Plasma exchange

Core Curriculum 2023

花蓮慈濟腎臟內科 張賀翔

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Outline

- Apheresis modality
- Technique of plasma exchange (PE)
- Treatment indication of PE
- General consideration
- Prescription principles
- Special consideration
- Complication

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$_2$-macro-globulin, low-density lipoprotein cholesterol, and IgM)
Therapeutic plasma exchange	Plasma (exchanged for replacement fluid)
Thrombocytapheresis	Platelets

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Technique of plasma exchange

- Membrane filtration TPE: extracts fraction of plasma 30%
- Centrifugation TPE: 80%, U.S.A.

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.

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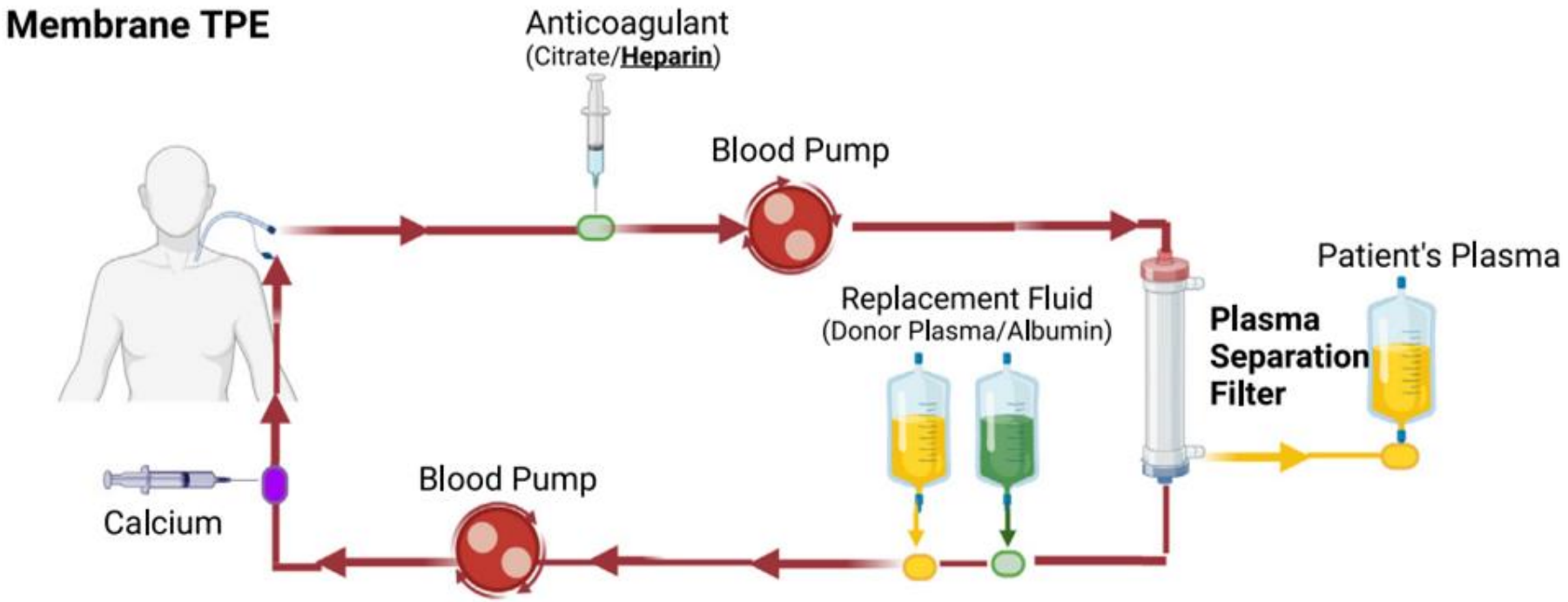

- Plasmaflo OP (聚乙烯, γ-ray 消毒)
- Prismaflex TPE series (聚丙烯, 環氧乙烷消毒)
- The **separation efficiency**
  - plasma filtration rates
  - membrane properties (pore size and surface area)
  - sieving coefficients

