Plasmapheresis/Plasma Exchange

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DESCRIPTION

Therapeutic Plasmapheresis or plasma exchange (PE) is a procedure in which the plasma is isolated, then discarded or replaced with a substitution fluid such as albumin. The goal of therapeutic plasmapheresis/plasma exchange is the removal of harmful plasma components. Theoretically, decreasing the concentration of the harmful plasma component, will improve the course of the disease. Abnormal components potentially removed with therapeutic plasmapheresis/plasma exchange (PE) include toxins, metabolic substances, and plasma components (i.e., antibodies, complement system [part of the immune system, consists of small number of proteins that are synthesized by the liver, and circulate in the blood as inactive precursors]). Therefore, diseases thought to be caused by these abnormal constituents might best be treated with this form of therapy. Diseases benefiting from plasmapheresis are largely autoimmune or neurological disorders. Plasmapheresis/plasma exchange techniques are not intended to be curative treatments for most indications. Rather, they are used to address related symptoms.

Therapeutic plasmapheresis/plasma exchange (PE) is essentially symptomatic therapy, because it does not remove the source of the pathogenic factors. Therefore, the success of therapeutic plasmapheresis/plasma exchange will depend on whether the pathogenic substances are accessible through the circulation and whether the rate of production and transfer to the plasma component can be adequately addressed by plasmapheresis/plasma exchange.

Applications of therapeutic plasmapheresis/plasma exchange (PE) can be broadly subdivided into three general categories:

- Acute self-limited diseases
- Acute fulminant exacerbations of chronic diseases; and
- Chronic diseases

In self-limited diseases and acute exacerbations of fulminant exacerbations of chronic diseases, therapeutic plasmapheresis/plasma exchange is used to acutely lower the circulating pathogenic substance. In chronic disease, there is ongoing production of pathogenic autoantibodies. Because therapeutic plasmapheresis/plasma exchange does not address underlying pathology, and, due to phenomenon of rebound antibody production, its use in chronic diseases has been less effective than in acute, self-limiting diseases. For this reason, chronic conditions are not amendable to plasmapheresis treatment.

The terms plasmapheresis, apheresis, and plasma exchange (PE) are often used interchangeably, however there are some differences. The American Society of Apheresis (ASFA) definitions for these procedures are as follows:

Apheresis: is a general term describing removal of blood from a subject; a portion of the blood is separated and retained while the rest is returned to the donor.

Plasmapheresis: removes a smaller amount of plasma, usually less than 15% of the patient's blood volume and therefore does not require replacement of the removed plasma.

Plasma Exchange (PE): is the procedure that is preformed most commonly. A large volume of plasma is removed from a patient. The volume removed is such that if it were not replaced, significant hypovolemia resulting in vasomotor collapse would occur. As a result, the removed plasma must be replaced with some form of replacement fluid such as albumin.

Therapeutic plasmapheresis/plasma exchange (PE) are typically performed in outpatient settings, including blood banks, dialysis centers, hospital clinics, and physician's offices. Reinfusion with human plasma may cause anaphylaxis and bleeding complications, and though rare, may require replacement of clotting factors. Therefore, plasmapheresis procedures should be performed by appropriately trained clinicians in a setting that can respond to medical emergencies at all times.

Summary of Evidence
Peer reviewed published medical literature and medical society guidelines support the clinical effectiveness and safety of therapeutic plasmapheresis/plasma exchange (PE) for the indications listed in the *Policy* section below. There is evidence for the accepted indications that the use of this procedure can result in an improvement of symptoms, primarily for the acute self-limited conditions, and subsequently improve quality of life (QOL). However, based on the literature and society guidelines the evidence also is limited and/or the optimum role of therapeutic plasmapheresis/plasma exchange (PE) to remove specific autoantibodies, proteins and complements in the pathogenesis of many other conditions have not been established or the evidence demonstrated the therapy could be ineffective or harmful and therefore are considered investigational as indicated in the *Policy* section below.

