Intensive Care Med
https://doi.org/10.1007/s00134-022-06793-z

REVIEW

Plasma exchange in the intensive care unit: a narrative review

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Abstract

In this narrative review, we discuss the relevant issues of therapeutic plasma exchange (TPE) in critically ill patients. For many conditions, the optimal indication, device type, frequency, duration, type of replacement fluid and criteria for stopping TPE are uncertain. TPE is a potentially lifesaving but also invasive procedure with risk of adverse events and complications and requires close monitoring by experienced teams. In the intensive care unit (ICU), the indications for TPE can be divided into (1) *absolute*, well-established, and evidence-based, for which TPE is recognized as first-line therapy, (2) *relative*, for which TPE is a recognized second-line treatment (alone or combined) and (3) *rescue* therapy, where TPE is used with a limited or theoretical evidence base. New indications are emerging and ongoing knowledge gaps, notably regarding the use of TPE during critical illness, support the establishment of a TPE registry dedicated to intensive care medicine.

Keywords: Plasma exchange, Plasmapheresis, Intensive care units, State-of-the-art review, Patient care team

Introduction

Therapeutic apheresis encompasses the removal of plasma (plasmapheresis) or blood cells (cytapheresis, i.e., erythrocytes, leukocytes, or platelets) from the patient's blood. If plasma is removed not for donation but for therapeutic purposes and is replaced by donor plasma, colloid, or crystalloids or a mixture thereof, it defines therapeutic plasma exchange (TPE) (Fig. 1). TPE serves to remove pathogenic substances (e.g., autoantibodies or toxic agents) and/or to administer deficient substances present in plasma of healthy donors (e.g., a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, ADAMTS13) though other potential immunomodulatory effects may be involved [1]. The indications for TPE have been refined over time. Many patients who require TPE are critically ill needing admission to the intensive care unit (ICU). TPE is an invasive procedure with often emergent indications, demanding its execution as soon as possible. Thus, a rapid response by experienced staff, with specific equipment, close monitoring, and multidisciplinary management are essential.

The goal of this article is to present a narrative review of the main indications for TPE in critically ill patients, as well as their main characteristics. A multidisciplinary group of intensivists, immunologists, nephrologists, pathologists, and hematologists reviewed and summarized the evidence on the rationale and indications for

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The members of the Nine-I Investigators are listed in the Acknowledgements section of the manuscript.

TPE in the ICU, shared their experience, and identified relevant issues that need to be known by the intensivists, as well as knowledge gaps that need to be filled by future research.

Indications for urgent TPE in critically ill patients

The American Society for Apheresis (ASFA) updated its guidelines on therapeutic apheresis in 2019 [2], and the Japanese Society in 2021 [3]. They identified four categories of use: first-line therapy (Category I), second-line therapy (Category II), role not established (Category III), and ineffective or harmful (Category IV). In the ICU, the indications for TPE can be divided into (1) *absolute*, well-established, and evidence-based, for which TPE is recognized as first-line therapy, (2) *relative*, for which TPE is a recognized second-line treatment alone or combined with other interventions and (3) *rescue* therapy, where TPE is used with limited evidence of benefits but a plausible theoretical rationale (Table 1) [4–7].

Mechanisms, kinetics, and goals of TPE

Mechanisms of TPE

TPE has two mechanisms of action (Fig. 1):

Take-home message

Therapeutic plasma exchange (TPE) procedures performed by trained personnel are a safe and effective therapeutic approach for patients suffering from diseases listed in the guidelines of the American Society for Apheresis.

The creation of a specific registry for TPE administered in the intensive care unit would allow for a robust database to assess efficacy and safety of TPE in critically ill patients.

