Therapeutic Plasma Exchange in the ICU

Subjects: Critical Care Medicine

Contributor: Guleid Hussein, Bolun Liu, Sumeet K. Yadav, Mohamed Warsame, Ramsha Jamil, Salim R. Surani, Syed A. Khan

Therapeutic plasma exchange (TPE) is a treatment paradigm used to remove harmful molecules from the body. In short, it is a technique that employs a process that functions partially outside the body and involves the replacement of the patient's plasma. It has been used in the ICU for a number of different disease states, for some as a first-line treatment modality and for others as a type of salvage therapy.

Keywords: plasmapheresis ; ICU ; TPE

1. Introduction

Therapeutic plasma exchange (TPE), also known as plasmapheresis, is an extracorporeal technique that replaces patients' plasma to remove pathogenic molecules. The common targets for removal are autoimmune antibodies, donor-specific antibodies, excessive paraproteins, cytokines, and endogenous and exogenous toxins [1]. TPE has become a commonly used, life-saving standard therapy for various conditions in intensive care settings.

2. Mechanisms and Principles of Therapeutic Plasma Exchange (TPE)

During a TPE session, the patient's blood is drawn a peripheral or central access site into the apheresis system. TPE is performed via two different major techniques: centrifugal separation and membrane separation [2]. In the centrifugal separation method, the blood is spun in an apheresis device and the different components are separated via specific gravity. In the membrane separation method, the blood crosses non-selective microporous membranes, which allow for the passage of molecules less than a certain weight and also allows for the retention of blood cells. The respective levels of efficacy of these two methods are comparable based on historical studies, although the centrifugal process was reported to be more time-efficient [3]. Notably, the membrane separation method is more commonly used in Japan and Germany, while the centrifugal separation method is dominant in the USA and the rest of Europe [4]. After the apheresis process, the blood is infused back into the patient along with healthy donor plasma or albumin (with or without normal saline).

Most TPE methods use albumin replacement to ensure less immunogenicity and improved safety. Certain hematological emergencies require replacement with plasma and cryoprecipitate to restore coagulation factors and normal coagulation function, such as thrombotic thrombocytopenic purpura (TTP), thrombotic microangiopathy (TMA) with factor H autoantibody, drug-induced TMA, and ANCA vasculitis-associated diffuse alveolar hemorrhage (DAH) [5].

TPE nonspecifically removes plasma molecules, including pathogenic molecules, normal coagulation factors, and immunoglobulin, which could put patients at higher risk of thrombosis, bleeding, infection, or allergic reaction (exclusively from plasma). Based on a single-center retrospective study in France, less than half of TPE sessions had at least one adverse effect, with hypocalcemia (19.6%) and hypotension (15.2%) being the most common; severe adverse effects only happened in 5.4% of patients [6]. Immunoadsorption (IA) was developed in the 1990s by using a specific plasma filter with bound antigens to target the immunoglobulin and preserve other plasma components. This approach could potentially minimize the risk of complication, and it is under investigation as a substitute for TPE in certain conditions [7][8].

ICU patients undergoing TPE can have multiple organ failure and require other extracorporeal supporting systems, such as intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), and extracorporeal membrane oxygenation (ECMO). Such procedures could be performed sequentially or simultaneously via single or multiple access points. Systems could be combined in series, parallel, or hybrid mode [9].

3. Indications for Therapeutic Plasma Exchange in the ICU

Since 1986, the American Society for Apheresis (ASFA) has comprehensively reviewed the scientific evidence of the indications of therapeutic apheresis and issued detailed guidelines. The most recent ninth edition was published in early 2023 and highlighted 77 diseases with 119 indications for therapeutic plasma exchange [5]. There are 20 indications with TPE listed as a first-line treatment (ASFA category I) and 23 indications with TPE listed as a second-line treatment (ASFA category II) for various diseases (see **Table 1**). The 'Kidney Disease: Improving Global Outcomes' (KDIGO) group and American Academy of Neurology (AAN) also provide guidelines covering a few specific indications under their specialties [10][11]. The British Society for Hematology and the Japanese Society for Apheresis also issued guidelines reflecting the local experts' consensus [12][13]. A great number of patients who require TPE are critically ill and will require intensive care monitoring. Guidelines have recommended individualized approaches based on the patient's condition and following the local organizational policy based on resources and standard practice.

Table 1. Indications for therapeutic plasma exchange (TPE) (adapted from ASFA 2023 guidelines).