Therapeutic Plasmapheresis/Plasmas Exchange in Covid-19 Patients
The use of therapeutic plasmapheresis/plasma exchange (TPE) in the treatment of severe COVID-19 infection has shown some positive results; however, the benefit has been limited in macrophage activation syndrome or sepsis complicated with MODS (multiple organ dysfunction syndrome) Theoretically, TPE could also remove the formed SARS-CoV-2 antibodies in addition to the “harmful” dysregulated inflammatory mediators, but it remains unclear if there is an antibody response during the cytokine storm or it develops subsequently. In this regard, the current recommendation of the American Plasma Exchange Association is as follows "the effectiveness of plasma exchange has not yet been determined and should be individually selected"

It is also necessary to administer TPE for the correct duration and volume, to monitor the potential drug removal of specific therapies such as immunomodulating agents and to practice the proper infection prevention and control measures. TPE is a tolerable procedure by most patients without adverse events; however, the procedure can be a challenge to perform in COVID-19 patients who are placed in a prone position.

In 2020, Khamis et. al. completed a retrospective single-center, case series study evaluating the therapeutic effectiveness of therapeutic plasmas exchange (TPE) in adults (31 patients) with severe Covid-19 infection. The analysis was performed using univariate statistics. Therapeutic plasma exchange (TPE) was performed on patients admitted to the intensive care unit (ICU) with confirmed or imminent acute respiratory distress syndrome (ARDS) or severe pneumonia. The TPE group was associated with higher extubation rates than the non-TPE cohort (73% versus 20%; $p = 0.018$). Additionally, patients on TPE had a lower 14 days (0 versus 35%; $p = 0.033$) and 28 days (0 versus 35%; $p = 0.033$) post plasma exchange mortality compared to patients not on TPE. However, all-cause mortality was only marginally lower in the TPE group compared to the non-TPE group (9.1% versus 45%; $p = 0.055$; power = 66%). Laboratory and ventilatory parameters also improved post TPE ($n = 11$). This single-center small trial is not without limitations. Although patients might have improved naturally, the laboratory and ventilatory changes before and after plasma exchange are encouraging for the TPE group. The use of the IL-6 antagonist, tocilizumab, could have contributed to TPE's beneficial effects. The current study is a case series with a small number of

patients; a larger well-powered randomized clinical trial is warranted to confirm the beneficial outcomes of TPE.

In 2020, Ma et. al. reported on the potential effect of blood purification which included plasma exchange in reducing cytokine storm as a late complication of critically ill Covid-19 patients. Based on this case series emerging evidence indicates the potential benefits of managing cytokine storm, via using steroid or IL-6/IL-6-receptor blocking antibodies. The capability of blood purification therapy (plasma exchange) in removing pathogenic antibodies or cytokines has been proven in multiple scenarios, but not in COVID-19 patients.

Summary Evidence
Based on the current peer reviewed medical literature regarding the treatment of Covid-19 using therapeutic plasma exchange (TPE) it is based on case series and retrospective reviews. While TPE has shown some promising results, however, the benefits have been limited in macrophage activation syndrome and sepsis complicated with MODS (multiple organ dysfunction syndrome). The capability of blood purification therapy (plasma exchange) in removing pathogenic antibodies or cytokines has been proven in multiple scenarios, but not in COVID-19 patients. The recommendation of the American Plasma Exchange Association is as follows "the effectiveness of plasma exchange has not yet been determined and should be individually selected." While TPE has been associated with improved outcomes in the treatment of Covid-19 patients, randomized controlled clinical trials (RCTs) are warranted to draw final, conclusive findings. The evidence is insufficient

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)
Multiple Myeloma Version 5.2022

- Supportive Care Treatment for Multiple Myeloma
    - Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity
- Management of Renal Disease in Multiple Myeloma – Supportive Care
    - Mechanical removal of serum FLCs; goal removal of 50%
        - High cuffoff dialysis filter
        - Plasmapheresis

Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity. Institutions differ in their use of plasmapheresis for adjunctive treatment of renal dysfunction.

Dialysis may be required in selected patients in addition to prompt institution of anti-myeloma therapy. Mechanical removal of light chains may be considered on a case by case basis. While the benefit of mechanical removal of free light chains has not been well established, there is limited evidence for the use of plasmapheresis or high cutoff dialysis to reduce pathogenic light chains.

Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 3.2022
Plasmapheresis should be performed for patients with symptomatic hyperviscosity, and before treatment with rituximab-containing regimen in patients with IgM ≥ 4000 mg/dl. IgM should be monitored closely in these patients thereafter and plasmapheresis should be considered again if symptomatic hyperviscosity recurs or if IgM is ≥ 4000 mg/dL while on rituximab containing therapy.

Primary Treatment Regimens
According to NCCN Panel, for patients requiring immediate disease control such as those with symptomatic hyperviscosity, initial plasmapheresis is recommended. After plasmapheresis, systemic therapy should be initiated as soon as possible.

Rituximab
Single agent rituximab is active in patients with WM. Transient increases in IgM titers (also called IgM flare) have been reported in 40% to 50% of patients after initiation of rituximab therapy, including in circumstances where rituximab has been used in combination therapy. The rituximab related IgM flare may lead to symptomatic hyperviscosity, as well as worsening of IgM related neuropathy, cryoglobulinemia and other IgM related complications. These levels may persist for months and do not indicate treatment failure but may necessitate plasmapheresis to reduce hyperviscosity. Prophylactic plasmapheresis can be considered in patients with high IgM levels (typically 4,000 mg/dL or higher) before rituximab exposure to minimize risk of symptomatic hyperviscosity.

American Academy of Neurology
In 2011, the American Academy of Neurology (Therapeutics and Technology Assessment Subcommittee) issued an evidence-based guideline on plasmapheresis in the treatment of neurological disorders. The primary conclusions based on their evidence review are as follows:

Acute Inflammatory Demyelinating Polyneuropathy/Guillain-Barre Syndrome	
What is the efficacy of plasmapheresis in the treatment of acute inflammatory demyelinating polyneuropathy (AIDP), also known as Guillain-Barre Syndrome (GBS)?	
Strong evidence	Plasmapheresis should be offered in the treatment of AIDP/GBS severe enough to impair independent walking or to require mechanical ventilation (Level A).
Good evidence	Plasmapheresis should be considered in the treatment of milder clinical presentations with AIDP/GBS (Level B).
Clinical context	IV immunoglobulin (IVIg) is an alternative treatment used in patients with AIDP/GBS. There is insufficient evidence to demonstrate the superiority of one treatment over the other.
Chronic Inflammatory Demyelinating Neuropathy	
What is the efficacy of plasmapheresis in the treatment of chronic inflammatory demyelinating neuropathy (CIDP)?	

Strong evidence	Plasmapheresis should be offered as a short-term treatment for patients with CIDP (Level A).
Clinical context	Steroids, IVIg, and immunosuppressants also have been used in the treatment of CIDP.
Dysimmune Neuropathies	
What is the efficacy of plasmapheresis in the treatment of dysimmune neuropathies?	
Good evidence	Plasmapheresis should be considered in polyneuropathy associated with IgA and IgG monoclonal gammopathy of undetermined significance (MGUS) (Level B).
	Plasmapheresis should not be considered in the treatment of polyneuropathy associated with IgM MGUS (Level B).
Myasthenia Gravis	
What is the efficacy of plasmapheresis in the treatment of myasthenia gravis (MG)?	
Insufficient evidence	Because of lack of randomized controlled studies with masked outcomes, there is insufficient evidence to support or refute the efficacy of plasmapheresis in the treatment of myasthenic crisis (Level U) or MG prethymectomy (Level U)
CNS Demyelinating Disease	
What is the efficacy of plasmapheresis in the treatment of CNS demyelinating disease?	
Strong evidence	Plasmapheresis should not be offered for chronic progressive or secondary progressive multiple sclerosis (MS) (Level A).
Good evidence	Plasmapheresis should be considered for the adjunctive treatment of exacerbations in relapsing forms of MS (Level B).
Weak evidence	Plasmapheresis may be considered in the treatment of fulminant CNS demyelinating diseases that fail to respond to high dose corticosteroid treatment (Level C).
Clinical context	No studies on the efficacy of plasmapheresis compared to other treatment options in MS are available.
Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection	
What is the efficacy of plasmapheresis in the treatment of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS)?	
Insufficient evidence	There is insufficient evidence to support or refute the use of plasmapheresis in the treatment of acute obsessive-compulsive disorder (OCD) and tic symptoms in the setting of PANDAS (Level U).
Sydenham Chorea	
What is the efficacy of plasmapheresis in the treatment of Syndenham Chorea?	
Insufficient evidence	There is insufficient evidence to support or refute the use of plasmapheresis in the treatment of Sydenham chorea (Level U).