1. Removal of a pathogenic substance from the plasma (e.g., IgG in myasthenia gravis, IgM in Waldenström macroglobulinemia, or IgG and IgM iso-agglutinins prior to ABO incompatible organ transplantation [8]). To be efficiently cleared by TPE, the substance should ideally be identified and assayed and have a high molecular weight, low distribution volume (chiefly in plasma), long half-life, and low turnover rate. Of note, the degree of substance removal does not necessarily correlate with the alleviation of the clinical symptoms like in myasthenia gravis [9].
2. Delivery of large amounts of deficient plasma components (e.g., ADAMTS13 in thrombotic thrombocytopenic purpura (TTP)). The fluid used for plasma

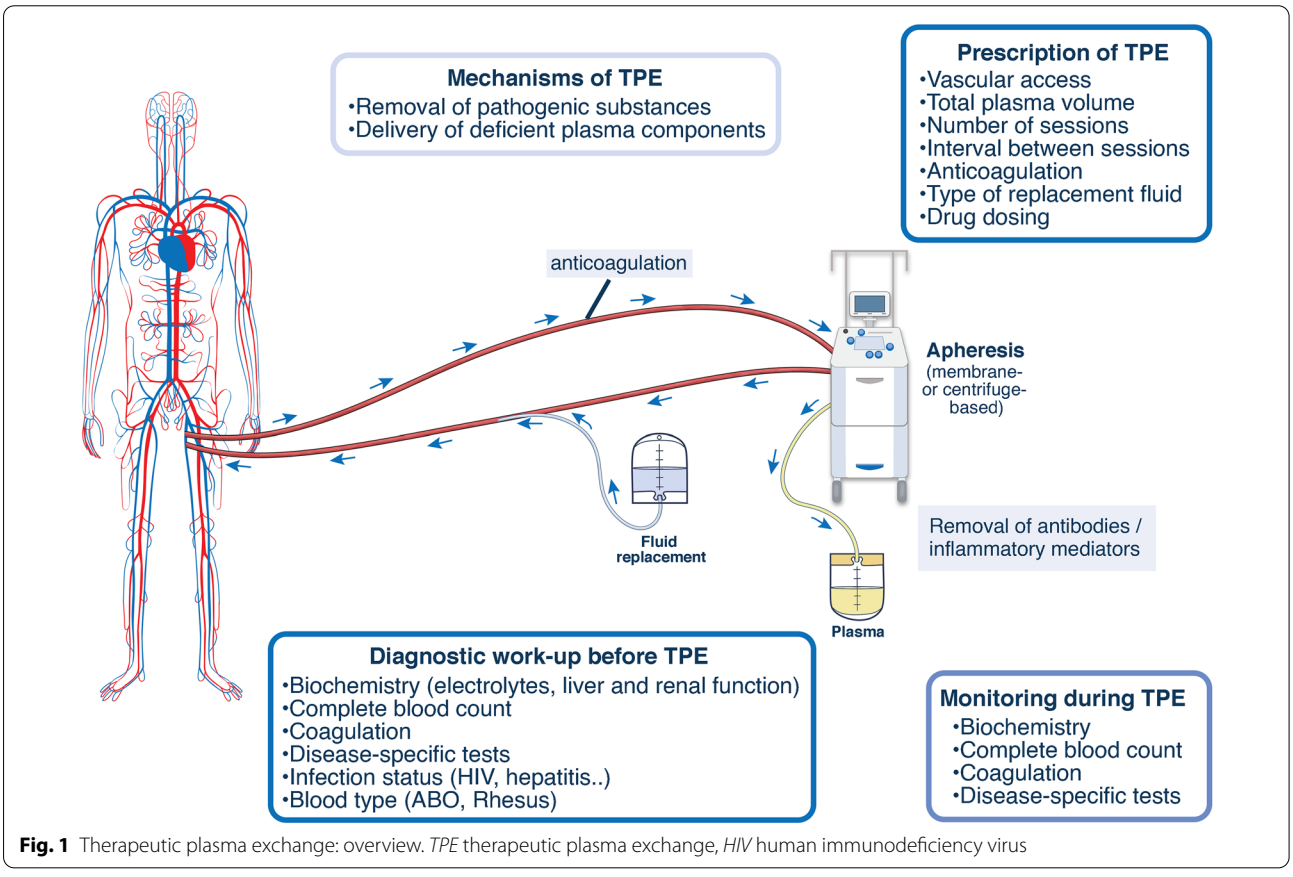

Fig. 1 Therapeutic plasma exchange: overview. *TPE* therapeutic plasma exchange, *HIV* human immunodeficiency virus

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

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

Table 1 (continued)

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

Table 1 (continued)

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

Table 1 (continued)

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

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

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

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

replacement should be, or be derived from, healthy donor plasma [1].

