Therapeutic Plasma Exchange in CNS Inflammatory Demyelinating Disease

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Apheresis

- Apheresis from the Greek - “to remove”
- A procedure in which blood of the patient or donor is passed through a medical device that **separates out one or more components of blood and returns the remainder** with or without extracorporeal treatment or replacement of the separated component

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

Definition

- **Plasmapheresis**
  - A procedure in which blood of the patient or the donor is passed through a medical device which separates plasma from other components of blood and the plasma is removed (i.e., less than 15% of total plasma volume) without the use of colloid replacement solution. This procedure is used to collect plasma for blood components or plasma derivatives.

- **Therapeutic plasma exchange (TPE)**
  - A therapeutic procedure in which blood of the patient is passed through a medical device which separates plasma from other components of blood. The plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin and/or plasma) or a combination of crystalloid/colloid solution..

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

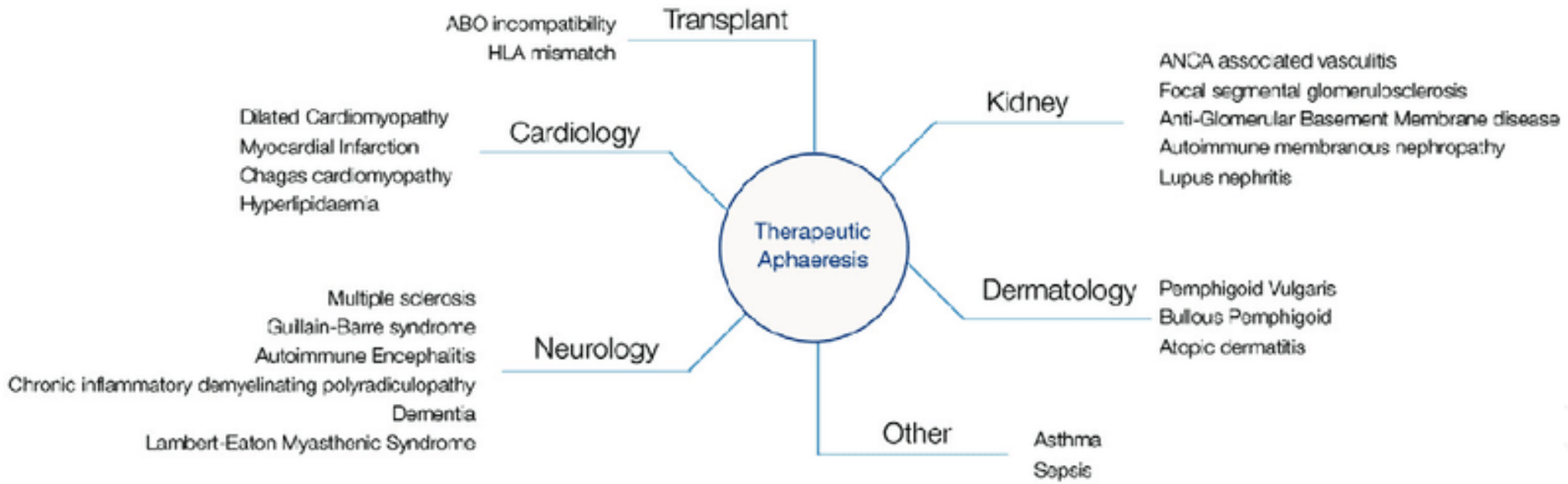
Therapeutic Plasma Exchange (TPE)

- Plasma of the patient is separated from other components of blood, either by membrane filtration (mTPE) or centrifugation (cTPE).
- The **plasma is removed with subsequent substitution of a replacement solution** (e.g., human albumin and/or plasma) or a combination of crystalloid/colloid solution.

- Very effective at removing
  - Plasma proteins, particularly of higher molecular weights (>30,000 Daltons)
  - Compounds bound to plasma proteins (>80%)
  - Substances with a low volume of distribution (Vd)
- Not a targeted removal methodology
  - Pathologic and non-pathologic substances removed by TPE

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

Clinical Application of Therapeutic Apheresis



Hamilton P, Harris R, Mitra S. Immunoadsorption Techniques and Its Current Role in the Intensive Care Unit. 2019.

Therapeutic Apheresis

- **Plasmapheresis**
  - Plasma collection from donors (AB type plasma- universal donor)
  - Plasma Exchange
  - Immunoadsorption
  - LDL apheresis
- **Cytapheresis**
  - Thrombocytapheresis
  - Leukocytapheresis
    - Hematopoietic progenitor cell collection
    - Photopheresis
  - Erythrocytapheresis
    - Red Cell Exchange (O type- universal donor)

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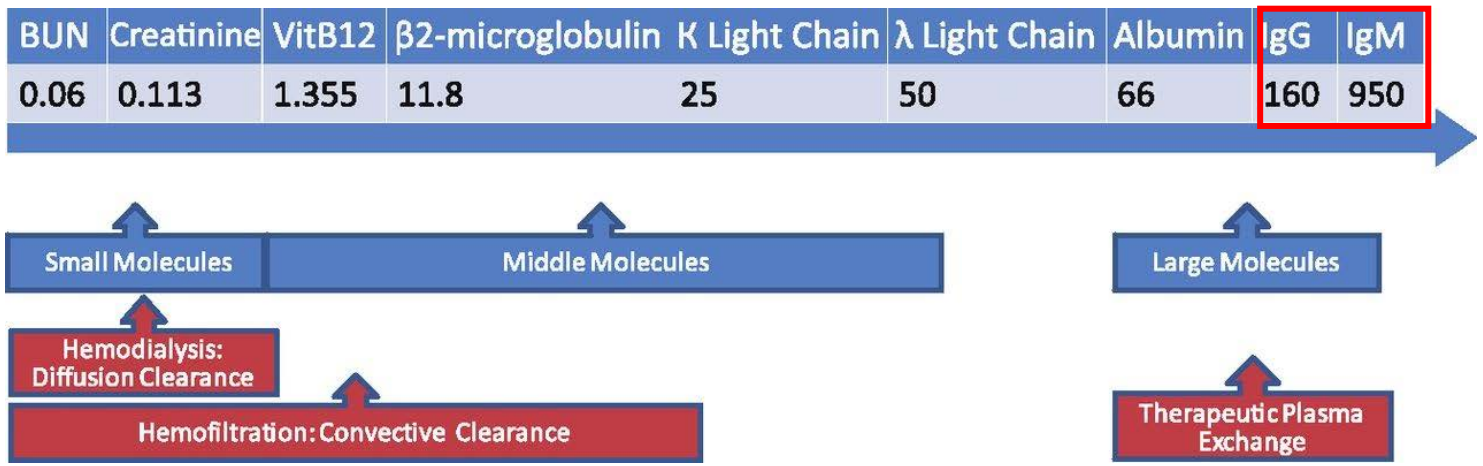
Modalities of Therapeutic Apheresis

Technique	Method	Type of pathogen removed
Plasma exchange	Centrifugation or filtration method of plasma separation – requires supplemental fluids	Antibodies, immunological complexes, other pathological proteins
Double filtration	Centrifugation or filtration method of plasma separation complemented with refiltration, requires supplemental fluids	Immunological complexes, autoantibodies, other pathological proteins
Cryofiltration	Centrifugation or filtration method of plasma separation complemented with re-filtration and cooling, does not require supplemental fluids	Cryoproteins
Plasma adsorption	Centrifugation or filtration method of plasma separation, adsorption on phenylalanine, tryptophan or polymyxin B-filled columns	Anti-DNA antibodies, myeloperoxidase, ANCA, IgG immunoglobulins, lupus-like anticoagulant, endotoxins, cytokines, C-reactive protein, immunological complexes, TNFα, VEGF, macrophage inflammatory protein
Immunoadsorption	Protein A, anti-IgG Fc antibodies adsorption (i.e. dextran sulfate)	Antibodies, protein complexes
LDL apheresis	Chemical compounds adsorption (tryptophan, polyacrylate)	LDL lipoprotein
Cytapheresis	Centrifugation method of plasma separation	CD8 lymphocytes, CD4, activated platelets, granulocytes

Korsak J, Wańkowicz Z. New Options of Apheresis in Renal Diseases: How and When? Blood Purif. 2016;41(1-3):1-10.

Ideal target molecule characteristics for therapeutic plasma exchange

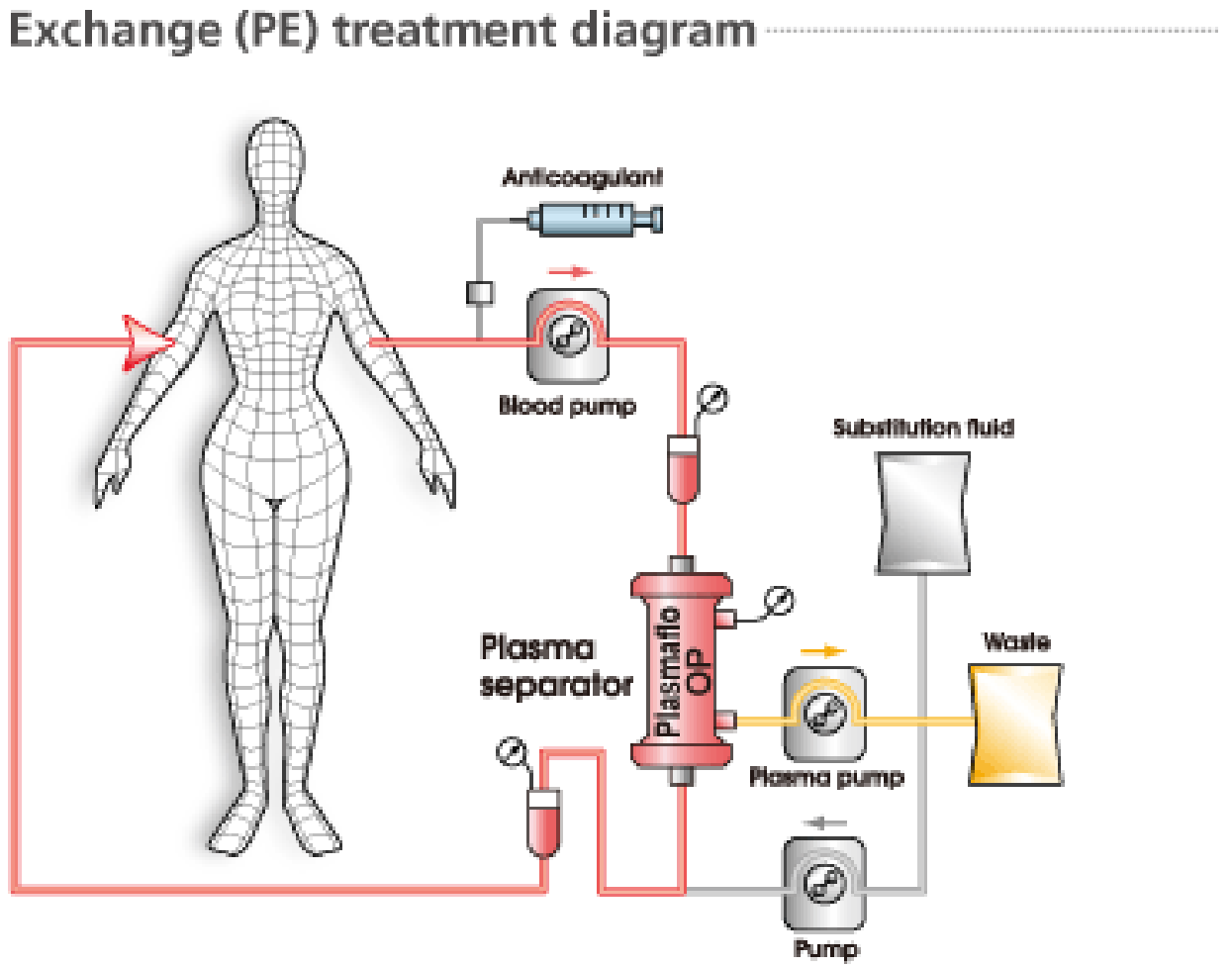
- Identified etiologic agent or toxic substance
- High molecular mass (≥15 kDa) so it cannot be easily removed by less expensive purification techniques such as hemofiltration or high-flux hemodialysis.
- Sufficiently long half-life
- Slow rate of formation
- Low turnover
- Low volume of distribution



Williams ME, Balogun RA. Principles of separation: indications and therapeutic targets for plasma exchange. *Clin J Am Soc Nephrol*. 2014;9(1):181-190.

