Medical Coverage Policy

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Plasmapheresis

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Overview

This Coverage Policy only addresses plasmapheresis, also known as therapeutic plasma exchange (TPE), which is one type of therapeutic apheresis. Plasmapheresis is a process by which plasma is removed via a cell separator and the red cells, white cells, platelets and a sterile plasma substitute (e.g., plasma protein fractions or albumin with sterile saline) are transfused back into the body.

Therapeutic apheresis is an inclusive term for the following procedures (which are not addressed in the policy with the exception of therapeutic plasma exchange): adsorptive cytapheresis, $ß_2$-microglobulin adsorption, double filtration plasmapheresis, erythrocytapheresis, extracorporeal liver support systems/artificial liver support systems, extracorporeal photopheresis, hemoperfusion, immunoadsorption, leukocytapheresis, lipoprotein apheresis, red blood cell exchange, therapeutic plasma exchange, and thrombocytapheresis.

Coverage Policy

Plasmapheresis is considered a medically necessary primary therapy for ANY of the following indications:

- acute inflammatory demyelinating polyradiculoneuropathy (AIDP) (Guillain-Barré syndrome), primary treatment
- anti-glomerular basement membrane disease (Goodpasture's syndrome) for EITHER of the following:
  - individual is dialysis independent
  - individual has diffuse alveolar hemorrhage (DAH)
- catastrophic antiphospholipid syndrome (CAPS)
- chronic acquired demyelinating polyneuropathies (CADP), associated with immunoglobulin G (IgG), immunoglobulin A (IgA) or immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance (e.g., MGUS)
- chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), chronic acquired demyelinating polyneuropathy
- focal segmental glomerulosclerosis (FSGS) recurrent in transplanted kidney
- hyperviscosity syndrome in hypergammaglobulinemia (e.g., Waldenström's macroglobulinemia, multiple myeloma)
- myasthenia gravis (acute, short-term treatment) for moderate-severe disease including myasthenic crisis, unstable or refractory disease, unstable disease activity pre-thymectomy
- n-methyl D-aspartate receptor antibody encephalitis (NMDAR)
- thrombotic microangiopathy (TMA) secondary to ticlopidine or Factor H antibodies
- thrombotic thrombocytopenic purpura (TTP)
- transplantation, kidney, ABO compatible with antibody mediated rejection (AMR)
- transplantation, kidney, ABO compatible with elevated human leukocyte antigens (HLA)/elevated panel reactive antibodies (PRA) desensitization, live donor
- transplantation, kidney, ABO incompatible; desensitization, live donor
- transplantation, liver, ABO incompatible; live donor liver transplant

- vasculitis, anti-neutrophil cytoplasmic antibodies (ANCA)-associated (microscopic polyangiitis, granulomatosis with polyangiitis [e.g., Wegner's], eosinophilic granulomatosis with polyangiitis)
- Wilson disease presenting as fulminant hepatic failure with hemolysis

Plasmapheresis is considered a medically necessary adjunctive secondary therapy for the following conditions when the individual has failed to respond to conventional pharmacotherapy:

- acute disseminated encephalomyelitis (ADEM), steroid refractory
- cardiac transplantation, desensitization
- cold agglutinin disease (CAD/cold autoimmune hemolytic anemia), severe
- cryoglobulinemia, severe/symptomatic
- erythropoietic protoporphyria (EPP), liver disease
- familial hypercholesterolemia (FH) (i.e., homozygotes/heterozygotes
- Hashimoto's encephalopathy (HE); steroid responsive encephalopathy associated with autoimmune thyroiditis
- hypertriglyceridemic acute pancreatitis, severe (levels >10,000 mg/dL)
- Lambert-Eaton myasthenic syndrome (LEMS)
- Multiple sclerosis, acute attack/relapse; acute central nervous system inflammatory demyelinating disease
- mushroom poisoning
- myasthenia gravis (long-term treatment)
- myeloma associated with acute renal failure (myeloma cast nephropathy)
- neuromyelitis optica spectrum disorders (NMOSD); acute
- phytanic acid storage disease (Refsum's disease)
- post-transfusion purpura (PTP)
- systemic lupus erythematosus (SLE), severe complications without nephritis
- thyroid storm
- transplantation, hematopoietic stem cell, ABO incompatible
- transplantation, kidney, ABO incompatible; antibody mediated rejection/humoral rejection
- vasculitis, other (hepatitis B virus [HBV] polyarteritis nodosa [PAN])
- voltage gated potassium channel (VGKC) antibody-related diseases (i.e., limbic encephalitis, neuromyotonia, and Morvan's syndrome)