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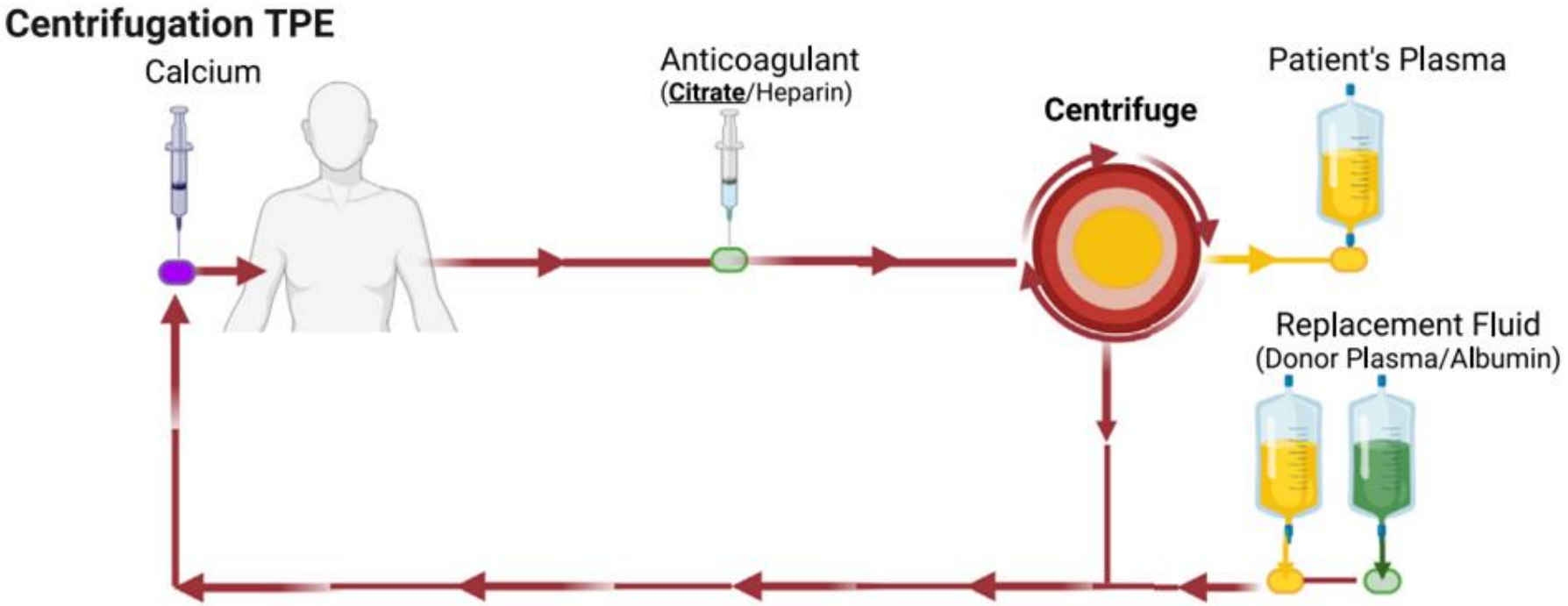
離心每分鐘 2,000-2,500 轉



Pack RBC to a Hct ≥80% --> removal of larger plasma volumes and shorter sessions --> lower blood flow rates --> **peripheral vein access**

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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.

When to Consider TPE

- The **ideal characteristics** of a substance
  a. large molecular weight (>15,000 Da)
  b. slow rate of formation
  c. prolonged half-life
  d. higher-percentage intravascular distribution
  e. low turnover rate

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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Vascular access

- Blood flow rates
  - centrifugation: 50-120 mL/min
  - membrane filtration: 150-200 mL/min

- Large-Bore Peripheral Intravenous Access
  - adults: 17-19–gauge needles
  - children: 19-22–gauge needles
- **Central Venous Catheters for Dialysis: 11.5-F**
- Ports: heparin locks at 1,000 U/mL
- Arteriovenous Fistulas or Grafts