Kinetic models

Kinetic models for prediction of substance removal have been developed [10]. The half-life and volume of distribution of the substance to be removed must be considered when planning the intensity and frequency of TPE sessions. The plasma volume to be replaced is determined by calculating the total blood volume and the total plasma volume (TPV) of the patient [11]. For a substance that is neither rapidly synthesized nor redistributed and limited to the intravascular space, the first session of plasma exchange will remove 65–70% of the target substance. With additional plasma volumes exchanged, the absolute amount removed becomes progressively smaller due to the exponential nature of the removal (Fig. 2) The second session will remove an additional 23% and the third session only an additional 9% of the target substance. The net reduction will be affected by the redistribution from extravascular to intravascular compartments, production rate and by volumes of distribution. For example, one standard TPE session replacing 1.2 times the TPV will remove 10 g of IgG and 0.3 g of IgM due to the amount of IgG present in the intravascular space and its ability to redistribute from the extravascular compartment, which does not occur in an appreciable amount with IgM [12]. It also depends on the level of IgG at baseline (Fig. 2). In patients who are IgG depleted, TPE can replace the missing IgG [13].

The 2019 ASFA recommendations suggest exchanging 1.0–1.5 times the individually calculated TPV [2]. However, several clinical studies have shown a frequent failure to reach this TPE target [14]. A study in Germany reports exchanging only 0.4–1.0 times the estimated TPV

[15]. In a recent study from India, the overall exchange volume during TPE for various indications was only 2.1 L with an overall response rate of 84% [16]. The optimal exchange volume is not known and may depend on the disease. Small volume plasma exchange will remove less substances from the plasma but may be more affordable and still effective. For instance, in Bangladesh, where most patients with Guillain–Barré syndrome (GBS) cannot afford standard treatment with intravenous immunoglobulin or a standard TPE course, a small clinical study in 20 adult patients with GBS demonstrated the feasibility and safety of small volume plasma exchange as a potential alternative low-cost treatment [17]. A detrimental effect of high-dose TPE has not been described but it should be remembered that TPE also removes drugs that are aimed at treating the underlying disease, such as rituximab or caplacizumab or essential drugs such as antibiotics or anticoagulants. Also, if the aim is to remove larger substances, the efficacy of TPE will decrease as the total exchanged volume increases, as the removed larger amounts of a pathologic substance may need hours to days to diffuse from the extravascular to the intravascular compartment [12]. In this case, it may be more efficacious to repeat TPE sessions rather than continuing high-volume TPE beyond 1–1.5 plasma volumes. Knowledge about the characteristics and kinetics of the substance(s) to be removed is essential to guide the TPE prescription. The most rational approach to achieve the most efficient substance removal is to consider the nature of the toxin(s) to be removed and the best combination of exchange volume, treatment frequency and timing [18].

Therapeutic goals of TPE

The therapeutic goals of TPE depend on the pathophysiology of the disease. For instance, in Waldenström macroglobulinemia, the goal is to decrease the IgM level to reduce plasma viscosity and eliminate symptoms of hypoperfusion. In TTP, the aim is to raise the platelet count above 150,000/μL and reversing hemolysis by removing anti-ADAMTS13 inhibitory antibodies, removing ultralarge von Willebrand factors multimers and replacing ADAMTS13 enzyme [19]. In myasthenia gravis, the aim is to achieve a rapid clinical stabilization by removing acetylcholine receptor antibodies, especially in case of myasthenic crisis. In GBS, the goal is to improve muscle strength and to reduce the need for mechanical ventilation and hasten recovery. Table 1 shows the main parameters to monitor and endpoints for the different TPE indications in the ICU (Table 1).