System	Lines	Diagnosis	Specific Condition
Neurological disorders	First-line	Acute inflammatory demyelinating polyneuropathy	
		Chronic acquired demyelinating polyneuropathies, IgG/IgA/IgM-related	
		Chronic inflammatory demyelinating polyradiculoneuropathy	
		Myasthenia gravis	Acute, short-term treatment
		N-methyl-D-aspartate receptor antibody encephalitis	
	Second-line	Lambert–Eaton myasthenic syndrome	
		Multiple sclerosis	Acute attack/relapse; long-term treatment
		Neuromyelitis optical spectrum disorder	Acute attack/relapse
		Pediatric autoimmune neuropsychiatric disorders	PANDAS/PANS, exacerbation
		Steroid-responsive encephalopathy associated with autoimmune thyroiditis	
Hematological disorders	First-line	Catastrophic antiphospholipid syndrome	
		Hyperviscosity in hypergammaglobulinemia	Prophylaxis for rituximab; symptomatic hyperviscosity syndrome
		Thrombotic microangiopathy, complement-mediated	Factor H autoantibody-related only
		Thrombotic microangiopathy, drug-induced	Ticlopidine-related only
		Thrombotic microangiopathy, thrombotic thrombocytopenic purpura	
	Second-line	Lambert–Eaton myasthenic syndrome	
		Multiple sclerosis	Acute attack/relapse; long-term treatment
		Neuromyelitis optical spectrum disorder	Acute attack/relapse
		Pediatric autoimmune neuropsychiatric disorders	PANDAS/PANS, exacerbation
		Steroid-responsive encephalopathy associated with autoimmune thyroiditis	
Transplantation-associated complications	First-line	Transplantation, kidney, ABO-compatible	Antibody-mediated rejection; Desensitization/prophylaxis, living donor

System	Lines	Diagnosis	Specific Condition
		Transplantation, kidney, ABO-incompatible	Desensitization, living donor
		Transplantation, liver	Desensitization, ABOi, living donor
	Second-line	Transplantation, heart	Desensitization; rejection prophylaxis
		Transplantation, hematopoietic stem cell, ABO-incompatible	Major ABO incompatible: HPC(M); HPC(A)
		Transplantation, kidney, ABO-incompatible	Antibody-mediated rejection
Renal disorders	First-line	Antiglomerular basement membrane disease	Diffuse alveolar hemorrhage; dialysis-independent disease
		Focal segmental glomerulosclerosis	Recurrent in kidney transplant
Hepatic disorders	First-line	Acute liver failure (TPE-HV preferred over regular TPE)	Other than acute fatty liver of pregnancy
		Wilson disease, fulminant	
Other Systems	Second-line	Systemic lupus erythematosus	
		Thyroid storm	
		Familial hypercholesterolemia	
		Phytanic acid storage disease	
		Hepatitis B related polyarteritis nodosa vasculitis	
		Voltage-gated potassium channel antibody-related diseases	
		Mushroom poisoning	

PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS, pediatric acute-onset neuropsychiatric syndrome; HPC(M), hematopoietic progenitors from bone marrow; HPC(A), allogeneic hematopoietic progenitor cell; TPE-HV, therapeutic plasma exchange—high volume.

The optimal timing of initiation of TPE varies significantly by condition, from emergent use (within 4–6 h) to urgent use (within 24 h) to planned routine treatment. Intensivists should carefully weigh the risks and benefits of TPE based on the clinical context. TPE should be initiated as early as possible in combination with other treatment modalities for organ- or life-threatening conditions, such as TTP, catastrophic antiphospholipid syndrome (CAPS), mushroom intoxication, symptomatic hyperviscosity syndrome, severe myasthenia gravis, fulminant Wilson's disease, and diffuse alveolar hemorrhage caused by autoimmune disease [14][15][16][17]. For devastating neurological conditions, such as Guillan-Barre/acute inflammatory demyelinating polyneuropathy and N-methyl-D-aspartate receptor antibody encephalitis, early initiation to stop ongoing injury processes could prevent permanent damage to the neurological system and may lead to better outcomes [18].

Since the COVID-19 pandemic, TPE has also been investigated for severe COVID-19 infection in the hope of removing excessive cytokines to alleviate significant inflammation and cytokine release syndrome. There are retrospective studies and a pilot randomized controlled trial showing potential survival benefits in severely ill patients [19][20][21]. However, this topic remains controversial. The continued fluctuation of epidemics calls for more scientific evidence regarding TPE use in critical COVID-19 patients.

References

1. David, S.; Russell, L.; Castro, P.; van de Louw, A.; Zafrani, L.; Pirani, T.; Nielsen, N.D.; Mariotte, E.; Ferreyro, B.L.; Kielstein, J.T.; et al. Research priorities for therapeutic plasma exchange in critically ill patients. Intensive Care Med. Exp. 2023, 11, 26.