Plasmapheresis for ANY other indication including any of the following is considered not medically necessary:

- acquired pure red cell aplasia
- acute liver failure
- acute toxins, venoms, and poisoning (envenomation; other: drug overdose, poisoning, mechanical hemolysis and methemoglobinemia)
- alzheimer's disease
- amyloidosis, systemic, dialysis related
- amyotrophic lateral sclerosis
- anti-neutrophil cytoplasmic antibodies (ANCA)-associated rapidly progressive glomerulonephritis (RPGN) (granulomatosis with polyangiitis [e.g., Wegner's] and microscopic polyangiitis [MPA]) in dialysis independent patients
- anti-glomerular basement membrane disease (Anti-GBM) (Goodpasture's syndrome) in dialysis dependent patients and no diffuse alveolar hemorrhage (DAH)
- aplastic anemia
- atopic (neuro-) dermatitis (atopic eczema), recalcitrant
- autoimmune dysautonomia

- burn shock resuscitation
- cardiac neonatal lupus
- cardiac transplantation, antibody medicated rejection (AMR)
- chronic acquired demyelinating polyneuropathies (CADP); anti-myelin-associated glycoprotein (MAG) neuropathy
- coagulation factor deficiency and inhibitors
- complex regional pain syndrome
- dermatomyositis or polymyositis
- hemolysis, elevated liver enzymes and low platelets (HELLP syndrome)
- hemophagocytic lymphohistiocytosis (HLH); hemophagocytic syndrome (HS); macrophage activating syndrome
- Henoch-Schonlein purpura; IgA vasculitis (IgAV); IgA vasculitis with nephropathy (IgAVN)
- heparin induced thrombocytopenia and thrombosis (HIT/HITT)
- idiopathic dilated cardiomyopathy (iDCM) NYHA II-IV
- idiopathic inflammatory myopathies
- immune checkpoint inhibitors, immune-related adverse events
- immune thrombocytopenia (ITP)
- immunoglobin A (IgA) nephropathy (Berger's Disease)
- inclusion body myositis
- multiple myeloma with polyneuropathy
- multiple sclerosis, chronic progressive
- nephrogenic systemic fibrosis (NSF)
- neuromyelitis optica spectrum disorders (NMOSD); maintenance
- paraneoplastic autoimmune retinopathies
- paraneoplastic neurologic syndromes
- pediatric postinfectious autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS); Sydenham's chorea
- pemphigus vulgaris
- polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS)
- prevention of hypertriglyceridemic pancreatitis
- progressive multifocal leukoenchephalopathy (PML)
- pruritus due to hepatobiliary disease
- psoriasis
- Rasmussen encephalitis (chronic focal encephalitis)
- red blood cell alloimmunization in pregnancy
- rheumatoid arthritis
- rheumatoid vasculitis
- schizophrenia
- sepsis with multi-organ failure
- stiff-person syndrome
- sudden sensorineural hearing loss (SSHL)
- systemic sclerosis
- thrombotic microangiopathy (TMA), coagulation mediated
- thrombotic microangiopathy (TMA), complement mediated (except for factor H autoantibiodies)
- thrombotic microangiopathy (TMA), drug- associated (except for ticlopidine) or hematopoietic stem cell transplant-associated
- thrombotic microangiopathy (TMA), infection associated; hemolytic uremic syndrome (HUS), Shiga toxin mediated (STEC-HUS, severe), Streptococcus pneumoniae (pHUS)
- thrombotic microangiopathy (TMA), pregnancy associated
- toxic epidermal necrolysis (TEN)
- transplantation, hematopoietic stem cell (HSCT), HLA desensitization

- transplantation, intestine; antibody mediated rejection and desensitization
- transplantation, kidney, ABO compatible, and elevated panel reactive antibodies (PRA) desensitization, deceased donor
- transplantation, liver, ABO incompatible; deceased donor; antibody mediated rejection/humoral rejection
- transplantation, lung, antibody mediated rejection/allograft rejection, desensitization
- vaccine-induced immune thrombotic thrombocytopenia (VITT)
- vasculitis, IgA (crescentic rapidly progressive glomerulonephritis, severe extra-renal manifestations)
- vasculitis, other (Kawasaki disease, Multisystem inflammatory syndrome in children)
- warm autoimmune hemolytic anemia (WAIHA)

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

General Background

Plasmapheresis (PP), plasma exchange (PE), or therapeutic plasma exchange (TPE) is a process by which plasma is removed via a cell separator and the red cells, white cells, platelets and a sterile plasma substitute (e.g., plasma protein fractions or albumin with sterile saline) are transfused back into the body. The goal of PP is to decrease the concentration of harmful plasma constituents, allowing a disease course to improve. The abnormal blood constituents implicated in diseases and removed by PP include toxins, metabolic substances and plasma components (e.g., complement antibodies). The procedure takes one to three hours, and the number of treatments needed (e.g., six to ten treatments over a two- to ten-week period) depends upon the patient's condition and underlying disease.