Principle of TPE

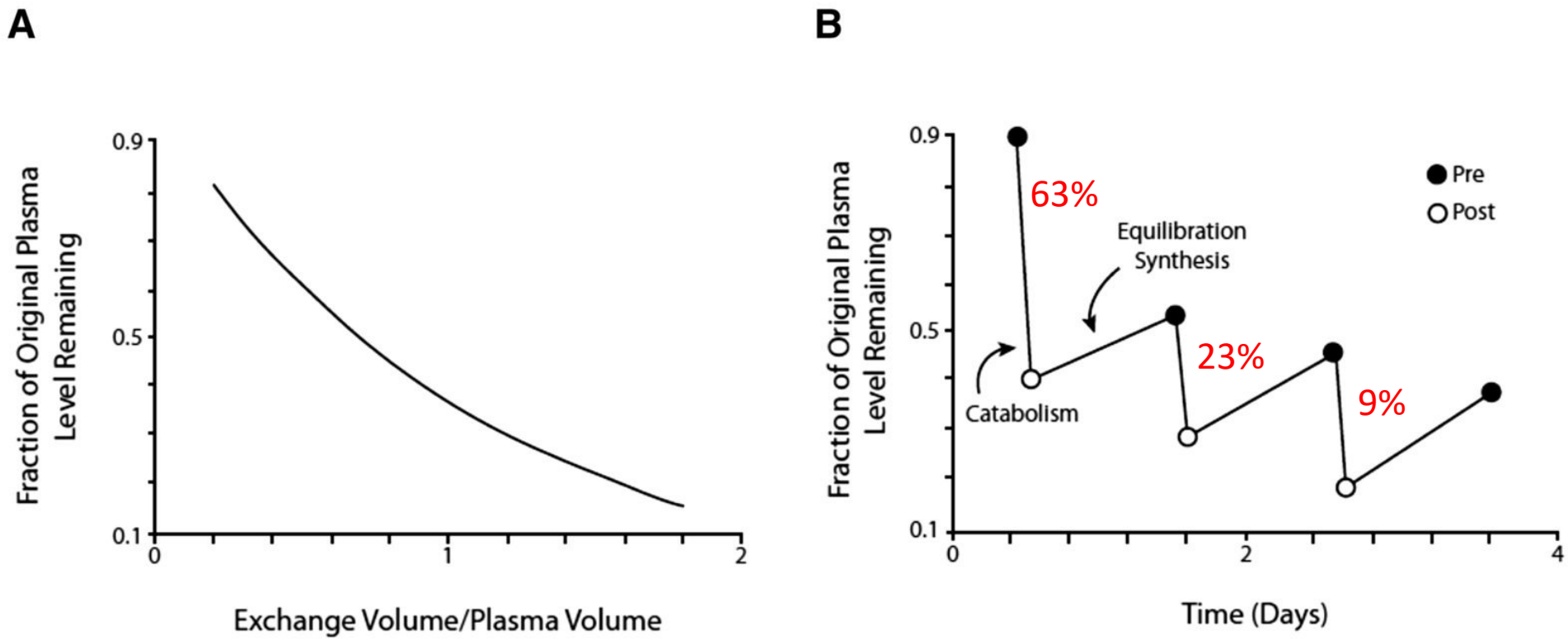
- Removal substance: fixed proportion (65%–70%) of 1 plasma volume
- The percent decrease in plasma concentration diminishes as higher total plasma volume is removed
- Reduction of targeted substance will be affected by
  - The redistribution from extravascular to intravascular compartments
  - Rates of synthesis
  - plasma t1/2 of target substance



Williams ME, Balogun RA. Principles of separation: indications and therapeutic targets for plasma exchange. *Clin J Am Soc Nephrol*. 2014;9(1):181-190.

Target molecule kinetics during therapeutic plasma exchange

1-1.5 PV exchange remove 63-78% of pathology substance



Estimated plasma volume (in liters) = 0.07 x weight (kg) x (1 - hematocrit)

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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

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.

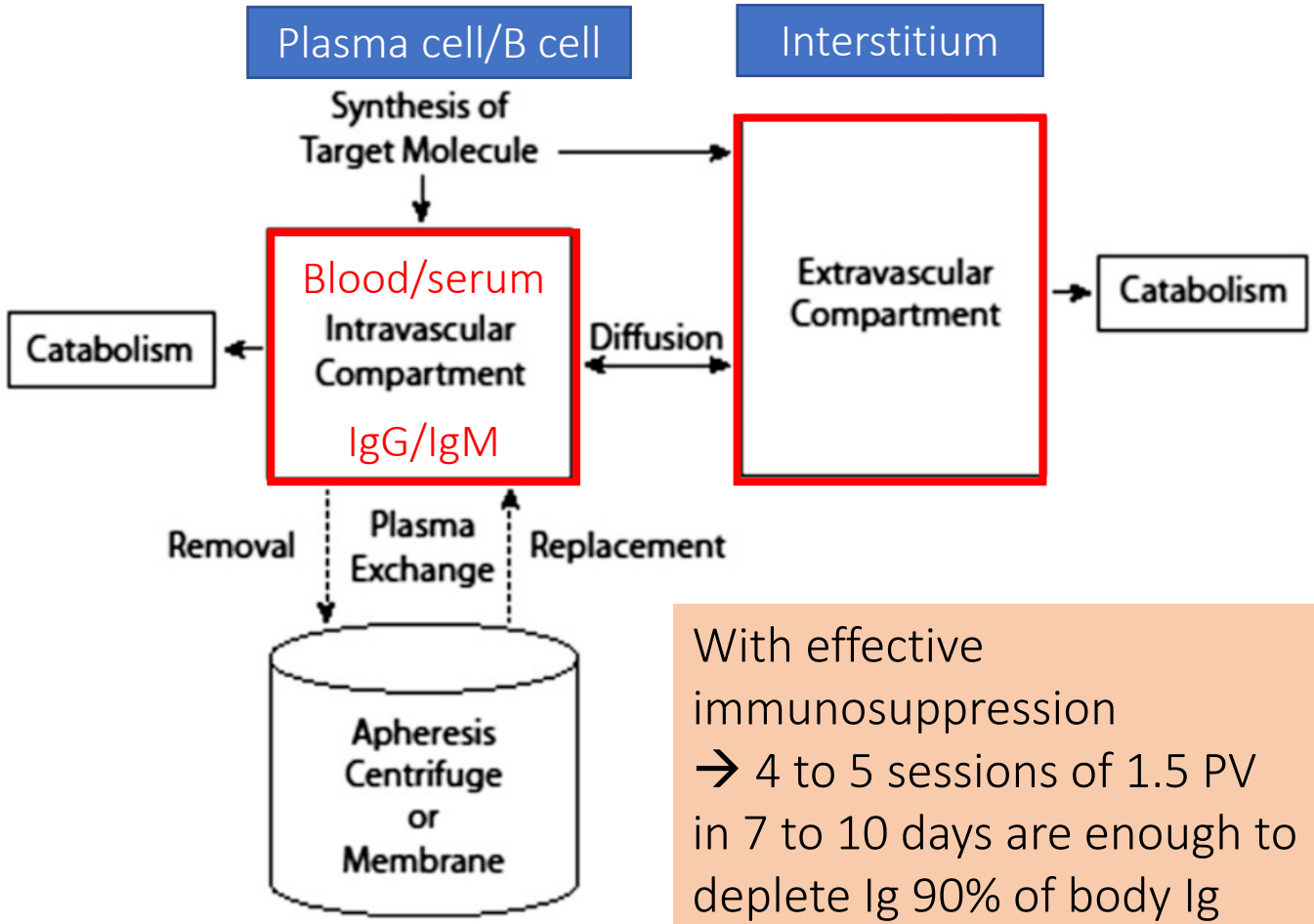
Cervantes CE, Bloch EM, Sperati CJ. Therapeutic Plasma Exchange: Core Curriculum 2023. Am J Kidney Dis. 2023;81(4):475-92.

	IgM	IgG	IgA	IgE	IgD
Heavy Chain	μ	γ	α	ε	δ
MW (Da)	900 K	150 K	385 K	200 K	180 K
% of total antibody in serum	6%	80%	13%	0.00%	1%
Fixes complement	Yes	Yes	No	No	No
Function	Primary response, fixes complement monomer serves as B-cell receptor	Main blood antibody, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva	Antibody of allergy and anti-parasitic activity	B-cell receptor
Half-life (days)	5	23	6	2.5	3

Muhammed Y. The Best IgG Subclass for the Development of Therapeutic Monoclonal Antibody Drugs and their Commercial Production: A Review. Immunome Research. 2020;16:1-12

Relationships between internal compartmental and external distribution

- **IgM**
  - 75% in intravascular
  - T1/2 : 5 days
  - • 1-2 sessions of PE enough for rapid reduce IgM
- **IgG**
  - Pathogenic Ab are mainly IgG
  - 30-45% in intravascular
  - T1/2 : 21 days
  - High rebound: IgG will return to 40% of pre-Rx level at 48 hours
  - PE x 6 to decrease IgG or 1/5 – 1/6 of baseline levels



With effective immunosuppression
→ 4 to 5 sessions of 1.5 PV in 7 to 10 days are enough to deplete Ig 90% of body Ig

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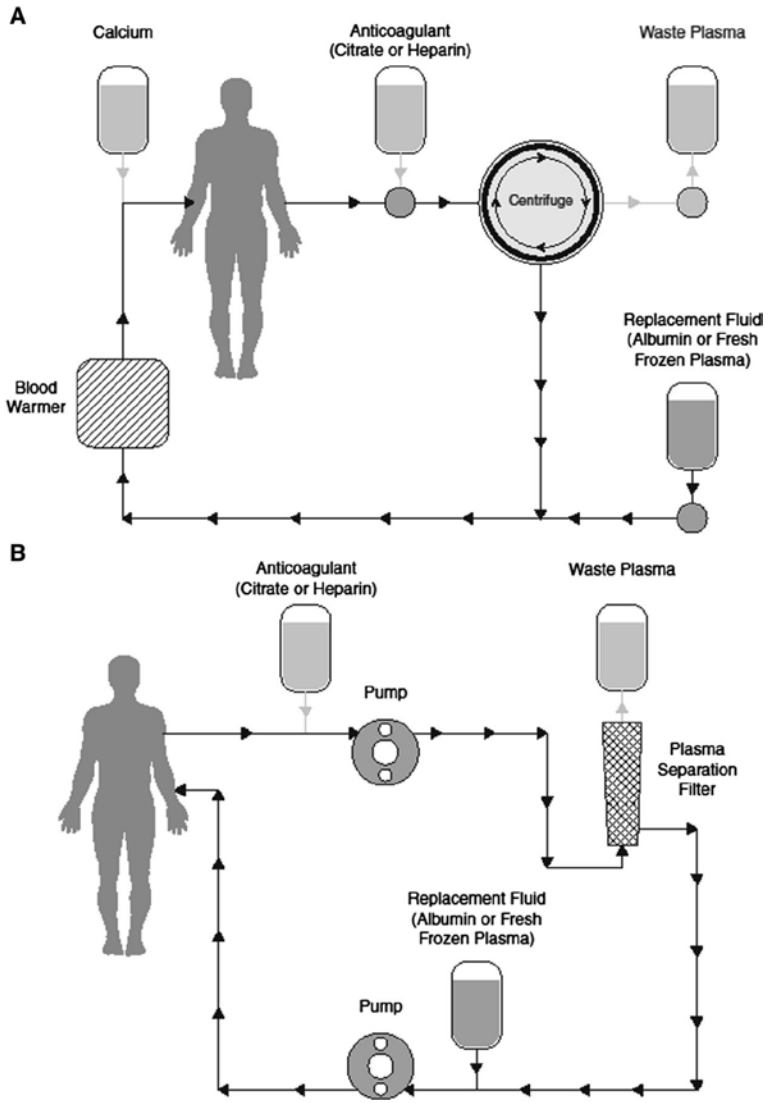
Apheresis Methods