2. Ward, D.M. Conventional apheresis therapies: A review. J. Clin. Apher. 2011, 26, 230–238.
3. Ahmed, S.; Kaplan, A. Therapeutic Plasma Exchange Using Membrane Plasma Separation. Clin. J. Am. Soc. Nephrol. 2020, 15, 1364–1370.
4. Lozano, M.; Rivero, A.; Cid, J. Plasma exchange activity in the European Union. Transfus. Apher. Sci. 2019, 58, 278–280.
5. Connelly-Smith, L.; Alquist, C.R.; Aqui, N.A.; Hofmann, J.C.; Klingel, R.; Onwuemene, O.A.; Patriquin, C.J.; Pham, H.P.; Sanchez, A.P.; Schneiderman, J.; 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, 77–278.
6. Coirier, V.; Lesouhaitier, M.; Reizine, F.; Painvin, B.; Quelven, Q.; Maamar, A.; Gacouin, A.; Tadié, J.; Le Tulzo, Y.; Camus, C. Tolerance and complications of therapeutic plasma exchange by centrifugation: A single center experience. J. Clin. Apher. 2022, 37, 54–64.
7. Ludolph, A.C. Immunoadsorption Versus Plasma Exchange for Treatment of Guillain-Barré Syndrome (GBS). 2023. Available online: https://www.clinicaltrials.gov (accessed on 1 September 2023).
8. Dorst, J.; Fangerau, T.; Taranu, D.; Eichele, P.; Dreyhaupt, J.; Michels, S.; Schuster, J.; Ludolph, A.C.; Senel, M.; Tumani, H. Safety and efficacy of immunoadsorption versus plasma exchange in steroid-refractory relapse of multiple sclerosis and clinically isolated syndrome: A randomised, parallel-group, controlled trial. EClinicalMedicine 2019, 16, 98–106.
9. Sanchez, A.P.; Ward, D.M.; Cunard, R. Therapeutic plasma exchange in the intensive care unit: Rationale, special considerations, and techniques for combined circuits. Ther. Apher. Dial. 2022, 26 (Suppl. S1), 41–52.
10. Cortese, I.; Chaudhry, V.; So, Y.T.; Cantor, F.; Cornblath, D.R.; 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, 294–300.
11. Cattran, D.C.; Feehally, J.; Cook, H.T.; Liu, Z.H.; Fervenza, F.C.; Mezzano, S.A.; Floege, J.; Nachman, P.H.; Gipson, D.S.; Praga, M.; et al. Kidney disease: Improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int. Suppl. 2012, 2, 139–274.
12. Howell, C.; Douglas, K.; Cho, G.; El-Ghariani, K.; Taylor, P.; Potok, D.; Rintala, T.; Watkins, S. Guideline on the clinical use of apheresis procedures for the treatment of patients and collection of cellular therapy products. Transfus. Med. 2015, 25, 57–78.
13. Abe, T.; Matsuo, H.; Abe, R.; Abe, S.; Asada, H.; Ashida, A.; Baba, A.; Eguchi, K.; Eguchi, Y.; Endo, Y.; et al. The Japanese Society for Apheresis clinical practice guideline for therapeutic apheresis. Ther. Apher. Dial. 2021, 25, 728–876.
14. Russi, G.; Marson, P. Urgent plasma exchange: How, where and when. Blood Transfus. 2011, 9, 356–361.
15. Kazzaz, N.M.; McCune, W.J.; Knight, J.S. Treatment of catastrophic antiphospholipid syndrome. Curr. Opin. Rheumatol. 2016, 28, 218–227.
16. Pham, H.P.; Staley, E.M.; Schwartz, J. Therapeutic plasma exchange—A brief review of indications, urgency, schedule, and technical aspects. Transfus. Apher. Sci. 2019, 58, 237–246.
17. Saheb, S.; Gallo, A. Urgent therapeutic plasma exchange. Transfus. Apher. Sci. 2020, 59, 102991.
18. Llufriu, S.; Castillo, J.; Blanco, Y.; Ramio-Torrenta, L.; Rio, J.; Valles, M.; Lozano, M.; Castella, M.D.; Calabia, J.; Horga, A.; et al. Plasma exchange for acute attacks of CNS demyelination: Predictors of improvement at 6 months. Neurology 2009, 73, 949–953.
19. Faqihi, F.; Alharthy, A.; Abdulaziz, S.; Balhamar, A.; Alomari, A.; AlAseri, Z.; Tamim, H.; Alqahtani, S.A.; Kutsogiannis, D.J.; Brindley, P.G.; et al. Therapeutic plasma exchange in patients with life-threatening COVID-19: A randomised controlled clinical trial. Int. J. Antimicrob. Agents 2021, 57, 106334.
20. Al-Hashami, S.; Khamis, F.; Al-Yahyay, M.; Al-Dowaiki, S.; Al-Mashaykhi, L.; Al-Khalili, H.; Chandwani, J.; Al-Salmi, I.; Al-Zakwani, I. Therapeutic plasma exchange: A potential therapeutic modality for critically ill adults with severe acute respiratory syndrome coronavirus 2 infection. J. Clin. Apher. 2022, 37, 563–572.
21. Fonseca-González, G.; Alamilla-Sánchez, M.; García-Macas, V.; Herrera-Acevedo, J.; Villalobos-Brito, M.; Tapia-Rangel, E.; Maldonado-Tapia, D.; López-Mendoza, M.; Cano-Cervantes, J.H.; Orozco-Vázquez, J.; et al. Impact of plasmapheresis on severe COVID-19. Sci. Rep. 2023, 13, 163.