Anticoagulation

- Citrate
  - short half-life (30-60 min), regional effect
  - **80%** is removed with the discarded plasma
  - Whole blood to anticoagulant ratios of 10:1-14:1 (expressed in milliliters)
- Heparin
  - short half-life (23 min to 2.48 hrs), **cheap**
  - almost entirely cleared during TPE
  - **first choice in membrane** TPE
  - loading : 3,000-5,000 U, followed by 1,000 U/h

Replacement Fluids

- Albumin
  - 50%-60% reduction in anticoagulant factors
  - Lower risk of hypersensitivity reactions
  - Cost: **albumin–saline(8:2)** solutio combination(7:3)
    → elevated hypotension risk
- Frozen Plasma(FP)
  - In TTP and bleeding patients (eg, diffuse alveolar hemorrhage [DAH])
  - Risk for citrate toxicity ⬆ (7 mmol citrate/U)
  - **Exchange 3 L -> 10-15 U FP**
  - Allergic reactions

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Journal of Clinical Apheresis ASFA WILEY

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue

- **I** = Apheresis is **first-line** therapy
- II = Second line therapy, conventional therapy first
- III = Individualized
- **IV** = Apheresis is **ineffective or harmful**

Category IV	HELLP syndrome(Antepartum) Paraproteinemic demyelinating Neuropathies(Multifocal motor neuropathy) Disseminated pustular Psoriasis Gemcitabine/quinine related TMA Idiopathic polyarteritis nodosa vasculitis

Neurology

Acute disseminated encephalomyelitis	Steroid refractory	TPE	II	2C
Acute inflammatory demyelinating polyradiculoneuropathy	Primary treatment	TPE	I	1A
		IA	I	1B
Chronic acquired demyelinating polyneuropathies	IgG/IgA/IgM related	TPE	I	1B
	Anti-myelin-associated glycoprotein	TPE	III	1C
	CANOMAD/CANDA[a]	TPE	III	2C
Multiple sclerosis	Acute attack/relapse	TPE	II	1A
		IA	II	1B
	Chronic primary or secondary progressive	TPE/IA	III	2B
Myasthenia gravis	Acute, short-term treatment	TPE/DFPP/IA	I	1B
	Long-term treatment	TPE/DFPP/IA	II	2B
Neuromyelitis optical spectrum disorder	Acute attack/relapse	TPE	II	1B
		IA	II	1C
	Maintenance	TPE	III	2C
N-methyl-D-aspartate receptor antibody encephalitis		TPE/IA	I	1C

Autoimmune disease

Systemic lupus erythematosus	Severe	TPE	II	2C
Catastrophic antiphospholipid syndrome		TPE	I	2C
Autoimmune hemolytic anemia, severe	Severe cold agglutinin disease	TPE	II	2C
	Severe warm autoimmune hemolytic anemia	TPE	III	2C

Liver disease

Acute liver failure	Acute liver failure	TPE-HV	I	1A
		TPE	III	2B
	Acute fatty liver of pregnancy[a]	TPE	III	2B
Wilson disease, fulminant		TPE	I	1C

Nephrology-Specific Indications for TPE

Cryoglobulinemia	Severe/symptomatic	TPE/DFPP	II	2A
		IA	II	2B
Myeloma cast nephropathy		TPE	II	2B
Nephrogenic systemic fibrosis		ECP/TPE	III	2C
Amyloidosis, systemic, dialysis related		$ß_2$-microglobulin adsorption	II	2B

Anti-glomerular basement membrane disease	Diffuse alveolar hemorrhage	TPE	I	1C
	Dialysis-independence	TPE	I	1B
	Dialysis-dependence, no diffuse alveolar hemorrhage	TPE	III	2B

Thrombotic microangiopathy

Thrombotic microangiopathy, thrombotic thrombocytopenic purpura		TPE	I	1A
Thrombotic microangiopathy, coagulation mediated	*THBD, DGKE*, and *PLG* mutations	TPE	III	2C
Thrombotic microangiopathy, complement mediated	Factor H autoantibody	TPE	I	2C
	Complement factor gene mutations	TPE	III	2C
Thrombotic microangiopathy, drug induced	Ticlopidine	TPE	I	2B
	Clopidogrel	TPE	III	2B
	Gemcitabine	TPE	IV	2C
	Quinine	TPE	IV	2C
Thrombotic microangiopathy, infection associated	STEC-HUS, severe	TPE/IA	III	2C
	pHUS	TPE	III	2C
Thrombotic microangiopathy, pregnancy associated	Pregnancy associated, severe	TPE	III	2C
	Extremely preterm preeclampsia, severe[a]	TPE/LA	III	2C