Diagnostic workup for TPE indications and monitoring

TPE is used in various medical conditions. The diagnostic work-up serves to identify the underlying disease and determine its characteristics (Table 2). During TPE, close monitoring is essential to prevent adverse events and to ensure efficacy and safety. The criteria for discontinuing TPE should be determined a priori. Many routine biomarkers (e.g., C-reactive protein (CRP), creatinine, bilirubin etc.) will be reduced after a TPE session, potentially for many hours, and therefore, must be interpreted with caution. Changes in the amount of a substance removed by TPE may not necessarily represent improvement in the disease process and additional evidence of clinical response such as symptom resolution should be sought (Table 1S). Similarly, a decrease in CRP level after TPE does not necessarily mean that inflammation and/or infection are under control.

Technical aspects

Machines and devices

During TPE, the plasma can be separated from the corpuscular components of the blood by centrifugation, membrane filtration, or both [20]. Centrifugation is based on the differences in density of the various blood components. Mature red blood cells (RBCs) have the greatest relative density, followed by young erythrocytes (neocytes), granulocytes, mononuclear cells, platelets and, finally, plasma. Filtration takes advantage of differences in particle size to separate plasma from cells.

Currently licensed TPE devices can operate with a continuous or an intermittent flow [21]. Both, centrifugal and membrane-based devices are available. In apheresis units based in transfusion medicine or hematology departments, TPE is usually performed with centrifugal systems (cTPE) that often use citrate for anticoagulation. In most nephrology departments and ICUs, the preferred devices are membrane-based (mTPE), including multifunctional renal replacement therapy (RRT) machines. In both cTPE and mTPE, the cell-rich blood that remains after plasma removal is mixed with the replacement fluid (e.g., albumin, plasma, or crystalloid) and returns to the patient to prevent hypovolemia. To reduce costs and donor exposures, up to 30% of the replacement fluid may be a suitable crystalloid. In low-resource healthcare systems, plasma, crystalloid, or non-plasma colloid beyond 30% of the replaced volume may be used for replacement due to the expense of albumin substrates, and availability and safety profile of plasma products.

Plasma removal efficiency (PRE) is the metric used to compare TPE devices. It describes the fraction (%) of plasma that passes through the device and is removed per procedure. PRE estimate may vary according to the

Table 2 Disease-specific workup for the most common indications

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

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

mathematical formulas used [22–26]. With cTPE devices, PRE is faster and higher than with mTPE devices [12, 26]. Rates of removal are comparable with cTPE and mTPE for IgG but not for fibrinogen [12].

Vascular access

The choice of vascular access for TPE depends primarily on the method used: cTPE typically requires lower blood flow rates (Qb) (50–120 mL/min) than mTPE (150–200 mL/min) [27]. A lower Qb enables the use of narrower catheters such as peripheral devices (e.g., 18-Gauge needle) or standard triple-lumen central venous catheters (e.g., 7 Fr). With a peripheral vein, single-needle access is feasible when using cTPE [28] but might increase the treatment time. Peripherally inserted central catheters are not suitable because their narrow catheter gauge will collapse with the negative pressures exerted during TPE [29]. The mTPE devices often require higher Qb and, therefore, wider catheters such as temporary hemodialysis catheters or large-diameter dual-lumen catheters (e.g., 13.5 French) [30]. The optimum characteristics of a catheter for TPE include rigid walls, a large diameter, and a short length to reduce resistance and decrease instrument alarms. Machines used for cTPE can concentrate RBCs to a hematocrit of 80% or higher, which allows for more plasma per volume to be processed compared to mTPE devices [11]. A higher Qb is needed with mTPE devices as they usually extract only about 30–35% of processed plasma to prevent RBC damage from a high hematocrit. Thus, with mTPE devices three or four times more plasma volume must be processed to remove similar plasma volume as with cTPE devices.