Plasmapheresis (PP), plasma exchange (PE), or therapeutic plasma exchange (TPE) is a type of therapeutic apheresis. Therapeutic apheresis is a general phrase that denotes replacement of plasma with another fluid such as colloid, crystalloid, or allogeneic plasma; or removal or replacement of abnormal or excessive cells (Fridey and Kaplan, 2025). Therapeutic apheresis is an inclusive term for the following types of procedures or modalities: adsorptive cytapheresis, $ß_2$-microglobulin adsorption, double filtration plasmapheresis, erythrocytapheresis, extracorporeal liver support systems/artificial liver support systems, extracorporeal photopheresis, hemoperfusion, immunoadsorption, leukocytapheresis, lipoprotein apheresis, red blood cell exchange, therapeutic plasma exchange (plasmapheresis), and thrombocytapheresis (Connelly-Smith, et al., 2023).

Plasmapheresis is a recognized treatment modality for multiple conditions. The American Society for Apheresis (ASFA) (Connelly-Smith, et al., 2023) updated guidelines for PP include four categories that were developed based on the quality of the evidence and the strength of recommendations derived from the evidence. These categories rate the indications for PP by condition and include the following:

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

In the ASFA guideline, the grade system was used to assign recommendation grades for therapeutic apheresis to enhance the clinical value of the ASFA categories:

- Grade 1A: Strong recommendation, high-quality evidence
- Grade 1B: Strong recommendation, moderate-quality evidence
- Grade 1C: Strong recommendation, low-quality or very low-quality evidence
- Grade 2A: Weak recommendation, high-quality evidence
- Grade 2B: Weak recommendation, moderate-quality evidence
- Grade 2C: Weak recommendation, low-quality or very low-quality evidence

The updated Ninth Edition 2023 ASFS guideline consists of 91 fact sheets for relevant diseases and medical conditions, with 166 graded and categorized indications and/or therapeutic apheresis modalities. For certain diseases there are several apheresis based modalities available. Several conditions or diseases were reviewed in consideration for the development of a new fact sheet. To meet criteria for a new fact sheet, the committee required a minimum of 10 cases published in the last decade in peer-reviewed journals, ideally by more than one group. Based on these criteria, there were seven new disease categories added to the 2023 guideline. The fact sheets address therapeutic indications in ASFA categories I through IV, with many diseases categorized having multiple clinical presentations/situations which are individually graded and categorized. Some previously published fact sheets were renamed to group fact sheets together by similar disease pathology and/or treatment.

Category I Indications

The evidence in the published peer-reviewed scientific literature and/or professional societies support plasmapheresis (PP) (i.e. therapeutic plasma exchange [TPE]) as an established primary treatment option for the following conditions (Connelly-Smith, et al., 2023):

- acute inflammatory demyelinating polyradiculoneuropathy (AIDP) (Guillain-Barré Syndrome), primary treatment (Grade 1A)
- anti-glomerular basement membrane disease (Anti-GBM) (Goodpasture's syndrome) in dialysis independent patients (Grade 1B) or when diffuse alveolar hemorrhage (DAH) is present (Grade 1C)
- catastrophic antiphospholipid syndrome (CAPS) (Grade 2C)
- chronic acquired demyelinating polyneuropathies (CADP) associated with immunoglobulin G (IgG), immunoglobulin A (IgA) or immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance (e.g., MGUS) (Grade 1B)
- chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), chronic acquired demyelinating polyneuropathy (Grade 1B)
- focal segmental glomerulosclerosis (FSGS) recurrent in transplanted kidney (Grade 1B)
- hyperviscosity syndrome in hypergammaglobulinemia (e.g., Waldenström's macroglobulinemia, multiple myeloma) (Grade 1B-C)