Classification of Recommendations:

- A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies).*
- B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies).
- C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies).
- U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

American Heart Association (AHA)

In 2015, the American Heart Association (AHA) issued a scientific statement regarding antibody-mediated rejection (AMR) in cardiac transplantation, which included the following:

The following are 10 points to remember from this American Heart Association Scientific Statement about antibody-mediated rejection (AMR) in cardiac transplantation:

1. AMR is a "clinical entity with specific histopathologic, immunopathologic, and serological characteristics."
2. Risk factors for AMR includes elevated PRA, CMV seropositivity, prior mechanical circulatory support, prior treatment with muromoab-CD3 and development of antibodies against mouse monoclonal muromonab-CD3, history of retransplantation, multiparity, and positive crossmatch on T-cell flow cytometry.
3. It may present hyperacutely (within 0-7 days after transplantation), early (within the first month after transplantation), or late (months to years after transplantation).
4. Key diagnostic findings includes a) Clinical evidence of graft dysfunction, b) histopathologic evidence of acute capillary injury including changes in capillary endothelium and macrophages in capillaries, c) immunopathologic evidence for antibody-mediated injury including changes in C3d and/or C4d immunofluorescence staining or CD68 or C4d immunoperoxidase staining or severe fibrin in vessels, and d) serological evidence of anti-HLA or anti-donor antibodies.
5. The presentation of AMR may vary from mild heart failure to cardiogenic shock.
6. Endomyocardial biopsy is the gold standard for establishing the development of AMR.
7. There have been no large randomized clinical trials to evaluate therapies for AMR and hence there are no level I recommendations and all recommendations are therefore based on consensus.

8. The guiding principles for the management of AMR include removing circulating alloantibodies, reducing production of additional antibodies, and suppressing T-cell and B-cell responses.
9. Commonly used agents utilized in the treatment of AMR include: a) corticosteroids (act by suppression of T- and B-cell response), b) plasmapheresis (acts by eliminating circulating antibodies), c) IVIG (act by inhibiting residual antibodies and inhibition of complement), whereas less commonly used agents include: a) rituximab or splenectomy (act by suppression or depletion of B cells), b) bortezomib (act by suppression or depletion of plasma cells), c) eculizumab (by inhibition of complement), and d) mycophenolate mofetil, anti-lymphocyte antibodies, photopheresis, or total lymphoid irradiation (these act by suppression of T-cell response). In addition to treating AMR with cytotoxic or antibody-directed therapy, the background regimen should be optimized using potent B-cell receptors (mycophenolate and sirolimus).
10. AMR is associated with allograft failure, increased mortality, increased incidence of coronary artery vasculopathy, and overall poor prognosis.

American Society for Apheresis (ASFA)

In 2019, the American Society for Apheresis (ASFA) released the eighth special issue of their guidelines on the use of therapeutic apheresis in clinical practice. The therapeutic apheresis procedures considered in this guideline include therapeutic plasma exchange (TPE).

Category Definitions for Therapeutic Apheresis

Category	Description
I	Disorders for which apheresis is accepted as first line therapy, either as primary standalone treatment or in conjunction with other modes of treatment
II	Disorders for which apheresis is accepted as second line therapy, either as 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 suggest apheresis to be ineffective or harmful. Institutional Review Board (IRB) approval is desirable if apheresis treatment is undertaken in these circumstances

Grading Recommendations: Strength and Quality of Evidence

Recommendation	Description	Quality of Evidence	Implications
Grade 1A	Strong recommendation, high quality evidence	Randomized controlled trials (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	Randomized controlled trials (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	Randomized controlled trials (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,	Randomized controlled trials (RCTs) with	Weak recommendation, best action may

	moderate quality evidence	important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	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

Recommendations for Therapeutic Apheresis Exchange (TPE)