Characteristic	Centrifuge	Membrane
Mechanism	Centrifugal force	Capillary membrane filter
Blood flow, mL/min	10-150 (potential peripheral access)	100-250, 150 average (requires central access)
Plasma extraction, %	80	30
Plasma removal, mL/min	Variable	30
Anticoagulation	Citrate	Heparin
Separation	Specific gravity	Molecular size
Blood volume in circuit, mL	Approximately 180	Approximately 125
Molecular weight cutoff, D	N/A	3 million
Sterilization	γ-radiation or ethylene oxide	Ethylene oxide
Fluid replacement	Albumin, fresh frozen plasma	Albumin, fresh frozen plasma



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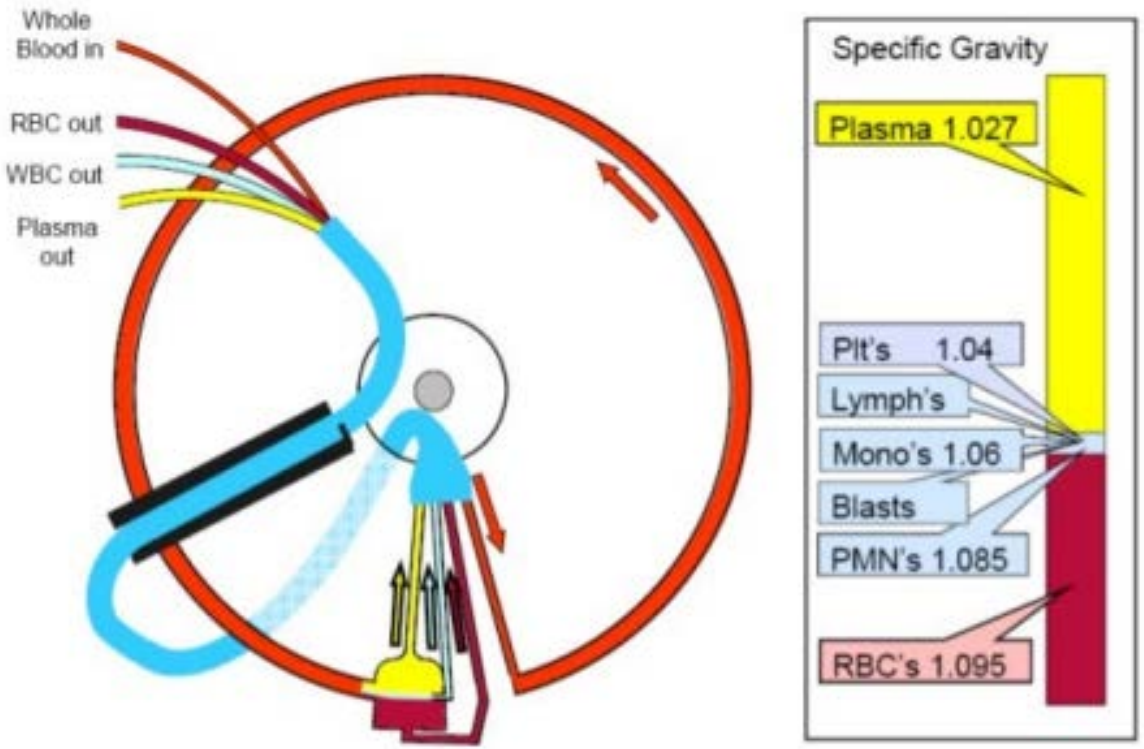
Centrifugation Apheresis

- Centrifugation and separation by specific gravity
  - Plasma 1,027
  - Platelets 1.04
  - Lymphocytes
  - Monocytes 1.05
  - Blast
  - PMN 1.085
  - Red blood cells 1.095
  - Immunoglobulin



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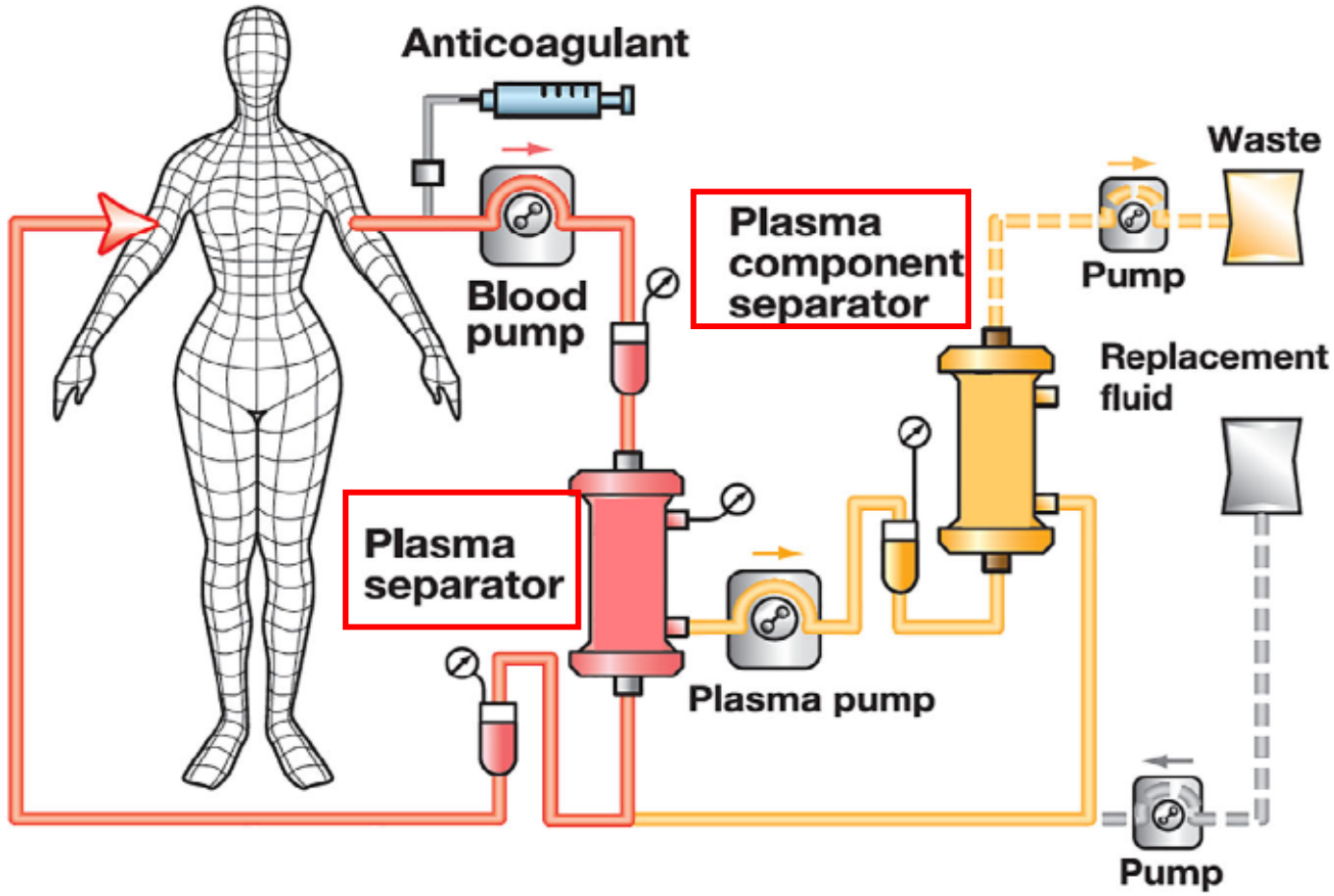
Double-filtration plasmapheresis (DFPP)

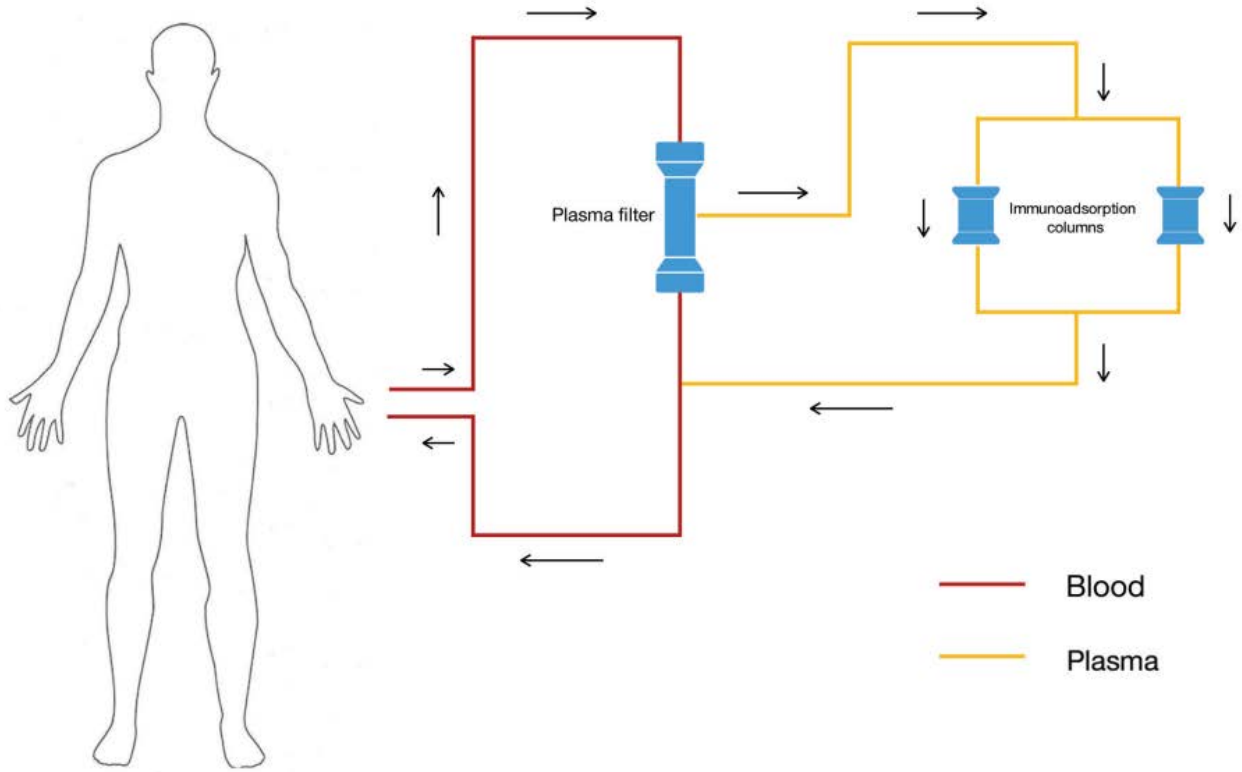
- A filter-based therapeutic procedure that removes pathogenic substances from separated plasma based on size
- 1st Plasma separator: remove plasma
- 2nd Plasma component separator: fractionated large and small molecular weight (e.g., autoantibodies, immune complexes, lipoproteins)
- More selective removal of pathogenic substances
- Reduce volume discarded and replacement fluid



Hirano R, Namazuda K, Hirata N. Double filtration plasmapheresis: Review of current clinical applications. Ther Apher Dial. 2021;25(2):145-51.