Anticoagulation

Anticoagulation for TPE aims to achieve a delicate balance between preventing circuit failure with loss of expensive blood components and preventing bleeding. Systemic heparin and regional citrate are the most common anticoagulants, while epoprostenol can also be used, when citrate is unavailable, and heparin is contraindicated. In the past, citrate was generally used for cTPE and heparin for mTPE, but citrate is now also used for mTPE [12, 31, 32]. According to the World Apheresis Registry, in which two-thirds of apheresis procedures were therapeutic, 73% of procedures were provided with citrate anticoagulation [33].

Both heparin and citrate anticoagulation have advantages and drawbacks (Table 2S). The risk of bleeding during TPE is lower with citrate than with heparin. However, when citrate is used with a mTPE device, side effects are more frequent, mainly because more citrate is required as a result of a higher Qb, plus, removal of less plasma leads to more citrate entering the patient's systemic circulation [11]. Symptomatic hypocalcemia is also more common with citrate and can be prevented by prophylactic calcium administration [34]. Commercially available mTPE devices with integrated citrate administration adjusted for Qb and calcium supplementation according to effluent rate reduce the risk. When using heparin for anticoagulation, estimation of the required dosage should factor in extracorporeal losses of the drug and its cofactor antithrombin [35]. Moreover, antithrombin loss may hamper anticoagulation with heparin as well as the interpretation of chromogenic anti-Xa assays that add exogenous antithrombin.

Fluid replacement

Albumin or plasma can be used as replacement fluid, alone or in combination, and with or without the addition of a crystalloid such as saline. Albumin is used most often, as it is associated with a lower frequency of allergic or immune reactions (e.g., transfusion-related acute lung injury) compared to plasma and not associated with a risk of transfusion transmitted disease [12, 36, 37]. Table 3S summarizes pros and cons of each alternative (Table 3S). When albumin is used as replacement solution, metabolic acidosis may be seen after the TPE session because albumin has an acidic profile [38]. Albumin substitution may also affect the concentrations of fibrinogen and other coagulant factors resulting in profound derangement of thromboelastography parameters [39].

Plasma is indicated when aiming to replace plasma components (e.g., ADAMTS13 in TTP). Despite the absence of hard evidence, many centers also use plasma to prevent depletion of coagulation factors (e.g., if a bleeding diathesis is present or an invasive procedure is planned). Established guidelines for hemostasis monitoring/management during TPE are lacking but the extracorporeal losses of both pro- and anticoagulant factors need to be considered [40].

A recent survey by an ASFA subcommittee found wide practice variation in the type of replacement fluid but the potential bleeding risk most often determines the choice [41]. Because of the large volume, the number of donor exposures, and often prolonged duration of therapy, the risk of allergic reactions is higher with plasma than with albumin, and some centers administer antihistamines and/or glucocorticoids when using plasma [42]. When plasma is used as replacement solution, metabolic alkalosis may occur because of metabolism of citrate used as anticoagulant and citrate present in stored plasma. For every citrate molecule metabolized, there is a consumption of hydrogen ions and production of three sodium bicarbonate molecules, thus increasing serum pH levels [43].

Crystalloid can be added for cost-containment and in patients with hyperviscosity syndrome. However, replacing plasma with crystalloid carries a risk of hypotension if the proportion of replacement with crystalloid exceeds 30% [44]. In this setting, significant fluid shifts can occur as water follows its concentration gradient from the intravascular space into the extravascular space. When crystalloid is used as a portion of the replacement, it should be administered at the beginning of the exchange and not at the end to avoid significant fluid shifts and hypotension. Hydroxyethyl starch (HES) is no longer recommended in critically ill patients due to its harmful effects on both renal function and coagulation. However, it is still occasionally used as a replacement fluid (e.g., 3% HES with 5% human albumin), especially in low-resource healthcare systems [45, 46]. It may also be used in patients who refuse blood products.

