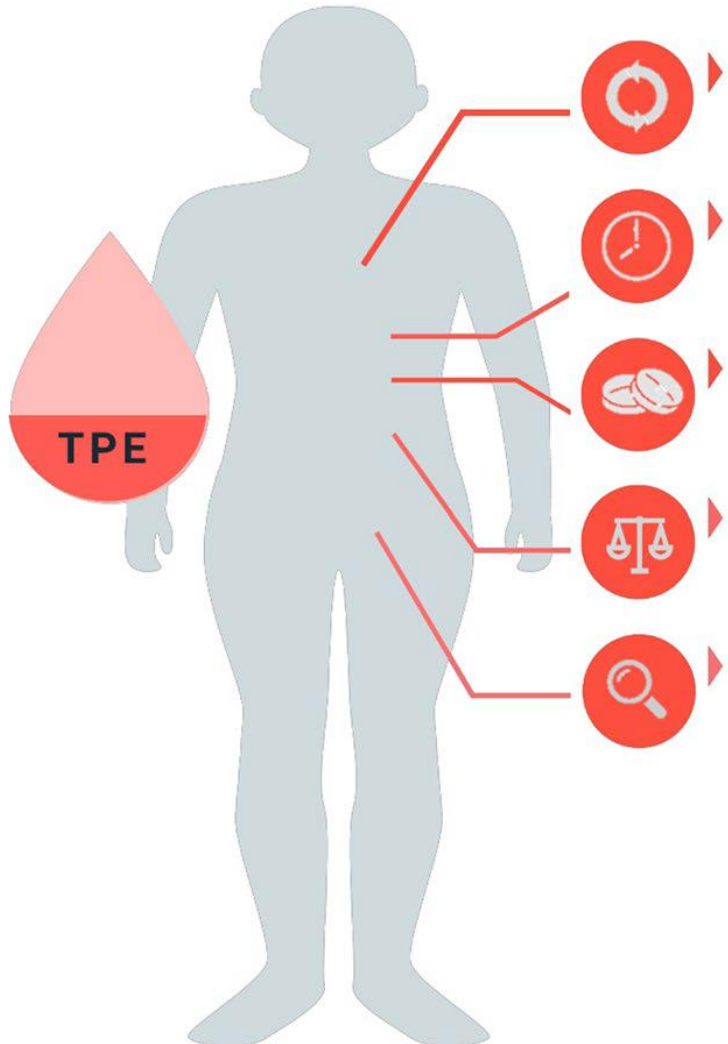
TPE Research Agenda



Removal and Replacement

What is the pathophysiological role of removal and replacement in critical illness?

Timing

What is the optimal timing of TPE in respect to other critical treatments?

Dosing and Regimen

What is the optimal dose and regimen of TPE in critical illness?

Risk - Benefit

How to identify critically ill patients at risk and avoid complications?

Explorative indications

What are explorative indications for critically ill patients?

Conclusion

TPE, is a routine method that separates plasma from blood cells to remove pathological factors or to deliver deficient ones. Consistently, it is used for numerous diseases characterized by the presence of harmful circulating factors or the deficiency of protective components.

It can be organ and life saving in many diseases.

In patients with TTP and anti GBM disease, the efficacy of TPE has been confirmed.