Immunoadsorption (IA)

- A selective method of therapeutic apheresis
- Patient plasma is passed through an absorber column which has a capacit to remove immunoglobulins and immune complexes by binding them to select ligands
- Advantage
  - Eliminating immunoglobulins and immune complexes without the necessity of human plasma product substitution



Multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-Barré syndrome (GBS), Autoimmune Encephalitis

Hamilton P, Harris R, Mitra S. Immunoadsorption Techniques and Its Current Role in the Intensive Care Unit. 2019.

Immunoadsorption type	Binding material	Available columns
Selective	Sepsis and septic shock	Pocard Toxipak
	CRP	PentraSorb CRP
	C1q	Miro
	ABO	Gylcosorb ABO and ABO Adsopak
	PDCM075 and PDCM349	Coraffin
	IgE	IgEnio
	Cholesterol	DALI
	Lipoproteins and macromolecules	MONET
	LDL cholesterol	Pocard LDL Lipopak
	Lipoprotein(a)	Pocard Lp (a) Lipopak
Semi-selective	Staphylococcal protein A	Immunosorba
	Sheep anti-human Ig	Therasorb and Ig-Adsopak
	Peptide-GAM	Globaffin and Ligasorb
Non-selective	Phenylalanine	Immunosorba PH
	Tryptophan	Immunosorba TR-350
	Dextran sulphate	Selesorb
Extracorporeal devices	oXiris	Endotoxins and cytokines
	CytoSorb	Cytokines
	Toraymyxin	Endotoxins

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Replacement Fluids

	Albumin	FFP
Advantages	• No infectious transmission risk • Allergic reaction are rare • No concern about blood group • Stored at room temperature • Depleted inflammation mediators	• Contain coagulation factors • Contain immunoglobulin (benefit) TTP, concomitant bleeding → FFP
Disadvantages	• Expensive • No immunoglobulin • Coagulopathy	• Increase infectious transmission risk • Allergic reaction • Cool storage • Must be ABO-compatible • Citrate load (hypocalcemia, alkalosis*)

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Apheresis Prescription

- ✓ Vascular access
- ✓Anticoagulant (citrate, heparin)
- ✓Volume processed (1-1.5 Plasma volume)
- ✓Replacement fluid (albumin, plasma, red blood cells)
- ✓Treatment plan (frequency and duration)

Prepare and Monitoring during TPE

- Body weight
- Lab: CBC, PT, aPTT, fibrinogen, electrolyte, calcium
- Vital signs and EKG monitoring
- Monitor complications during TPE e.g. hypotension, allergic reaction

Example

Dose: 1-1.5 x PV (0.07 x weight (kg) x (1 - Hct)

Vascular access: insert DLC at right IJV

BFR (Blood flow rate): 120 ml/min (100-150)

Plasma removal rate: 40 ml/min

Replacement fluid: Albumin

Anticoagulant: Heparin prime 1000 U Other

Medication: 10% calcium gluconate 10 ml iv

When

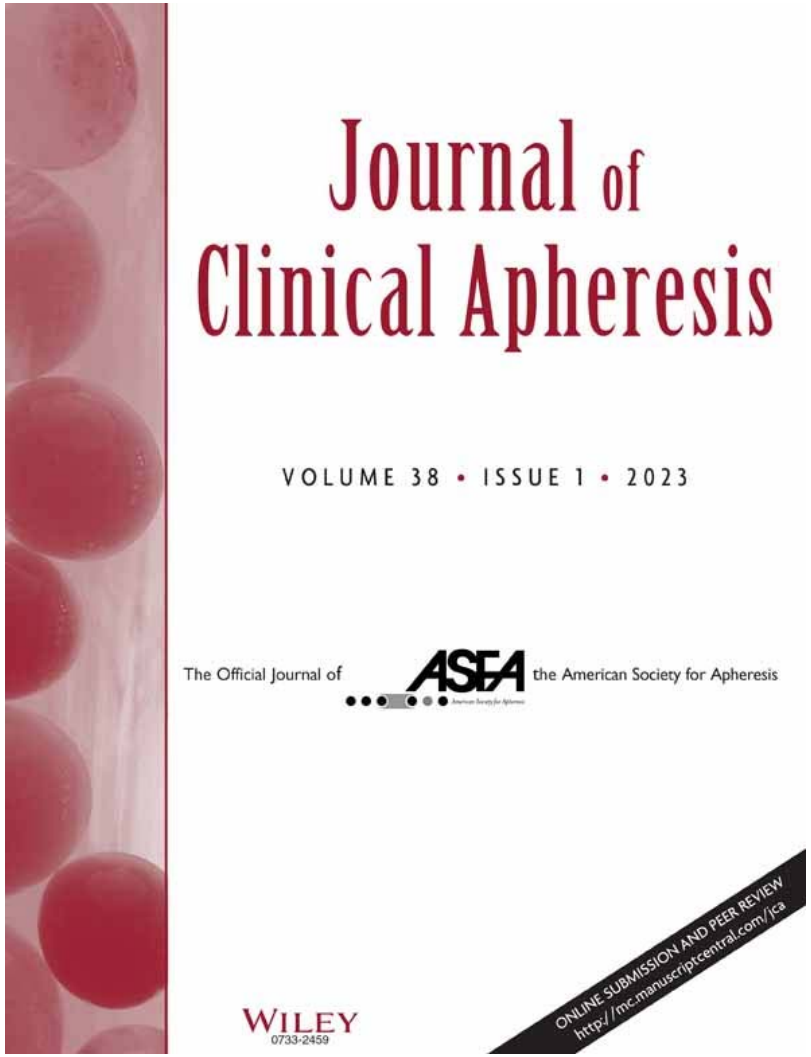


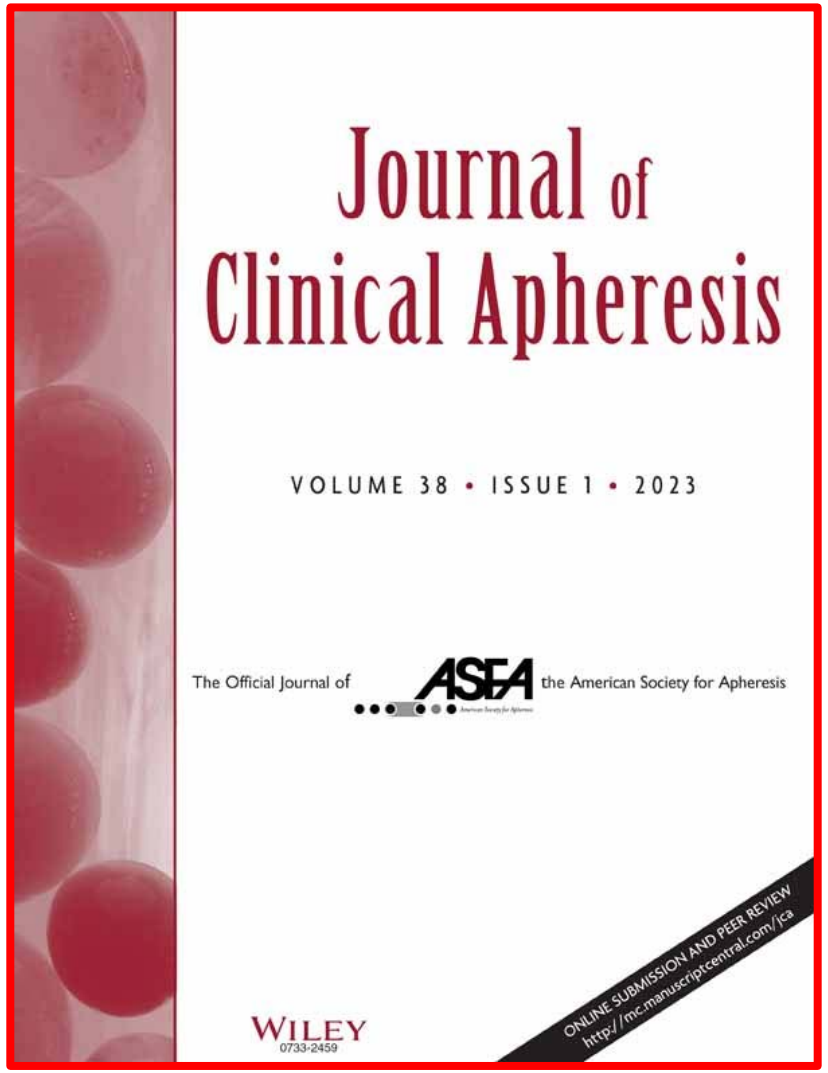
TABLE III. Modified McLeod's Criteria for Evaluation of Therapeutic Apheresis Efficacy

Evidence	McLeod's criteria	Explanation
Mechanism	"Plausible Pathogenesis"	The current understanding of the disease process supports a clear rationale for the use of therapeutic apheresis modality.
Correction	"Better Blood"	The abnormality, which makes therapeutic apheresis plausible, can be meaningfully corrected by its use.
Clinical Effect	"Perkier Patients"	There is a strong evidence that therapeutic apheresis confers benefit that is clinically worthwhile, and not just statistically significant.

45-284 (2013)

Schwartz J, Winters JL, Padmanabhan A, 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 sixth special issue. *J Clin Apher*. 2013;28(3):145-284.

When



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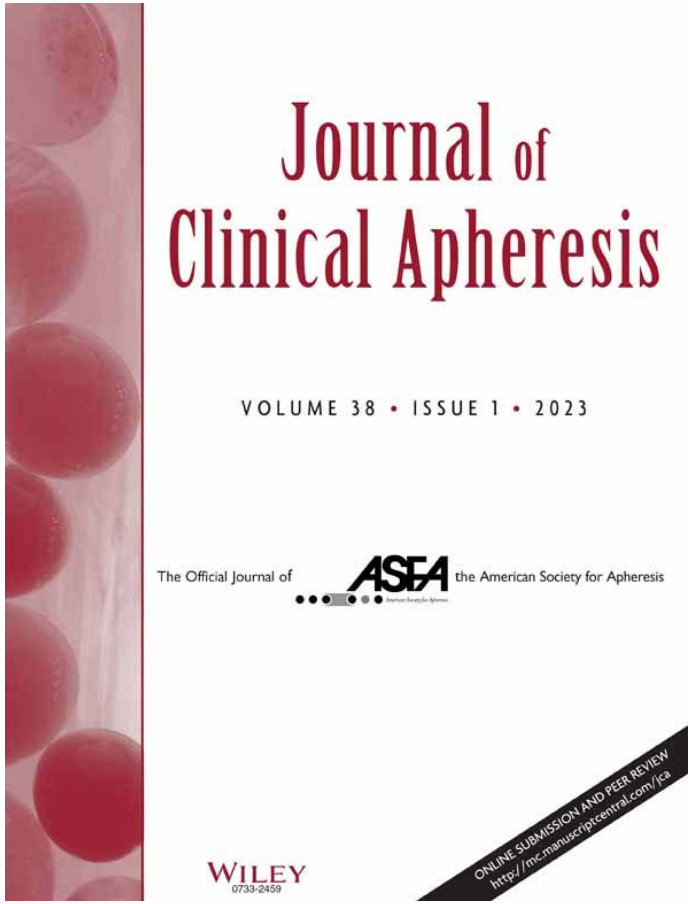
ASFA Special Issue/Guidelines