Clinical response

The expected benefits and potentially deleterious effects of TPE are dependent on the timing of the procedure with respect to the onset of the illness, the volume of fluid exchanged, the type of replacement solution, and the frequency and intervals of plasma removal. The individual criteria for "clinical response" are highly disease specific, ranging from changes in individual or multiple hematological parameters, antibody concentrations or biochemistry to improvement of clinical signs and symptoms. The impact of TPE can be rapid or slow and may last for weeks to months, depending on the underlying disease. However, long-term effects, including psychological well-being and the risk of chronic organ dysfunction beyond the acute illness are rarely reported.

Complications

TPE is a relatively safe procedure and usually well tolerated. Complications include catheter-related and procedure-related events. The incidence of adverse events has declined over time [47, 48] and now ranges from 5 to 36% depending on vascular access used, type of replacement fluid, and anticoagulation (Table 4S). Catheter-related infections, pneumothorax, and local bleeding have been reported in 0.4–1.6% of patients [49, 50]. In critically ill patients, bleeding disorders were rare (< 10%) but catheter dysfunction was the most common complication (32%) [30]. Complication rates were similar with mTPE and cTPE [30]. Potentially life-threatening complications, dominated by anaphylactoid reactions and severe hypotension, have been reported in 1–2% of TPE sessions in critically ill patients [30, 51]. They should be minimized by the judicious choice of a vascular access in close collaboration with the apheresis specialist.

Citrate anticoagulation and plasma replacement are risk factors for hypocalcemia and paresthesia [52]. Plasma replacement is associated with a higher risk of anaphylactoid reactions. On the other hand, replacement with albumin does not correct the depletion and balancing of coagulation factors and immunoglobulins, resulting in a potential risk of bleeding and infection, respectively.

Drug removal by TPE

Data on drug removal by TPE are scarce and based on case reports or case series only [53, 54]. For most drugs, either no information is available, or it is not important. For highly protein-bound drugs with a low volume of distribution, and for chimeric antibodies, there is very effective removal. Factors associated with clinically meaningful drug removal include drug characteristics (volume of distribution, protein-binding affinity, rate of endogenous clearance, distribution half-life, dose-related pharmacodynamics), TPE characteristics (volume of plasma removed, interval between sessions, time between first and last session) and timing of drug administration [54–57]. Important inter- and intra-individual differences in pharmacokinetics and the multi-compartmental kinetic patterns seen during TPE can make predictions very difficult.

Antibiotic removal during TPE was reviewed recently [53, 56]. Whether an antibiotic should be administered before or after TPE depends also on its pharmacodynamic characteristics. Aminoglycosides can be best administered before the procedure to benefit from both a high peak with bactericidal effect and reduced toxicity related to a low trough level through extracorporeal removal. Beta-lactam plasma levels, on the other hand, should be maintained above the minimum inhibitory concentration which often requires a supplementary dose post-procedure. Monoclonal antibodies such as rituximab have a small volume of distribution and a long distribution half-life and therefore are significantly removed by TPE [58]. During TPE, total clearance of the drug decreases over time as the plasma levels decrease [59]. Although levels of monoclonal antibodies correlate with clinical effects, they may not correlate with pharmacodynamic markers (i.e., the CD20 + B-cell count for rituximab) [54]. Significant removal of enoxaparin, tacrolimus, and mycophenolic acid during TPE has been reported [60, 61]. Most studies involved administering medications after TPE and scheduling the next TPE session 24–36 h later. In general, therapeutic drug monitoring should be applied whenever possible in critically ill patients undergoing serial TPE sessions, especially if the drug has a narrow therapeutic index. Timing of sampling

should account for post-procedure redistribution with rebound of plasma concentration.