Disease	Therapeutic Apheresis Modality	Indication	Category	Grade
Acute disseminated encephalomyelitis (ADEM)	TPE	Steroid Refractory	II	2C
Acute Inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre Syndrome)	TPE	Primary Treatment	I	1A
Acute liver failure	TPE		III	2B
Amyloidosis, systemic	TPE	Other Causes	IV	2C
Anti-glomerular basement membrane disease (Goodpasture's syndrome)	TPE	Dialysis dependence and no diffuse alveolar hemorrhage (DAH)	III	2B
	TPE	Dialysis independence	I	1B
	TPE	Diffuse alveolar hemorrhage (DAH)	I	IC

Disease	Therapeutic Apheresis Modality	Indication	Category	Grade
Atopic (neuro) dermatitis (atopic eczema), recalcitrant (new in 2016)	TPE/DFPP (double filtration plasmapheresis)		III	2C
Autoimmune hemolytic anemia, severe	TPE TPE	Severe cold agglutinin disease Severe warm autoimmune	II III	2C 2C
Burn shock resuscitation	TPE		III	2B
Cardiac neonatal lupus	TPE		III	2C
Catastrophic antiphospholipid syndrome (CAPS)	TPE		I	2C
Chronic focal encephalitis (Rasmussen encephalitis)	TPE		III	2C
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	TPE/IA (Immunoadsorption)		I	1B
Coagulation factor inhibitors	TPE		III	2C
Complex regional pain syndrome	TPE	Chronic	III	2C
Cryoglobulinemia	TPE	Severe/symptomatic	II	2A
Dilated cardiomyopathy, idiopathic	TPE	NYHA II-IV	III	2C

Disease	Therapeutic Apheresis Modality	Indication	Category	Grade
Erythropoietic protoporphyria, liver disease	TPE		III	2C
Familial hypercholesterolemia	TPE	Homozygotes/ heterozygotes	II	1B
Focal segmental glomerulosclerosis (FSGS)	TPE/IA (Immunoadsorption) TPE	Recurrent in kidney transplant Steroid resistant in native kidney	I III	1B 2C
Hemolysis, elevated liver function tests and low platelets (HELLP) syndrome	TPE TPE	Postpartum Antepartum	III IV	2C 2C
Hemophagocytic: lymphohistiocytosis (HLH); Hemophagocytic syndrome; Macrophage activating syndrome	TPE		III	2C
Heparin induced thrombocytopenia and thrombosis (HIT/HITT)	TPE TPE	Pre-cardiopulmonary bypass Thrombosis	III III	2C 2C
Hypertriglyceridemic pancreatitis	TPE/LA (Lipoprotein apheresis) TPE/LA (Lipoprotein apheresis)	Severe Prevention of relapse	III III	1C 2C
Hyperviscosity in hypergammaglobulinemia	TPE TPE	Symptomatic Prophylaxis for rituximab	I I	1B 1C

Disease	Therapeutic Apheresis Modality	Indication	Category	Grade
IgA nephropathy (Berger's Disease)	TPE	Crescentic	III	2B
	TPE	Chronic Progressive	III	2C
Immune thrombocytopenia (ITP)	TPE/IA (Immunoadsorption)	Refractory	III	2C
Lambert Eaton myasthenic syndrome	TPE		II	2C
Multiple sclerosis	TPE	Acute attack/relapse	II	1A
	TPE	Chronic	III	2B
Myasthenia gravis	TPE/IA (Immunoadsorption)	Acute, short-term treatment	I	1B
	TPE/IA (Immunoadsorption)	Long-term treatment	II	2B
Myeloma cast nephropathy	TPE		II	2B
Nephrogenic systemic fibrosis	ECP/TPE (Extracorporeal photophoresis/therapeutic plasma exchange)		III	2C
Neuromyelitis optica spectrum disorders (NMOSD)	TPE	Acute attack/relapse	II	1B
	TPE	Maintenance	III	2C
N-methyl-D-aspartate receptor antibody encephalitis	TPE/IA (Immunoadsorption)		I	1C
Overdose, envenomation and poisoning	TPE	Mushroom Poisoning	II	2C
	TPE	Envenomation	III	2C