- Every 3-7 years, panel of apheresis experts convenes to review relevant literature – 1986, 1993, 2000, 2007, 2010, 2013
- Based on the published evidence
- – Disease-specific indications and guidance for use of therapeutic apheresis technologies are assigned
- – Accompanying fact sheets for disease pathophysiology, current treatment options, and rationales for therapeutic apheresis



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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 2023

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The ASFA Disease Categories

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

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The ASFA Recommendation GRADEs

- Recommendation Grades
  - Grade 1 – Strong recommendation
  - Grade 2 – Weak recommendation
  - A – High quality Evidence
  - B – Moderate quality evidence
  - C – Low or very low quality evidence

Recommendation	Description	Methodological quality of supporting evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
Grade 2A	Weak recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

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ASFA Categories

- Category I - Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
- Example of Category I indications – plasma exchange
  - TTP
  - AIDP
  - CIDP
  - MG
  - Hyperviscosity in monoclonal gammopathies
  - Cryoglobulinemia

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ASFA Categories

- Category II - Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment
- Example of Category II indications
  - Babesiosis
  - Acute Central Nervous system Demyelination
  - LEMS

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ASFA Categories

- Category III - Optimum role of apheresis therapy is not established. Decision making should be individualized.
- Example of category III
  - Acute liver failure (2B)
  - ANCA – associated rapidly progressive glomerulonephritis, dialysis independent (2C)
  - Warm AIHA (2C)

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ASFA Categories

- Category IV- Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances
- Examples of Category IV indications
  - Systemic amyloidosis
  - Amyotrophic Lateral Sclerosis
  - POEMS
  - Dermatomyositis/polymyositis

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Therapeutic Apheresis in Neurological Disorders

Disease	TA MODALITY	Indications	Category	Grade	Timeline/procedure frequency
Acute disseminated encephalomyelitis (ADEM)	TPE	Steroid refractory	II	2C	5-7 treatments, every other day, clinical response within days
Acute inflammatory demyelinating polyradiculoneuropathy (GBS)	TPE IA	Primary treatment Primary treatment	I I	1A 1B	Exchange 1–1.5 plasma volumes, 5-6 times over 10–14 days; some patients may need additional treatments
Age related macular degeneration, dry	Rheopheresis	High-risk	II	2B	Clinical benefit of a single course of treatment, reported to last for up to 4 years; repeated treatment over several years not systematically investigated
Amyloidosis, systemic	TPE	Other causes	IV	2C	NA
Chronic focal encephalitis (Rasmussen encephalitis)	TPE		III	2C	NA
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	TPE IA		I I	1B 1B	TPE or IA short-term benefit, rapid deterioration may occur; maintenance treatment may be necessary, with repeated TPE, IA (2-3/week or monthly until improvement); frequency tailored to symptoms and tolerability of the patient
Complex regional pain syndrome	TPE	chronic	III	2C	NA
Lambert-Eaton myasthenic syndrome	TPE		II	2C	Treatment until clear clinical and EMG response, at least 2–3-week course of TPE. Repeated courses in case of neurological relapse. TPE regimens: 5–15 TPE over 5–19 days to 8–10 TPE, at 5–7-day intervals
Multiple sclerosis	TPE IA TPE IA	Acute attack/ relapse Acute attack/ relapse Chronic Chronic	II II III III	1A 1B 2B 2B	Acute MS attack/relapse unresponsive to steroids, 5–7 TPE or IA procedures (response rate: >50%). Frequency: Acute attack/relapse: 5–7 TPE over 10–14 days NA

Transfus Med Hemother 2023;50:88–97

Therapeutic Apheresis in Neurological Disorders

Disease	TA MODALITY	Indications	Category	Grade	Timeline/procedure frequency
Neuromyelitis optica spectrum disorders (NMOSD)	TPE IA TPE	Acute attack/ relapse acute attack/relapse Maintenance	II II III	1B 1C 2C	Acute attack/relapse: daily or every other day. 5 procedures on average for acute exacerbation; range: 2–20 procedures. Early initiation of apheresis (≤5 days since clinical onset). Individually adjusted intervals for maintenance treatment
N-methyl-D-aspartate receptor antibody encephalitis	TPE/IA		I	1C	5-12 treatments with TPE or IA over 1–3 weeks; individually adjusted number of and intervals between treatments. If patients do not improve rapidly after TPE or IA, longer periods are required
Paraneoplastic neurological syndromes	TPE/IA		III	2C	NA
Paraproteinemic demyelinating neuropathies; Chronic acquired demyelinating polyneuropathies	TPE TPE TPE TPE	IgG/IgA/IgM Anti-MAG neuropathy Multiple myeloma Multifocal motor neuropathy	I III III IV	1B 1C 2C 1C	Typical course is 5–6 treatments over 10–14 days, regimen guided by clinical response NA NA
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS); Sydenham's chorea	TPE TPE	PANDAS exacerbation Sydenham's chorea, severe	II III	1B 2B	Daily or every other day. Three to 6 procedures over 1–2 weeks NA

Adapted from ASFA Guidelines, 2019

Transfus Med Hemother 2023;50:88–97

Therapeutic Apheresis in Neurological Disorders

Disease	TA MODALITY	Indications	Category	Grade	Timeline/procedure frequency
Progressive multifocal leukoencephalopathies (PMLs) associated with natalizumab	TPE		III	1C	NA
Steroid-responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto's encephalopathy)	TPE		II	2C	Daily to every other day 3–9 procedures, mostly commonly 5
Stiff-person syndrome	TPE		III	2C	NA
Sudden sensorineural hearing loss	LA/ rheopheresis/ TPE		III	2A	NA
Voltage-gated potassium channel (VGKC) antibody related diseases	TPE/IA		II	1B	5–10 treatments with TPE or IA over 7–14 days adjusted to the individual curse. Disease activity/symptom severity monitored by anti-VGKC titers. Treatment course: response of clinical symptoms

Adapted from ASFA Guidelines, 2019

Transfus Med Hemother 2023;50:88–97

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Evidence-based guideline update: Plasmapheresis in neurologic disorders

Disease	Conclusion	Quality
Acute inflammatory demyelinating polyneuropathy/Guillain-Barré syndrome	Established effective	Class I
Chronic inflammatory demyelinating polyneuropathy, short-term treatment	Established effective	Class I
Polyneuropathy with monoclonal gammopathies of undetermined significance		
Immunoglobulin A/immunoglobulin G	Probably effective	Class I
Immunoglobulin M	Probably ineffective	Class I
Myasthenia gravis		
Preoperative preparation	Insufficient evidence	Class III
Crisis	Insufficient evidence	Class III
Fulminant demyelinating CNS disease	Possibly effective	Class II
Chronic or secondary progressive multiple sclerosis	Established ineffective	Class I
Relapses in multiple sclerosis	Probably effective	Class I
Sydenham chorea	Insufficient evidence	Class III
Acute obsessive-compulsive disorder and tics in PANDAS	Insufficient evidence	Class III

Cortese I, Chaudhry V, So YT, Cantor F, Cornblath DR, Rae-Grant A. Evidence-based guideline update: Plasmapheresis in neurologic disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2011;76(3):294-300

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 2023

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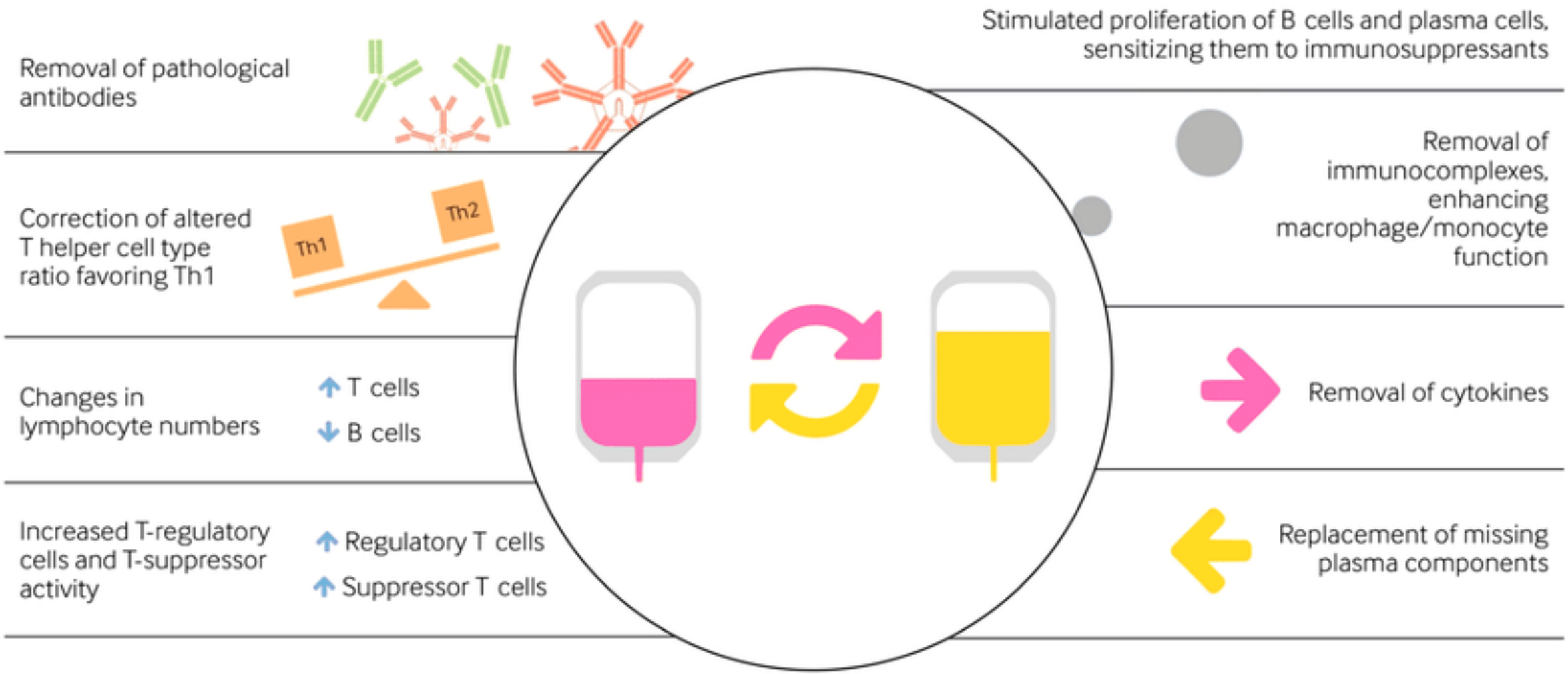
Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

Therapeutic Apheresis in CNS –IDD and Autoimmune Encephalitis

Proposed Mechanism of Action of PLEX



Jacob S, Mazibrada G, Irani SR, Jacob A, Yudina A. The Role of Plasma Exchange in the Treatment of Refractory Autoimmune Neurological Diseases: a Narrative Review. J Neuroimmune Pharmacol. 2021;16(4):806-17.