Vasculitis

Vaccine-induced immune thrombotic thrombocytopenia[a]	Refractory	TPE	III	2C
Vasculitis, ANCA associated	Microscopic polyangiitis	TPE	III	1B
	Granulomatosis with polyangiitis	TPE	III	1B
	Eosinophilic granulomatosis with polyangiitis	TPE	III	2C
Vasculitis, IgA	Crescentic rapidly progressive glomerulonephritis	TPE	III	2C
	Severe extra-renal manifestations	TPE	III	2C
Vasculitis, other	Hepatitis B polyarteritis nodosa	TPE	II	2C
	Kawasaki disease[a]	TPE	III	2C
	Multisystem inflammatory syndrome in children[a]	TPE	III	2C

2020 update.

Disease	Modality	Indication	Category
AAV	TPE	MPA/GPA/RLV: RPGN, Scr ≥5.7 mg/dL	II[a]
	TPE	MPA/GPA/RLV: RPGN, Scr <5.7 mg/dL	III
	TPE	MPA/GPA/RLV: DAH	I
	TPE	EGPA	III

Transplant

Transplantation, kidney, ABO compatible	Antibody-mediated rejection	TPE/IA	I	1B
	Desensitization/prophylaxis, living donor	TPE/IA	I	1B
Transplantation, kidney, ABO incompatible	Desensitization, living donor	TPE/IA	I	1B
	Antibody mediated rejection	TPE/IA	II	1B
Transplantation, liver	Desensitization, ABOi, living donor	TPE	I	1C
	Desensitization, ABOi, deceased donor	TPE	III	2C
Graft-versus-host disease	Acute	ECP	II	1B
	Chronic	ECP	II	1B
Focal segmental glomerulosclerosis	Recurrent in kidney transplant	TPE/IA	I	1B
	All types	LA	II	2C
	Steroid resistant in native kidney	TPE	III	2C

Others

Sepsis with multiorgan failure		TPE	III	2A
Sickle cell disease, acute	Acute stroke	RBC exchange	I	1C
	Acute chest syndrome, severe	RBC exchange	II	1C
	Other complications[a]	RBC exchange/TPE	III	2C
Sickle cell disease, non-acute	Stroke prophylaxis	RBC exchange	I	1A
	Pregnancy	RBC exchange	II	2B
	Recurrent vaso-occlusive crises	RBC exchange	II	2B
	Pre-operative management	RBC exchange	III	2A
Hyperviscosity in hypergammaglobulinemia	Symptomatic	TPE	I	1B
	Prophylaxis for rituximab	TPE	I	1C
Lambert-Eaton myasthenic syndrome		TPE	II	2C
Lipoprotein(a) hyperlipoproteinemia	Progressive atherosclerotic cardiovascular disease	LA	II	1B
Familial hypercholesterolemia	Homozygotes	LA	I	1A
	Heterozygotes	LA	II	1A
	All patients	TPE	II	1B

Nephrology-Specific Indications

- Autoantibodies are frequently associated with primary kidney diseases and are ideal candidates for TPE.

  -> few kidney diseases have evidence

- The **2021 KDIGO** glomerular diseases guideline, the only recommendation for TPE is for **anti-GBM disease (KDIGO grade 1C)**.