Unanswered questions and research agenda

Potential novel mechanisms and emerging ICU indications for TPE

For the most urgent TPE indications in critical care listed in Table 1, the efficacy of TPE is thought to stem from the removal of pathogenic substances and/or provision of deficient protective molecules. This classical blood purification concept may apply to systemic inflammatory syndromes encountered in a wide variety of critical conditions, but timing and anti-/pro-inflammatory balance may be pivotal in determining benefit versus potential detriment. Thus, inflammatory processes with consumptive coagulopathy ranging from thrombocytopenia to disseminated intravascular coagulation might respond to TPE. Furthermore, TPE removes damage-associated molecular patterns (DAMPs) that are released by injured cells and may trigger and perpetuate multiorgan dysfunction. In patients with sepsis and multiorgan dysfunction, TPE can lead to shock reversal and improve vascular permeability and coagulation abnormalities, while also producing a trend toward improved survival [62–64].

Given the ability of TPE to modulate systemic inflammation and coagulopathy, potential benefits in patients with severe COVID-19 have generated interest [65, 66]. Moreover, TPE can correct the increased von Willebrand factor multimer and the decreased ADAMTS13 activity in COVID-19 patients [67]. Faster recovery but no effect on mortality was shown in one small randomized controlled trial [68]. Many studies, including randomized controlled trials, are ongoing to test various hypotheses using slightly different protocols. Apart from sepsis, clinical scenarios characterized by a systemic inflammatory response that may improve with TPE include hemophagocytic lymphohistiocytosis, macrophage activation syndrome, chimeric antigen receptor T-cell-associated cytokine release syndrome, severe pancreatitis, and severe burns. So far, the current evidence remains limited to case series and uncontrolled observational studies. Finally, TPE has been used recently in refractory cases of vaccine-induced thrombosis and thrombocytopenia which could be added to the list of rescue therapy although evidence is still limited [69].

Initiation of TPE

The appropriate timing of TPE initiation needs to be determined. Biomarker levels, antibody titers, or clinical symptoms that support TPE initiation vary across indications. Specific cut-offs associated with poor outcomes need to be identified. Of note, the inflammatory syndromes encountered in the ICU may also serve as markers for monitoring of the effectiveness of TPE, such as markers of endothelial activation and primary hemostasis. Although trauma and sepsis are different entities, in both, elevations of glycocalyx-shedding biomarkers such as syndecan-1 and heparan sulfate are associated with poor outcomes [70] and their levels can be reduced with TPE [71]. Also, an imbalance between ADAMTS13 and von Willebrand factor is found in both sepsis and trauma. Specific cut-offs have been suggested, but whether these are useful to guide TPE remains unknown.

Comparison of TPE to other interventions

For most conditions, the efficacy of TPE compared to other techniques is not known. In GBS and myasthenia gravis, the effectiveness of TPE was compared to that of IVIG or a combination of both [72]. For conditions related to a pathogenic antibody, limited-level evidence suggests that TPE and more selective immunoadsorption techniques might have similar efficacy, but more studies are needed. Also, new data may challenge the benefit of TPE in some instances. Trials such as the PEXIVAS study led the AFSA to change severe ANCA-associated vasculitis from a category I to category II indication for TPE [73, 74].

Technical aspects of TPE

Little evidence supports the standard TPE regimens in ICU patients. More specifically, all current regimens were developed based on long-term experience with ward patients or outpatients. ICU patients likely have altered volumes of distribution due to organ failures, capillary leakage, and/or hypoalbuminemia. Ideally, TPE regimens should be tailored to the needs of the individual patient. More information about the optimal TPE intervals and volumes for critically ill patients is needed, as well as the optimal replacement solutions and the stopping cut-offs associated with a low risk of rebound.

Conclusions

TPE is an established therapy in modern critical care. It includes centrifugal and membrane-based techniques and requires fluid replacement with plasma or albumin solution. We have summarized the key points for the non-TPE specialists (Table 3). Although TPE is considered as first- or second-line therapy in many disorders, significant knowledge gaps remain, especially with regard to the exact triggers and cut-offs for initiation, optimal markers for monitoring and triggers for discontinuation. Furthermore, the interpretation of routine laboratory blood tests and drug dosing are challenging during TPE. More observational and interventional studies are needed to fill the existing knowledge gaps, to identify patients who are likely