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

- The pathogenesis is though to be disseminated multifocal inflammation and patchy demyelination associated with transient autoimmune response against MOG or other autoantigen
- Current management
  - High-dose intravenous corticosteroids, such as methylprednisolone 2—30 mg/kg/day (maximum 1 gm/day), followed by a prolonged oral prednisolone taper over 3-6 weeks
  - IVIG 2 gm/kg/course, given over 2-5 days, is typically reserved for patients who are steroid unresponsive

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

Incidence: <1/100,000/years (age <20 years), adult estimates not available

Indication	Procedure	Category	Grade
Steroid refractory	TPE	II	2C

# reported patients: 100 to 300	RCT	CT	CS	CR
	0	0	20 (154)	NA

Controlled trials

Case Series

Case Report

- In patients with fulminant ADEM who respond poorly to steroid treatment and/or IVIG,
  - TPE can be considered as second-line therapy, when used alone or in conjunction with other therapeutic modalities
  - Early initiation of TPE (within 15 days of disease onset) was a predictor of clinical improvement in 6 months

- Volume treated: 1 to 1.5 TPV
- Frequency: Every other day
- Replacement fluid: Albumin

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

Multiple Sclerosis (MS)

- MS lesions can appear throughout the CNS and are recognized in the white matter as focal areas of demyelination, inflammation, and glial reaction
- MS pathophysiology is thought to be mediated by humoral and cell mediated autoimmunity as well as genetic and environmental factors (including EBV infection)
- Standard treatment
  - For CIS or acute MS attacks or relapses is high dose glucocorticoids.
  - In 20% to 25% of patients who do not respond to steroids after an interval of 10 to 14 days, treatment with therapeutic apheresis should be considered

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

Multiple Sclerosis (MS)

Prevalence: 300/100,000 (United States)

Indication	**Procedure**	**Category**	**Grade**
Acute attack/relapse	TPE	II	1A
	IA	II	1B
Chronic primary or secondary progressive	TPE/IA	III	2B

# reported patients: >300	**Procedure**	**RCT**	**CT**	**CS**	**CR**
Acute attack/relapse	TPE	4 (237)	2 (189)	NA	NA
	IA	2 (99)	4 (273)	NA	NA
Chronic primary or secondary progressive	TPE	4 (300)	2 (50)	NA	NA
	IA	0	0	2 (27)	0

- TPE or IA may benefit patients with MS by the immediate removal of plasma-based antibodies and immune complexes, induction of a redistribution of antibodies from the extravascular space, and subsequent immunomodulatory changes

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

SPECIAL ARTICLE

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Evidence-based guideline update: Plasmapheresis in neurologic disorders

Disease	Conclusion	Quality
Acute inflammatory demyelinating polyneuropathy/Guillain-Barré syndrome	Established effective	Class I
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Relapses in multiple sclerosis	Probably effective	Class I
Sydenham chorea	Insufficient evidence	Class III
Acute obsessive-compulsive disorder and tics in PANDAS	Insufficient evidence	Class III

- Plasmapheresis should be considered for the **adjunctive treatment** of exacerbations in relapsing forms of MS (Level B)
- Plasmapheresis may be considered in the treatment of **fulminant CNS demyelinating** diseases that **fail to respond to high-dose corticosteroid** treatment (Level C)
- Plasmapheresis **should not be offered for chronic progressive or secondary progressive MS**

Multiple Sclerosis (MS)

- Similar efficacy of TPE and IA (50-70%)
- In pregnancy, apheresis can be considered since currently available disease modifying therapies for MS are contraindicated
- TPE/IA also used for drug removal in patients with Natalizumab – PML (Category III, evidence 1C) → Not associated with decrease mortality and disability

- Volume treated: 1 to 1.5 TPV with TPE; 2 to 2.5 liters for tryptophan-IA (manufacturer's recommendation); up to 2.5 TPV with regenerative immune adsorbers
- Frequency: Acute attack/relapse: 5 to 7 over 10 to 14 days
- Replacement fluid: TPE: albumin; IA: NA

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)

- Autoantibodies against AQP4-IgG are pathogenic in NMOSD.
- Binding of AQP4-IgG to astrocyte AQP4 channels triggers classical complement cascade activation, followed by granulocyte, eosinophil, and lymphocyte infiltration, cytokine release, and blood-brain barrier disruption, culminating in injury first to astrocytes, then oligodendrocytes, demyelination, neuronal loss, and neurodegeneration.
- Standard treatment
  - High-dose intravenous corticosteroids (e.g., methylprednisolone, 1g daily for 3-5 days) followed by oral taper, and TPE or IA are the therapeutic mainstay for acute attacks
  - Immunosuppressive, monoclonal antibodies (CD20 –Rituximab, CD16-Inebilizumab), IL-6 inhibitor (Satralizumab), C5-inhibitor (Eculizumab) are used for long-term stabilization

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)

Incidence: <1/100,000/year

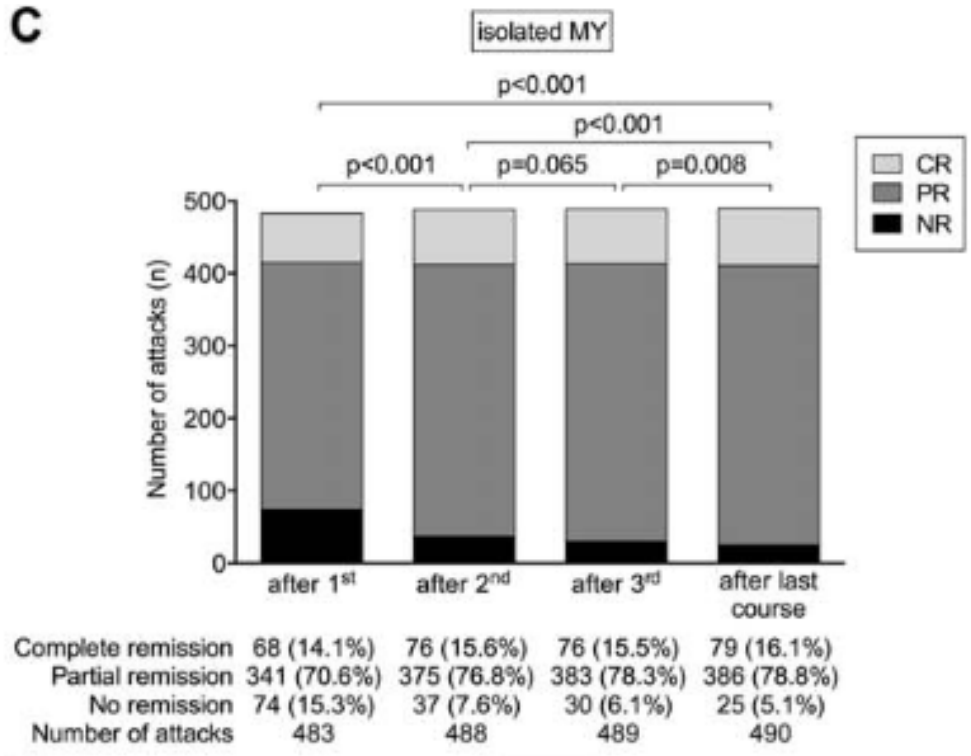
Indication	**Procedure**	**Category**	**Grade**
Acute attack/relapse	TPE	II	1B
	IA	II	1C
Maintenance	TPE	III	2C

# reported patients: >300	**Procedure**	**RCT**	**CT**	**CS**	**CR**
Acute attack/relapse	TPE	1 (11)	5 (297)	>10 (>200)	NA
	IA	0	1 (61)	5 (60)	17 (21)
Maintenance	TPE	0	1 (30)	1 (7)	1 (2)

- Early initiation of TPE or IA are recommended within 5 days from of onset
- TPE can be administered as first-line therapy or simultaneously with steroids in severe cases
- Prompt initiation of TPE is a strong predictor of beneficial outcomes in severe attack

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

Neuromyelitis Optica: Evaluation of 871 Attacks and 1,153 Treatment Courses



- Predictors for Complete Remission
  - Presence of myelitis (OR50.38, 95% CI50.21–0.70,p50.002)
  - CR from previous attack (OR56.85, 95% CI53.65–12.84,p<0.001)
  - First-line PE/IA versus HD-S(OR54.38, 95% CI51.54–12.50,p50.006).
- Isolated myelitis responded better to plasma exchange/immunoadsorption than high dose steroid as first treatment course

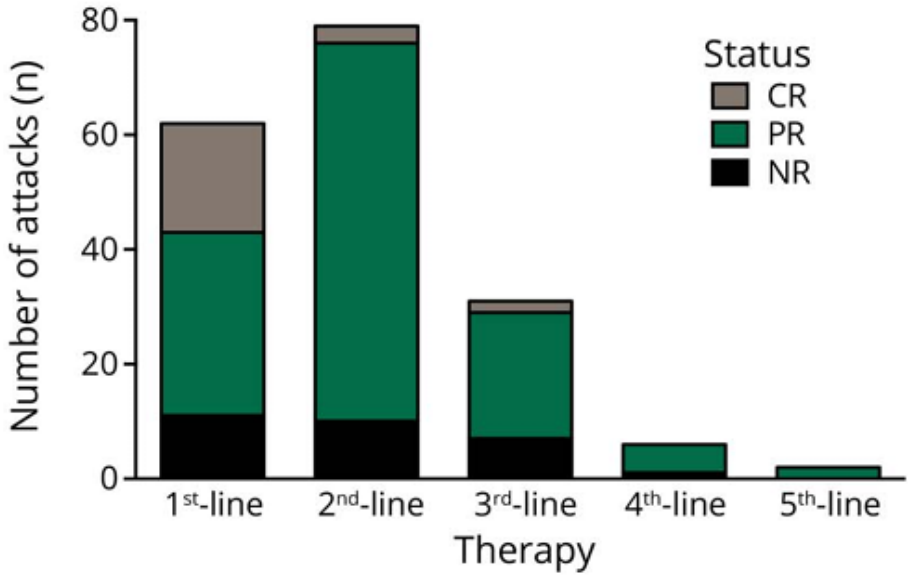
Kleiter I, Gahlen A, Borisow N, Fischer K, Wernecke KD, Wegner B, et al. Neuromyelitis optica: Evaluation of 871 attacks and 1,153 treatment courses. Ann Neurol. 2016;79(2):206-16.

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

Apheresis therapies for NMOSD attacks

A retrospective study of 207 therapeutic interventions

A. Remission status PE



	1st-line	2nd-line	3rd-line	4th-line	5th-line
Complete remission	19 (30.6%)	3 (3.8%)	2 (6.5%)	0	0
Partial remission	32 (51.6%)	66 (83.5%)	22 (70.9%)	5 (83.3%)	2 (100%)
No remission	11 (17.7%)	10 (12.7%)	7 (22.6%)	1 (16.7%)	0
Number of attacks	62	79	31	6	2

Table 3 Factors associated with complete remission from NMOSD attacks after apheresis therapy

	Multivariate analysis	
	***p* Value**	**OR (95% CI)**
Female sex (vs. male)	0.456	3.447 (0.13–89.40)
Age at attack (per 1 y)	0.081	0.925 (0.85–1.01)
Time from onset of disease to attack (per 1 y)	0.247	0.926 (0.81–1.06)
AQP4-ab positive (vs negative)	**0.019**	**33.338 (1.76–631.17)**
NMO (vs NMOSD)	0.316	2.951 (0.36–24.41)
MY present (vs absent)	0.726	1.350 (0.25–7.2)
Isolated ON or MY (vs simultaneous ON + MY)	**0.046**	**4.709 (1.03–21.62)**
Prophylactic immunotherapy present (vs absent)	0.532	1.683 (0.33–8.63)
Time from onset of attack to start of therapy (per 1 d)	**0.014**	**0.937 (0.89–0.99)**
First-line apheresis therapy (vs second-line)	**0.047**	**12.271 (1.04–144.91)**
PE (vs IA)	0.107	4.946 (0.71–34.59)
Center number	0.247	1.080 (0.95–1.23)

Kleiter I, Gahlen A, Borisow N, Fischer K, Wernecke KD, Hellwig K, et al. Apheresis therapies for NMOSD attacks: A retrospective study of 207 therapeutic interventions. Neurol Neuroimmunol Neuroinflamm. 2018;5(6):e504.