Disease	Therapeutic Apheresis Modality	Indication	Category	Grade
	TPE	Drug overdose/poisoning	III	2C
Paraneoplastic neurologic syndromes	TPE/IA (Immunoadsorption)		III	2C
Paraproteinemic demyelinating neuropathies; chronic acquired demyelinating polyneuropathies	TPE	IgG/IgA/IgM	I	1B
	TPE	Anti-MAG neuropathy	III	1C
	TPE	Multiple myeloma	III	2C
	TPE	Multifocal motor neuropathy	IV	1C
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS); Sydenham's chorea	TPE	PANDAS, exacerbation	II	1B
	TPE	Syndenham's chorea, severe	III	2B
Pemphigus vulgaris	TPE	Severe	III	2B
Phytanic acid storage disease (Refsum's disease)	TPE/LA (Lipoprotein apheresis)		II	2C
Post transfusion purpura (PTP)	TPE		III	2C
Progressive multifocal leukoencephalopathy (PML) associated with natalizumab				
Pruritus due to hepatobiliary disease, treatment resistant (new in 2016)	TPE	Treatment resistant	III	1C

Disease	Therapeutic Apheresis Modality	Indication	Category	Grade
Psoriasis	TPE	Disseminated pustular	IV	2C
Red cell alloimmunization prevention and treatment	TPE	Pregnancy, gestational age (GA) < 20 weeks	III	2C
Scleroderma (system sclerosis)	TPE		III	2C
Sepsis with multi-organ failure	TPE		III	2B
Steroid responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto's encephalopathy)	TPE		II	2C
Stiff person syndrome	TPE		III	2C
Sudden sensorineural hearing loss	TPE		III	2C
Systemic lupus erythematosus (SLE)	TPE	Severe complications	II	2C
Thrombotic microangiography, coagulation mediated	TPE	THBD, DGKE, and PLG mutations	III	2C
Thrombotic microangiopathy, complement mediated	TPE	Factor H autoantibody	I	2C
	TPE	Complement factor gene mutations	III	2C
Thrombotic microangiopathy, drug associated	TPE	Ticlopidine	I	2B
	TPE	Clopidogrel	III	2B
	TPE	Gemcitabine/Quinine	IV	2C

Disease	Therapeutic Apheresis Modality	Indication	Category	Grade
Thrombotic microangiopathy, infection associated	TPE/IA (Immunoadsorption) TPE	STEC-HUS severe pHUS	III III	2C 2C
Thrombotic thrombocytopenic purpura (TTP)	TPE		I	1A
Thrombotic microangiopathy, transplantation associated	TPE		III	2C
Thyroid storm	TPE		II	2C
Toxic epidermal necrolysis (TEN)	TPE	refractory	III	2B
Transplantation, cardiac	TPE TPE	Desensitization Antibody mediated rejection	II III	1C 2C
Transplantation, hematopoietic stem cell, ABO incompatible (ABOi)	TPE TPE TPE	Major ABOi HPC(M) Major ABOi HPC(A) Major/Minor ABOi with pure RBC aplasia	II II III	1B 2B 2C
Transplantation, hematopoietic stem cell, HLA desensitization	TPE		III	2C
Transplantation, liver	TPE TPE	Desensitization, ABOi living donor Desensitization, ABOi deceased donor/antibody mediated rejection	I III	1C 2C

Disease	Therapeutic Apheresis Modality	Indication	Category	Grade
Transplantation, lung	TPE	Antibody mediated rejection/desensitization	III	2C
Transplantation, renal ABO compatible	TPE/IA (Immunoadsorption)	Antibody mediated rejection	I	1B
	TPE/IA (Immunoadsorption)	Desensitization, living donor	I	1B
	TPE/IA (Immunoadsorption)	Desensitization, deceased donor	III	2C
Transplantation, renal, ABO incompatible	TPE/IA (Immunoadsorption)	Desensitization, living donor	I	1B
	TPE/IA (Immunoadsorption)	Antibody mediated rejection	II	1B
Vasculitis, ANCA associated (AAV)	TPE	MPA/GPA/RLV: RPGN, Cr $\geq$ 5.7	I	1A
	TPE	MPA/GPA/RLV: RPGN Cr < 5.7	III	2C
	TPE	MPA/GPA/RLV: DAH	I	1C
	TPE	EGPA	III	2C
Vasculitis, IgA (Henoch-Schonlein purpura)	TPE	Crescentic RPGN	III	2C
	TPE	Severe extrarenal manifestations	III	2C
Vasculitis, other	TPE	Hepatitis B polyarteritis nodosa	II	2C
	TPE	Idiopathic polyarteritis nodosa	IV	1B
	TPE	Behcet's disease	III	2C
Voltage gated potassium channel antibodies	TPE/IA (Immunoadsorption)		II	1B