Anti-GBM Disease

- **IgG Ab** directed against the **α3 chain of type IV collagen** -> GN and/or alveolar hemorrhage.
- Kidney failure: 55% of patients despite treatment
- No benefit from TPE: 100% crescents or >50% global glomerulosclerosis and no pulmonary hemorrhage.
- Management: corticosteroids, **cyclophosphamide**, and TPE
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - **Frequency: QD**
  - Replacement fluid: Albumin or FP if DAH
  - Duration: at least **10-20 days** and until resolution or Ab(-)

Catastrophic Antiphospholipid Syndrome (CAPS)

- 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. (large vessels).
- The 65% of episodes have a precipitating event.
- Management: **anticoagulation**, steroids, and TPE and/or IVIG
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - **Frequency: QD or QOD**
  - Replacement fluid: FP or (FP + albumin)
  - Duration: at least **3 to 5 sessions**

FSGS Following Kidney Transplant

- Etiology unknown, maybe **anti-nephrin antibodies**
- Occur: First allograft: 20%-50% and 80%-100% in subsequent allografts.
- 30%-60% of patients -> ESRD within 3-7 years
- Management: steroids, **rituximab**, and TPE and/or IV immunoglobulin, **lipoprotein apheresis (BIW * 3 weeks)**, or immunoadsorption with regenerative adsorbers
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - **Frequency: QD or QOD**
  - Replacement fluid: Albumin
  - Duration: **QD*3 and then 6 次/週* 2 週**

TMA: Factor H Autoantibody–Mediated

- Cause of thrombotic microangiopathy (TMA): activation of the **alternative pathway** of complement
- Genetic variants: 60% of patients, and an autoantibody inhibiting complement factor H function **<10%**.
- Management: TPE and/or **eculizumab** with immunosuppression
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - **Frequency: QD**
  - Replacement fluid: FP or (FP + albumin)
  - Duration: Until clinical response or Ab titer reduced to less than clinical threshold **(similar to immune TTP)**

TMA: Ticlopidine Associated

- Drug-induced TMA: ticlopidine, calcineurin inhibitors, and gemcitabine.
- Ticlopidine usually presents with severely diminished ADAMTS13 levels (<10%) **within 2 weeks of drug exposure**, -> Ab against ADAMTS13.
- Management: Drug discontinuation + TPE
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - Frequency: **QD-QOD**
  - Replacement fluid: FP
  - Duration: **QD** until recovery of hematologic parameters **(similar to immune TTP)**

TMA: TTP

- Management: Steroids and TPE; **rituximab** (和TPE要隔24小時); **caplacizumab** (against vWF)

- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - Frequency: **QD-QOD**
  - Replacement fluid: FP
  - Duration: **QD until PLT >150 × 10^3/μL** and LDH near normal for 2-3 consecutive days

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

- Management: AMR can be treated with TPE, double filtration plasmapheresis, and immunoadsorption, desensitization regimens include IVIG, rituximab, and optional additional immunosuppression
- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - Frequency: **QD-QOD**
  - Replacement fluid: Albumin or FP + IVIG 100-200 mg/kg
  - Duration:
    - For AMR, 5 or 6 sessions or based on clinical outcomes and decrease in donor-specific antibody titers
    - For desensitization, until cross-match < institution - dependent thresholds or at least 3 sessions post-OP

Living Donor ABO-Incompatible Kidney Transplant, Desensitization

- Management: TPE, immunoadsorption

- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - Frequency: **QD-QOD**
  - Replacement fluid: Albumin or FP(ABO compatible)
  - Duration: **Until cross-match < institution -dependent thresholds before transplant**

ANCA–associated vasculitis

- Management: Induction with **pulsed methylprednisolone** and **rituximab or cyclophosphamide** with or without TPE

- TPE prescription:
  - Plasma volume: 1-1.5 EPV
  - Frequency: **QD-QOD**
  - Replacement fluid: Albumin or FP if DAH
  - Duration: **7 -12 sessions** over a median 14 days