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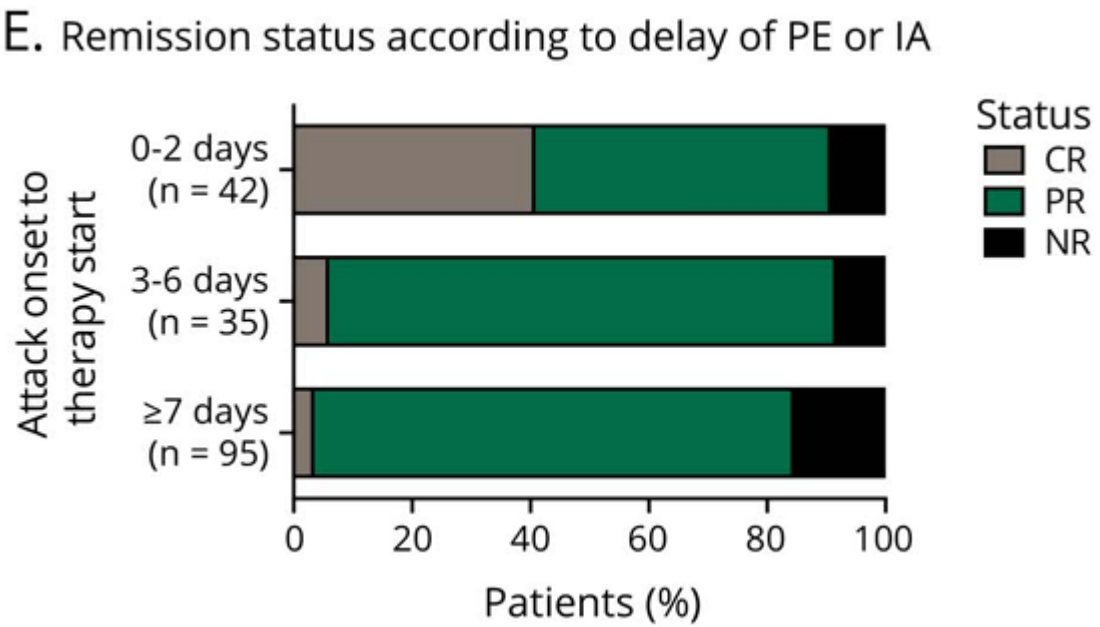
Apheresis therapies for NMOSD attacks

A retrospective study of 207 therapeutic interventions



- Strong predictors for CR were the use of apheresis therapy as first-line therapy (OR12.271;95%CI:1.04–144.91,p=0.047
- Time from onset of attack to start of therapy in days (OR0.937;95%CI:0.89–0.99,p=0.014)

Kleiter I, Gahlen A, Borisow N, Fischer K, Wernecke KD, Hellwig K, et al. Apheresis therapies for NMOSD attacks: A retrospective study of 207 therapeutic interventions. Neurol Neuroimmunol Neuroinflamm. 2018;5(6):e504.

RESEARCH PAPER

Short delay to initiate plasma exchange is the strongest predictor of outcome in severe attacks of NMO spectrum disorders

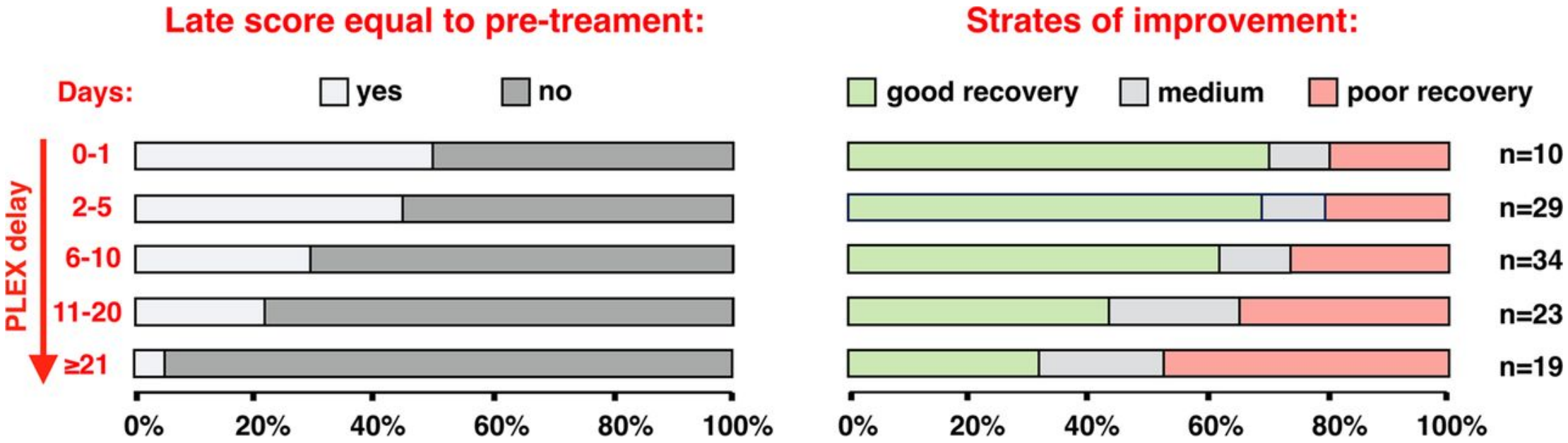
	OR (95% CI)	p Value
	Complete improvement	
Sex (male vs female)	3.2 (0.8 to 12.9)	0.11
Basal impairment	2.4 (1.0 to 5.8)	0.05
PLEX delay		p_{global}=0.01
Days 0–5 versus ≥day 11	5.3 (1.8 to 15.9)	<0.01
Days 6–10 versus ≥day 11	2.5 (0.8 to 8.2)	0.12
	Highest third improvement	
Type	2.0 (0.9 to 4.5)	0.10
Residence (foreign vs local)	0.4 (0.2 to 0.9)	0.03
PLEX delay		p_{global}=0.10
Days 0–5 versus ≥day 11	2.8 (1.1 to 7.3)	0.04
Days 6–10 versus ≥day 11	1.9 (0.7 to 5.1)	0.20
	Lower third improvement	
Residence (foreign vs local)	2.3 (1.0 to 5.2)	0.04
PLEX delay		p_{global}=0.29
Days 0–5 versus ≥day 11	0.44 (0.2 to 1.2)	0.12
Days 6–10 versus ≥day 11	0.6 (0.2 to 1.8)	0.39

- The shorter strata of PLEX delay (days 0–5) demonstrated a higher probability to regain a complete improvement than the longer strata (≥day 11) with OR 5.3 (1.8–15.9, p<0.01)

Bonnan M, Valentino R, Debeugny S, Merle H, Fergé JL, Mehdaoui H, et al. Short delay to initiate plasma exchange is the strongest predictor of outcome in severe attacks of NMO spectrum disorders. J Neurol Neurosurg Psychiatry. 2018;89(4):346-51

RESEARCH PAPER

Short delay to initiate plasma exchange is the strongest predictor of outcome in severe attacks of NMO spectrum disorders



- The probability to regain complete improvement continuously decreased from 50% for PLEX given at day 0 to 1%–5% after day 20
- Early initiation of PLEX (≤5 days) is more beneficial than delayed PLEX and suggests a better outcome if PLEX is started before day

Bonnan M, Valentino R, Debeugny S, Merle H, Fergé JL, Mehdaoui H, et al. Short delay to initiate plasma exchange is the strongest predictor of outcome in severe attacks of NMO spectrum disorders. J Neurol Neurosurg Psychiatry. 2018;89(4):346-51

Good prognostic factors of TPE for an acute attack of NMOSD

1. Short time between attack onset and start of therapy
2. Use as a first line (OR 12.27; 1.04–144.91, p = 0.047)
3. Presence of AQP4-Ab (OR 33.34;1.76–631.17, p = 0.019)
4. Location of the attack
    - 1st line Rx with TA may be superior to HDMP in attacks in cases of isolated myelitis, but not in ON.
5. Monofocal attack manifestation (OR 4.71; 1.03–21.62, p = 0.046)

Kleiter I, Gahlen A, Borisow N, Fischer K, Wernecke KD, Hellwig K, et al. Apheresis therapies for NMOSD attacks: A retrospective study of 207 therapeutic interventions. Neurol Neuroimmunol Neuroinflamm. 2018;5(6):e504.

NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)

- There is increasing experience using IA in addition to immunosuppressive therapy to treat patients with acute NMOSD with results essentially identical to TPE, and also in favor of first-line use.
- The strongest predictors of complete remission were use of apheresis as first-line therapy, time from onset of attack to start of apheresis therapy, and presence of AQP4-IgG

- Volume treated: TPE: 1 to 1.5 TPV; IA: 2 to 2.5 liters for tryptophan-IA (manufacturer's recommendation); up to 2.5 TPV with regenerative immune adsorbers
- Frequency: Acute attack/relapse: daily or every other day, median of 5 treatments over 10 days, individually adjusted intervals for maintenance treatment
- Replacement fluid: Albumin

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

NMDA encephalitis

Incidence: rare				
Procedure	**Category**		**Grade**	
TPE/IA	I		1C	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	0	3 (112)	>10 (>200)	NA

- Immunotherapy (steroids, IVIG, TPE) should be promptly initiated
- 50% responded to initial Rx, 50% required further Rx
- 80% improved at 24 months (50% within 4 wks), relapses in 12-20%
- To reduce antibody production, adjunctive immunosuppressive Rx and teratoma excision are necessary

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

NMDA encephalitis

- Antibody production and inflammatory changes occur behind the blood-brain barrier, lower the effectiveness of TPE
- Early initiation of TPE or TPE followed by IVIG provide a better outcome
- Equal efficacy of TPE and IA (60-70%)
- CSF antibody titers were reduced by 66% at early follow-up

- Volume treated: TPE: 1 to 1.5 TPV; IA: 2 to 2.5 liters for tryptophan-IA (manufacturer's recommendation) or up to 2.5 TPV with regenerative immune adsorbers
- Frequency: 5 to 12 treatments with TPE or IA over 1 to 3 weeks with individually adjusted numbers of and intervals between treatments
- Replacement fluid: Albumin

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VOLTAGE-GATED POTASSIUM CHANNEL ANTIBODY RELATED DISEASES

Incidence: rare

Procedure	**Category**		**Grade**	
TPE/IA	II		1B	
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	1 (21)	11 (96)	NA

- Application of steroids is fundamental in any combination therapy.
- For antibody-mediated autoimmune encephalitis (AME) in general, thus including VGKC-AME, TPE, or if available IA, is increasingly used as first-line treatment combined with steroids, and symptomatic drug treatment.
- Acute therapy for Morvan's syndrome or acquired neuromyotonia usually consists of steroids and/or IVIG. TPE, or IA is considered as a second-line option

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

VOLTAGE-GATED POTASSIUM CHANNEL ANTIBODY RELATED DISEASES

- Rapid decrease of VGKC-Ab with TPE, or IA is associated with clinical improvement
- IVMP (1 g/day for 3 days), TPE of 5 treatments over 7-10 days typically after completion of IVMP, followed by IVIG (2 g/kg over 5 days) and maintenance therapy with oral prednisolone (1 mg/kg)
- Clinical remission from 4-40 months, normalization of changes on MRI, and significantly decreased VGKC -Ab levels

- Volume treated: 1 to 1.5 TPV with TPE; 2 to 2.5 liters for tryptophan-IA up to 2.5 TPV with regenerative immunoadsorption columns
- Frequency: 5 to 10 treatments with TPE or IA over 7 to 14 days adjusted to the individual course
- Replacement fluid: TPE: albumin; IA: NA

PARANEOPLASTIC NEUROLOGICAL SYNDROMES

- Onconeuronal antibodies [Hu, CV2/CRMP5, Yo, Tr, and amphiphysin] are directed against intracellular antigens, it is presumed that the main pathogenic effect is carried out by cytotoxic T cell-mediated immune reactions, resulting in neuronal cell death
- Prompt initiation of anti-tumor therapy upon diagnosis can stabilize symptoms
- Treatment of PNS includes anti-tumor and immunosuppressive therapy
- Most patients have been treated with corticosteroids, followed by TPE/IA and/or IVIG, and with additional therapies such as rituximab and/or cyclophosphamide also used.
- Patients with ON-Abs to extracellular antigens are more likely to respond to immunosuppressive therapies