Disease	Therapeutic Apheresis Modality	Indication	Category	Grade
Wilson disease, fulminant	TPE		I	1C

Regulatory Status
FDA has a compliance program to ensure that source plasma, source leukocytes, and therapeutic exchange plasma for further manufacture into products for human use are safe, pure, potent, and appropriately labeled. The compliance program covers products intended for use both in injectable drug products (e.g., immune globulin, albumin) and noninjectable products (e.g., in vitro devices such as blood bank reagents).

PRIOR APPROVAL

Not applicable.

POLICY

Therapeutic plasmapheresis/plasma exchange may be considered **medically necessary** for any of the following conditions listed below:

- Acute disseminated encephalomyelitis (ADEM) steroid refractory
- Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome)
- Acute idiopathic transverse myelitis steroid refractory
- Anti-glomerular basement membrane disease (Goodpasture's syndrome)
    - Diffuse alveolar hemorrhage (DAH)
    - Dialysis independence
- Anti-neutrophil cytoplasmic antibodies (ANCA)-associated rapidly progressive glomerulonephritis
- Autoimmune hemolytic uremic syndrome – severe cold agglutinin
- Catastrophic antiphospholipid syndrome (CAPS)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Cryoglobulinemia severe/symptomatic
- Familial hypercholesterolemia
- Focal segmental glomerulosclerosis after kidney transplant
- Hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP Syndrome)
- Hyperviscosity syndromes associated with monoclonal gammopathies (such as multiple myeloma and Waldenstrom's macroglobulinemia)
- Lambert-Eaton Myasthenic Syndrome

- Multiple myeloma cast nephropathy (acute renal failure secondary to multiple myeloma)
- Multiple sclerosis (MS)
    - For adjunctive treatment of exacerbations in relapsing forms of MS
    - In the treatment of fulminant CNS demyelinating disease that fails to respond to high dose corticosteroid treatment (as second line therapy either as standalone treatment or in conjunction with or modes of treatment)
- Mushroom poisoning (wild mushrooms, particularly the Amanita family)
- Myasthenia gravis
- Neuromyelitis optica (also known as Devic's disease) acute attack/relapse
- N-methyl-D-aspartate receptor antibody encephalitis
- Paraproteinemic demyelinating neuropathies with IgA, IgG or IgM monoclonal gammopathy of undetermined significance (MGUS)
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), exacerbation
- Pemphigus Vulgaris as second line therapy, that is resistant to standard therapy (dapsone, corticosteroids, immunosuppressants such as azathioprine or cyclosporine)
- Phytanic acid storage disease (Refsum's Disease)
- Post transfusion purpura
- Progressive multifocal leukoencephalopathy associated with natalizumab (tysarbi)
- Steroid responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto's encephalopathy)
- Systemic lupus erythematous (SLE) with severe complications (diffuse alveolar hemorrhage (DHA), thrombotic microangiography, hyperviscosity, cryoglobulinemia, and CNS involvement)
- Thrombotic microangiopathy (Factor H autoantibody) and drug associated (Ticlopidine)
- Thrombotic thrombocytopenia purpura (TTP)
- Thyroid storm with severe symptoms who respond poorly to first line therapeutic measures
- Transplantation
    - Hematopoietic stem cell transplant:
        - ABO incompatible
        - Human leukocyte antigen (HLA) incompatibility with haplo-type transplant
    - Solid organ transplantation for the following:
        - Desensitization
        - Antibody-mediated rejection
        - ABO incompatible
- Voltage gated potassium channel antibodies
- Wilson Disease, fulminant