General Considerations

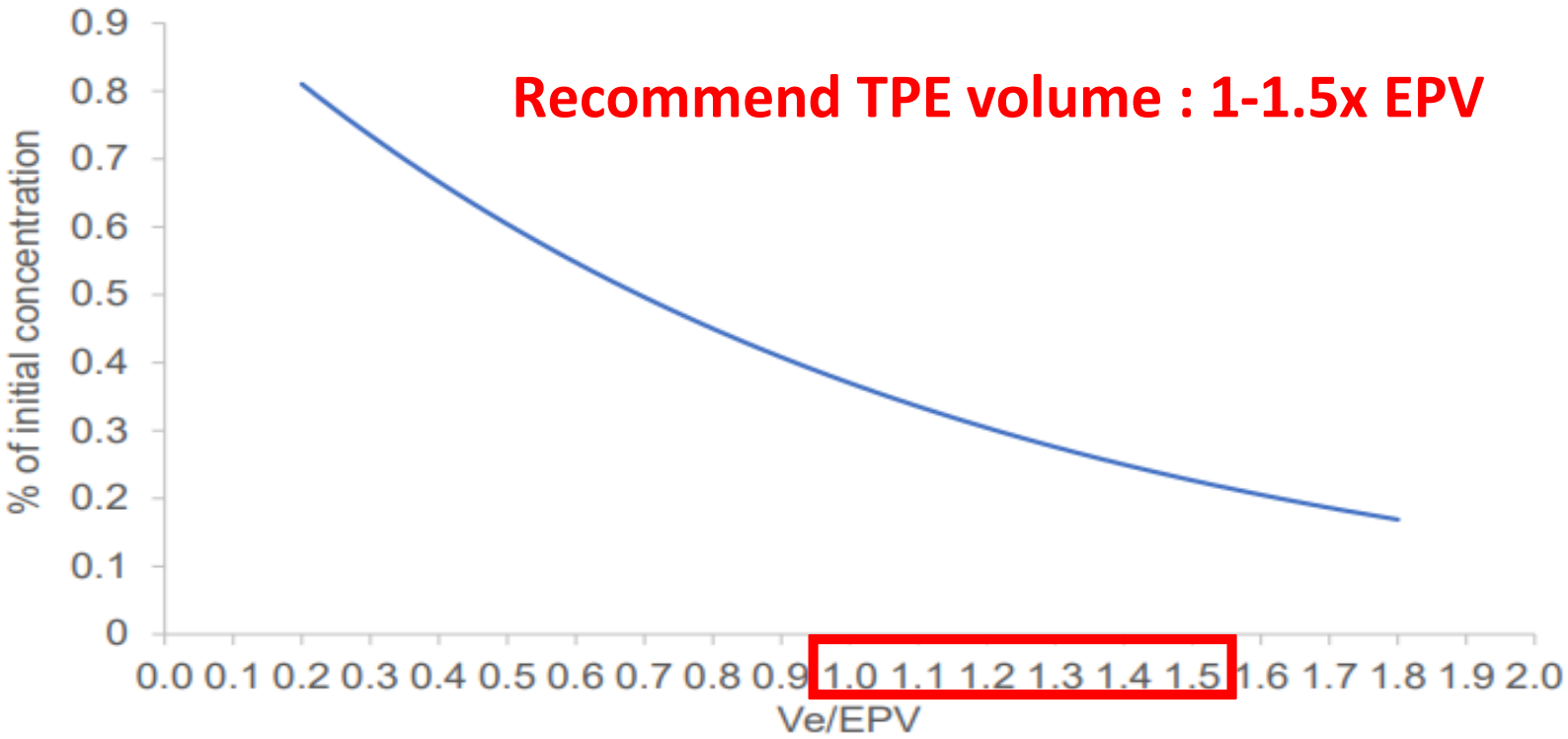
- Vascular access
  - CVC
  - AV fistula or graft
- Anticoagulant
  - Heparin
  - Citrate
- Replacement fluid
  - FFP
  - Albumin

Prescription principles

- Estimated plasma volume (EPV)

  = (0.065 × BW) × (1 – Hct)

- $X_1 = X_0 - V_e/EPV$ (X_1 : 最終血漿濃度, X_0初始濃度, V_e:交換的體積)