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PARANEOPLASTIC NEUROLOGICAL SYNDROMES

Incidence: 4 to 9/1,000,000 person years

Procedure	**Category**	**Grade**
TPE/IA	III	2C

# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
TPE	0	2 (35)	15 (111)	NA
IA	0	0	1 (13)	1 (1)

- If a patient presents prior to the development of severe neurological impairment but with a rapidly progressive syndrome, aggressive immunosuppression plus TPE/IA may be reasonable in an attempt to halt the process

- Volume treated: TPE: 1 to 1.5 TPV; IA: 2 to 4 TPV
- Frequency: TPE: Daily or every other day; IA: Twice weekly
- Replacement fluid: TPE: albumin; IA: NA

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IMMUNE CHECKPOINT INHIBITORS, IMMUNE-RELATED ADVERSE EVENTS

Incidence: 39% to 70% of patients treated with immune checkpoint inhibitors

Indication	**Procedure**		**Category**	**Grade**
	TPE		III*	2C
# Reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	0	9 (46)	75 (75)

- Cytotoxic T-lymphocyte-associated protein 4 (CLTA-4), programmed cell death-1 (PD-1), programmed cell death ligand 1 (PD-L1), lymphocyte activation gene 3 (LAG3)
- ICI-induced irAEs affect multiple organ systems including
  - cytokine release syndrome, myasthenia gravis [MG], diabetes, thyroiditis, hepatic (acute liver failure), pulmonary (pneumonitis), cardiovascular (myocarditis), musculoskeletal (myositis), and hematologic systems (thrombotic thrombocytopenic purpura (TTP) or other thrombotic microangiopathy)

Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, 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 Ninth Special Issue. J Clin Apher. 2023;38(2):77-278.

IMMUNE CHECKPOINT INHIBITORS, IMMUNE-RELATED ADVERSE EVENTS

- Treatment of ICI-induced irAE involves cessation of the ICI and initiation of corticosteroids. (based on ASCO)
- The ICIs are monoclonal IgG antibodies with half-lives ranging from 6 days (avelumab) to 27 days (atezolizumab).
- TPE remove
  - Monoclonal IgG antibodies
  - Autoantibodies that are precipitated by ICIs, including autoantibodies implicated in irAEs such as in MG, transverse myelitis, and TTP.
  - Circulating systemic inflammatory cytokines due to ICI-induced cytokine release syndrome
- For most irAEs such as MG, myocarditis, or myositis, a minimum of 5 to 7 treatments may be needed to deplete IgG-specific antibodies

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

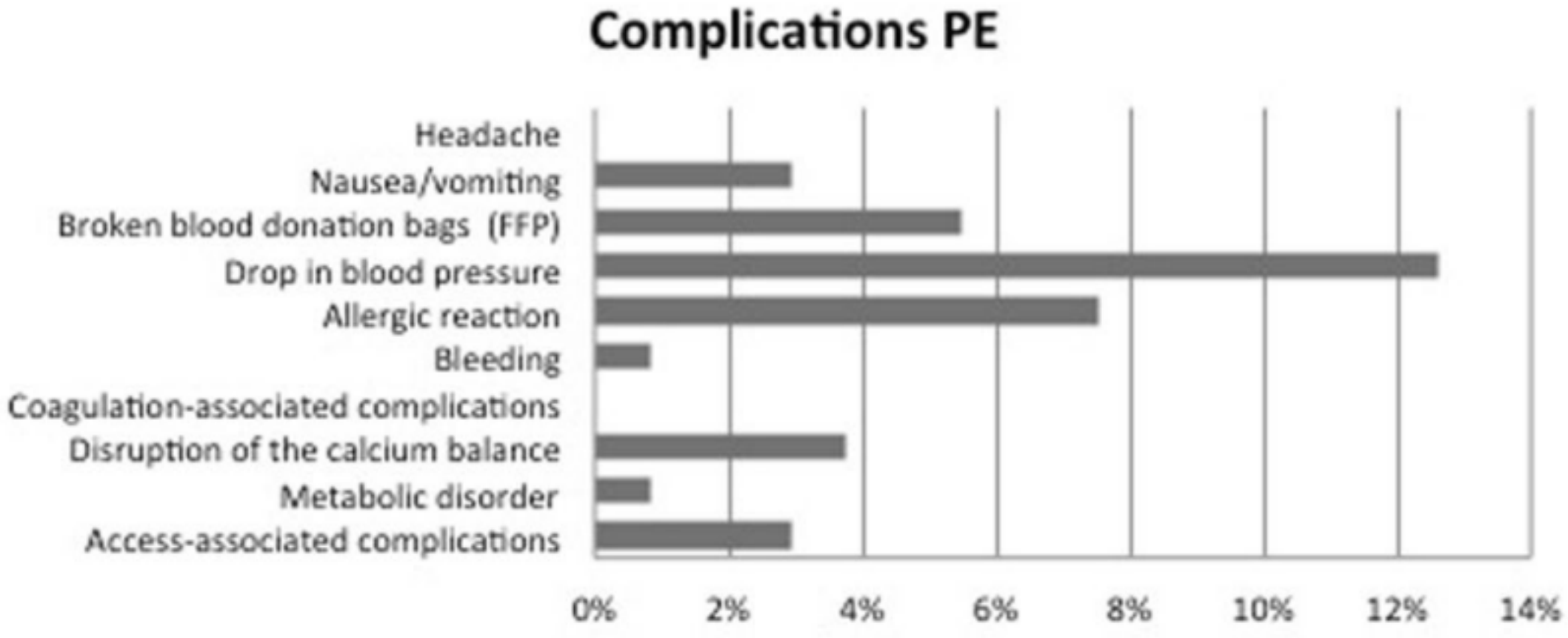
Cervantes CE, Bloch EM, Sperati CJ. Therapeutic Plasma Exchange: Core Curriculum 2023. Am J Kidney Dis. 2023;81(4):475-92.

Complications Associated With TPE

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

Cervantes CE, Bloch EM, Sperati CJ. Therapeutic Plasma Exchange: Core Curriculum 2023. Am J Kidney Dis. 2023;81(4):475-92.

Complication of Plasma Exchange



Klingele M, Allmendinger C, Thieme S, Baerens L, Fliser D, Jan B. Therapeutic apheresis within immune-mediated neurological disorders: dosing and its effectiveness. Scientific Reports. 2020;10(1):7925.

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

- High protein binding and low volume of distribution
- Prednisone is highly protein-bound → TPE removes only 1% of prednisolone.
- Cyclosporine and tacrolimus are predominantly intracellular and not affected by plasma exchange.
- Cyclophosphamide is unlikely to be removed by TPE.
- Rituximab has limited data, 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

Cervantes CE, Bloch EM, Sperati CJ. Therapeutic Plasma Exchange: Core Curriculum 2023. Am J Kidney Dis. 2023;81(4):475-92.
Mahmoud SH, Buhler J, Chu E, Chen SA, Human T. Drug Dosing in Patients Undergoing Therapeutic Plasma Exchange. Neurocrit Care. 2021;34(1):301-11
Ibrahim RB, Balogun RA. Medications in Patients Treated With Therapeutic Plasma Exchange: Prescription Dosage, Timing, and Drug Overdose. Seminars in Dialysis. 2012;25(2):176-89.

Thai Guideline 2557

ภาคผนวก 1 DISEASE MODIFYING THERAPIES FOR MS

Level of therapy	Level of pharmacological agent	Relapsing remitting active MS*	Aggressive relapsing remitting MS*	Secondary progressive MS with relapses
Initial Therapy	First-line	Interferon beta/ Glatiramer acetate*/ Teriflunomide/ Dimethyl fumarate*	Fingolimod/ Cladribine*/	Interferon beta
Escalation Therapy	Second-line	Fingolimod/ Natalizumab/ Cladribine*	Fingolimod/ Natalizumab/ Cladribine*	Ocrelizumab* Cyclophosphamide/ Mitoxantrone
	Third-line	Alemtuzumab/ Ocrelizumab*/ Cyclophosphamide/ Rituximab/ Mitoxantrone	Alemtuzumab/ Ocrelizumab*/ Cyclophosphamide/ Rituximab/ Mitoxantrone	
Relapse Therapy	First-line	Methylprednisolone		
	Second-line	Plasma Exchange		

ข้อบ่งชี้การรักษาด้วยวิธี plasma exchange (กรมบัญชีกลาง)

Plasma Exchange (ใช้เครื่อง Apheresis)
ข้อบ่งชี้การรักษาด้วยวิธี Plasma Exchange
1. Autoimmune encephalitis (membrane associatec antigen)
2. Acute severe demyelinating disease (neuromyelitis optica, multiple sclerosis, acute disseminated encephalomyelitis and transverse myelitis) with non-adequate response to high dose steroid
3. Acute inflammatory demyelinating polyradiculoneuropathy (Guillian-Barre syndrome)
4. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
5. Myasthenia gravis
6. Thrombotic thrombocytopenic purpura (TTP)
7. SLE ที่มีอาการรุนแรงมากและรักษาด้วยยากดภูมิขนาดสูงแล้วไม่ได้ผล
8. ANCA-associated rapidly progressive glomerulonephritis กรณี Dialysis dependence หรือ Diffuse alveolar hemorrhage
9. Anti-glomerular basement membrane กรณี Diffuse alveolar hemorrhage หรือ Dialysis independence
10. Focal segmental glomerulosclerosis กรณี Recurrent in transplanted kidney
11. Renal transplantation, ABO compatible กรณี Antibody mediated rejection หรือ Desensitization, living donor
12. Renal transplantation, ABO incompatible กรณี Antibody mediated rejection หรือ

ข้อบ่งชี้การรักษาด้วยวิธี plasma exchange (กรมบัญชีกลาง)

Inclusion criteria

1. ในกรณีของ autoimmune encephalitis: เมื่อสาเหตุของโรคเกิดจากภูมิคุ้มกันต่อ neuronal membrane protein หรือ neuronal channel protein เช่น Anti-NMDA, Anti-AMPA, Anti-GABAa, Anti-GABAb, Anti-Lgi1, Anti-Caspr2, Anti-DPPX, Anti-glycine, Anti-dopamine receptor
2. ในกรณีของ Acute severe demyelinating disease (neuromyelitis optica, multiple sclerosis, acute disseminated encephalomyelitis and transverse myelitis) เมื่อให้การรักษาด้วย high-dose steroid อย่างน้อย 5 วัน แล้วอาการไม่ดีขึ้น เช่น motor power ดีขึ้นน้อยกว่า 2 grade หรือยังต้องใช้เครื่องช่วยหายใจ หรือ visual acuity score ดีขึ้นน้อยกว่า 2 ระดับ
3. AIDP, CIDP และ MG เมื่อคนไข้ไม่สามารถเดินได้ด้วยตัวเองหรือมีปัญหาการกลืนต้องใส่สายยางหรือต้องใช้เครื่องช่วยหายใจ

- **Exclusion Criteria** : ผู้ป่วยมีระดับความดันต่ำหรือไม่คงที่ จนไม่สามารถทำ plasma exchange ได้

Take Home Messages

- Therapeutic apheresis has indication in neurological diseases
- The mechanism of action of plasma exchange include removing circulating pathogenic antibody from the circulation with additional immunomodulatory
- Understanding pathogenesis / mechanism of diseases
- Understanding kinetics of target molecules
- Use apheresis in combination with other modalities
- Early treatment provide better outcome
- TPE is generally a safe procedure, but the practitioner must be vigilant for numerous potential complications

THANK YOU