Therapeutic plasmapheresis/plasma exchange is considered **investigational** for all other conditions, including, but not limited, to the following, because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- Acute liver failure, except as indicated above for Wilson Disease
- Amyloidosis, systemic
- Amyotrophic lateral sclerosis (ALS)
- Anti-glomerular basement membrane disease (Goodpasture syndrome) – dialysis dependence, no diffuse alveolar hemorrhage (DAH)
- Aplastic anemia
- Asthma
- Atopic (neuro) dermatitis (atopic eczema), recalcitrant
- Autoimmune hemolytic anemia, severe: warm autoimmune hemolytic anemia (WAHA)
- Burn shock resuscitation
- Cardiac neonatal lupus
- Central nervous system demyelinating diseases (except as indicated above for the following indications: Acute disseminated encephalomyelitis (ADEM) steroid refractory, Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome), Acute idiopathic transverse myelitis steroid refractory)
- Chronic fatigue syndrome
- Chronic focal encephalitis (Rasmussen Encephalitis)
- Coagulation factor inhibitors (alloantibody and autoantibody)
- Complex regional pain syndrome
- Covid-19
- Dermatomyositis or polymyositis
- Dilated cardiomyopathy, idiopathic (NYHA II-IV)
- Erythropoietic protoporphyria, liver disease
- Focal segmental glomerulosclerosis except as indicated above
- Henoch-Schonlein purpura
- Hemolytic uremic syndrome (HUS)heal-related)
- Heparin induced thrombocytopenia (HIT)
    - Pre-cardiopulmonary bypass; or
    - Heparin induced thrombocytopenia with thrombosis (HITT)
- Hemophagocytic lymphocytosis (HLH); Hemophagocytic syndrome; Macrophage activating syndrome
- Hypertriglyceridemic pancreatitis
- Immune complex rapidly progressive glomerulonephritis
- Immune thrombocytopenia (refractory)
- Immunoglobin A nephropathy (Berger's Disease)
- Inclusion body myositis
- Inflammatory bowel disease (ulcerative colitis, Crohn's disease)
- Multiple Sclerosis, except as indicated above
- Nephrogenic systemic fibrosis

- Neuromyelitis Optica (Devic's syndrome) except as indicated above
- Overdose, envenomation, and poisoning
- Paraneoplastic neurological syndromes
- Paraproteinemic demyelinating polyneuropathies (except as indicated above) multiple myeloma; Anti-MAG neuropathy; multifocal motor neuropathy)
- Pediatric autoimmune neuropsychiatric disorders (PANDAS) (except as indicated above for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), exacerbation)
- Pemphigus vulgaris except as indicated above
- POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes)
- Progressive multifocal leukoencephalopathy associated with natalizumab (tysarbi), except as indicated above
- Pruritus due to hepatobiliary diseases
- Psoriasis
- Pure red cell aplasia
- Red cell alloimmunization in pregnancy
- Rheumatoid arthritis
- Schizophrenia
- Scleroderma (progressive systemic sclerosis)
- Sepsis with multiorgan failure
- Status epilepticus
- Stiff-person syndrome
- Sudden sensorineural hearing loss
- Sydenham's Chorea
- Systemic lupus erythematous except as indicated above
- Thrombotic microangiopathy (except as indicated above) - coagulation mediated: THBD, DGKE, and PLG mutations; complement mediated: complement factor gene mutations; drug associated: clopidogrel, gemcitabine or quinine; transplantation associated
- Thyroid storm except as indicated above
- Toxic epidermal necrolysis, refractory

Policy Guidelines

For the treatment of solid organ transplantation antibody-mediated rejection (ABMR or AMR) plasmapheresis is typically performed for this indication within the first year of the transplantation. There is a lack of evidence regarding the treatment of late onset (after the first year of transplantation) for antibody-mediate rejection with plasmapheresis.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 36514 Therapeutic apheresis; for plasmapheresis

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POLICY HISTORY		
Date	**Reason**	**Action**
May 2022	Annual Review	Policy Revised
May 2021	Annual Review	Policy Revised
May 2020	Annual Review	Policy Revised
September 2019	Interim Review	Policy Revised
May 2019	Annual Review	Policy Revised
May 2018	Annual Review	Policy Renewed
May 2017	Annual Review	Policy Revised
May 2016	Annual Review	Policy Revised
June 2015	Annual Review	Policy Revised
July 2014	Annual Review	Policy Revised
September 2013	Annual Review	Policy Revised
October 2012	Annual Review	Policy Renewed
October 2011	Annual Review	Policy Revised
September 2010	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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