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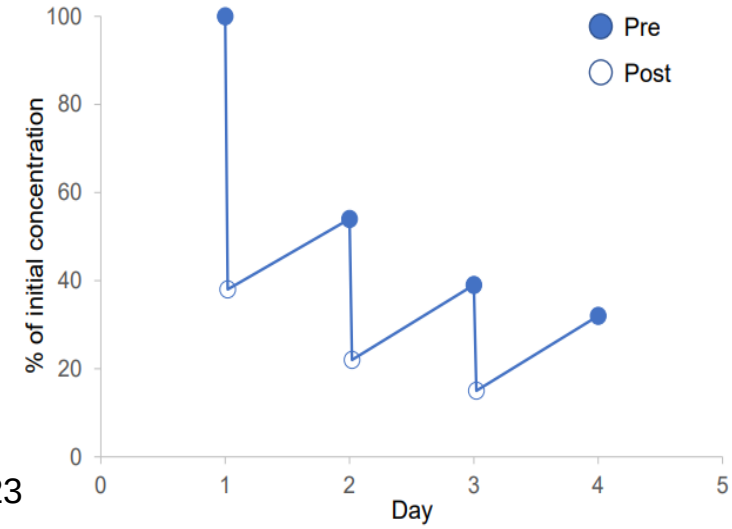
Number of Exchanges, Duration, and Discontinuation

- Example: 70 kg adult, Hct 34%
- Replacement Fluids: 3 L / each TPE course
- Duration: 離心 TPE: 1.5-2 hrs, 膜過濾 TPE : 3 hrs

- **Determinants of the efficiency** of TPE
  - Sieving coefficient: 0 - 1.0
  - Plasma half-life: t ½
  - Extravascular concentration
  - Rate of synthesis



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Number of Exchanges, Duration, and Discontinuation

- In general, TPE performed every other day**(QOD) for 6 treatments** will decrease circulating IgG levels to 16%-20% of the baseline level.

- Diseases with a high autoantibody production rate (eg, **anti-GBM disease**) require **daily sessions** with concomitant immunosuppression.

Special Considerations

- **ACEI: hold before TPE 24-48 hrs**

  (Bradykinin degradation -> hypotension)

  –> hydrophilic, electronegative membranes: polyacrylonitrile AN69 filter, dextran sulfate systems, albumin replacement fluids, and Plasmaflo OP.

- Drug removal
  - High removal: **aspirin, phenytoin, propranolol, thyroxine** --> need **additional dose**
  - Low removal: prednisone, cyclosporine, tacrolimus, cyclophosphamide, rituximab

- Daily medication after TPE

- **very low volume of distribution (<0.2 L/kg)**
- **high protein binding (>80%)**.

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).

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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.

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Simultaneous Extracorporeal Therapies

- 如果 RRT or ECMO的病人用同套管路進行 TPE,
  --> access pressure alarms, circuit clotting, and risk of air embolism
- H/D 病人: 鹼血症 if 用FP當置換液 --> 如果要同日進行，**TPE須先於H/D**
- TPE不能拿來脫水(超過濾)
- **ECMO** 因用heparin抗凝，首選用**FP當置換液**
- TPEC**回血端**需**接在氧合器前**以防空氣栓塞。
- Need lower ECMO blood flow rates

Complications

- **Hypocalcemia**: 9%-19.6%, more frequent with frozen plasma (20%) than albumin (9%).
- **Hypokalemia**: serum K lower 25% with albumin replacement.

  → intermittent or a continuous IV Ca/K infusion with the returning blood.
- **Hypotension**: 0.4%-15%, albumin–saline solution replacement.
- Mortality rate: 0.03% - 0.05%.

Potential mechanisms of hypotension

- delayed or inadequate volume replacement
- vasovagal episodes
- **low oncotic fluid replacement**
- anaphylaxis
- transfusion-associated lung injury
- arrhythmia
- **bradykinin reactions**
- **bleeding from vascular access**
- cardiovascular collapse

Table 7. Complications Associated With TPE

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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

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Take home messages

- To remove a single pathogenic substance from the plasma.
- Ideal characteristics: large MW, slow formation, prolonged t1/2, high intravascular distribution, and low turnover.
- In ASFA guidelines, category I indicated apheresis as first-line therapy.
- TPE sessions typically exchange 1-1.5 volume.
- TPE provided significant benefits of pro-inflammatory clearance and reduction of 60-days mortality in selected patients with COVID-19.