Table 3 Key points for the non-TPE specialists

The organization of the TPE service differs between institutions. In many hospitals, specialist apheresis physicians and nurses provide TPE for ICU patients in close collaboration with intensivists. Since critically ill patients are highly vulnerable and at risk of hemodynamic instability, electrolyte disturbances, and coagulation disorders, close monitoring is needed during TPE. The choice of intravenous access (peripheral or central) should be carefully reviewed. TPE can be performed in the outpatient and inpatient setting. The decision regarding ICU admission rests on the clinical status and not on the need for TPE
The decision to initiate TPE should be based on the rationale that there is a presence of a substance causing a potentially life-threatening disruption that can be removed by TPE or the need for replacing a deficient substance to improve clinical outcomes. It should be evidence-based whenever possible although appropriate trials are lacking in most settings
The following tests must be performed before TPE: ABO Rh blood group and, if appropriate, an RBC antibody screen (in case plasma or RBC priming is needed); ionized calcium, magnesium, and potassium (which may be affected by citrate anticoagulation); complete blood cell count (to determine device settings and to exclude significant cytopenia that may require correction); and coagulation tests (activated partial thromboplastin time, partial thromboplastin time, prothrombin time, and fibrinogen)
The changes in hemostasis and coagulation tests induced by TPE must be considered when interpreting test results and making clinical decisions. For example, instituting oral anticoagulation regimens should be avoided during a string of TPE sessions, since dosing can be challenging given the removal of coagulation factors, combined with the potential addition of coagulation factors (in case of replacement with plasma)
Aside coagulation tests, TPE alters most laboratory variables, including serological tests, and inflammatory markers. Therefore, sample collection must be timed accordingly. Furthermore, circulating biomarkers such as troponin, brain natriuretic peptide, CRP, and LDH are no longer reliable for assessing the disease course
Ideally, repeated TPE requires therapeutic drug monitoring for antibiotics, anticoagulants, and several medications
More is not necessarily better. Standard TPE replaces 1.0 to 1.5 times the TPV. Given removal kinetics, replacing two or three times more does not result in a two- or threefold increase in efficacy
In patients who also require renal replacement therapy (RRT), TPE should be performed first unless there are potentially life-threatening electrolyte disturbances mandating urgent RRT. The volume of replacement fluid given during TPE can be removed during RRT. In addition, fluid shifts that occur following RRT may result in hypotension when blood enters the extracorporeal circuit of the apheresis device during the TPE requiring fluid resuscitation which negates the benefit of volume removal during RRT. Tandem procedures combining TPE and RRT can also be performed in experienced centers
TPE involves replacement with colloids whose oncotic pressure is like the removed plasma. Therefore, in patients with volume overload before TPE, any decrease in the replacement fluid volume will decrease the intravascular volume and potentially cause hypotension. In contrast to dialysis, TPE cannot remove free water, which would lead to hemoconcentration and fluid shifts from the extravascular to the intravascular compartment
TPE has the potential to remove medications and there is limited pharmacokinetic data available. Practical recommendations to address this potential adverse effect include: once daily medications should be administered after TPE, not before; administration of IV medications should be avoided immediately prior to and during TPE; oral medications should be avoided within four hours prior to TPE to allow for adsorption and redistribution prior to the start of the TPE; chimeric antibodies, monoclonal antibodies, and IVIG are effectively removed and timing of administration of these agents and TPE must be coordinated to allow for maximum medication dwell time
In some clinical situations (e.g., Guillain–Barré syndrome), TPE and intravenous immunoglobulins (IVIG) have equivalent efficacy. Combining the two in these scenarios is not recommended and TPE may be reserved in case of failure to IVIG

to benefit from TPE and to avoid TPE in those who will not benefit or may come to harm.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06793-z.

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Declarations

Conflicts of interest

JC received speaker fees from Fresenius Kabi and Terumo Blood and Cell Technologies. JTK received speaker fees from Fresenius Medical Care and ExThera Medical.

Publisher's Note

Received: 8 April 2022 Accepted: 20 June 2022
Published online: 12 August 2022

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