- myasthenia gravis (acute, short-term treatment) for moderate-severe disease including myasthenic crisis, unstable or refractory disease, unstable disease activity pre-thymectomy (Grade 1B)
- *n*-methyl D-aspartate receptor antibody encephalitis (NMDAR) (Grade 1C)
- thrombotic microantiopathy (TMA), complement mediated secondary to Factor H antibodies (Grade 2C)
- thrombotic microangiopathy (TMA), drug associated secondary to ticlopidine (Grade 2B)
- thrombotic thrombocytopenic purpura (TTP) (Grade 1A)
- transplantation, kidney, ABO compatible with antibody mediated rejection (AMR) (Grade 1B)
- transplantation, kidney, ABO compatible with elevated human leukocyte antigens (HLA)/elevated panel reactive antibodies (PRA) desensitization, live donor (Grade 1B)
- transplantation, kidney, ABO incompatible; desensitization, live donor (Grade 1B)
- transplantation, liver, ABO incompatible; live donor liver transplant (Grade 1C)
- Wilson disease presenting as fulminant hepatic failure with hemolysis (Grade 1C)

Category II Indications

Evidence in the published peer-reviewed scientific literature, the Society for Apheresis, and other professional societies (e.g., National Cancer Institute), support PP as an acceptable adjunct therapy for the conditions listed below.

Acute Disseminated Encephalomyelitis, Steroid Refractory (ADEM) (Grade 2C): ADEM is an acute inflammatory monophasic demyelinating neurologic disease-causing inflammation of the brain and spinal cord. The standard first-line therapy is high-dose intravenous corticosteroids. PP is utilized for the removal of offending antibodies when the patient in unresponsive to standard therapy (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Brenton, 2018; Schwartz, et al., 2013, 2016).

Cardiac Transplantation, Desensitization (Grade 1C): The four types of cardiac allograft rejection include hyperacute in cases of ABO or major human leukocyte antigen (HLA) incompatibility, acute cellular (ACR), acute antibody-mediated (AMR) or chronic rejection (allograft vasculopathy). ACR is the most common form of rejection and is mediated by T cells. Rejection is treated by immunosuppression. Steroids are used for episodes of rejection. If AMR progresses, rituximab and TPE are considered. Many past studies focusing on desensitization were performed with older medical regimens. Newer agents, such as bortezomib, are now used for desensitization. Extracorporeal photopheresis (ECP) may be used to treat cellular rejection and allograft vasculopathy. PP has been proposed as a treatment modality during the acute rejection period to remove donor-specific antibodies and/or inflammatory mediators in AMR. However, the evidence is primarily in the form of case series, case reports and retrospective reviews. The clinical benefit of PP for cardiac allograft rejection has not been established (Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Cold Agglutinin Disease (CAD), Cold Autoimmune Hemolytic Anemia Severe (Grade 2C): CAD is a form of autoimmune hemolytic anemia (AIHA) caused by autoantibodies that react with red blood cells at temperatures < 37 degrees Celsius. CAD may be primary or secondary, is often transient, and requires no intervention. When indicated, treatment consists primarily of avoidance to cold temperatures. In cases involving fulminate hemolysis, PP is used in combination with immunosuppressive therapy to remove/reduce circulating autoantibodies (Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; Berentsen, et al., 2007).

Cryoglobulinemia, Severe/Symptomatic (Grade 2A): Cryoglobulins are immunoglobulins that reversibly precipitate below body temperature. This most commonly occurs on the skin of lower extremities because of exposure to lower temperatures. Management is based on the severity of

symptoms and treating the underlying disorder. Mild symptoms can be treated with cold avoidance and analgesics. More severe disease warrants the use of immunosuppressive therapy such as corticosteroids, cyclophosphamide, and rituximab. TPE removes cryoglobulins with reported improvement in 70–80% of treated patients. TPE has been used mostly in active moderate to severe cryoglobulinemia with renal impairment (membranoproliferative glomerulonephritis), neuropathy, arthralgia, and/or ulcerating purpura. TPE can be performed either alone or in conjunction with immunosuppressive therapy and has been used in both short- and long-term management (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2016).

Erythropoietic Protoporphyria, Liver Disease (EPP) (Grade 2C): EPP is a rare autosomal recessive disorder characterized by partial deficiency of mitochondrial ferrochelatase. That is the final enzyme in the heme biosynthetic pathway. Defective activity of ferrochelatase mainly in erythropoietic cells leads to the accumulation of metal-free protoporphyrin IX (PPIX) in bone marrow reticulocytes, and in circulating erythrocytes, and the plasma from which it is taken up by the liver and excreted in bile and feces. Clinical manifestations in EPP include a nonblistering painful photosensitivity, commonly presenting in childhood. Cholestatic liver failure is uncommon in EPP and the optimal therapeutic approach remains unknown. The goal of TPE during acute liver failure is to decrease the protoporphyrin level in the plasma and to prevent further deposition in the liver. It has been proposed that TPE may also be advantageous in removal of bile acids with improvement in pruritus. Treatment of acute, decompensated protoporphyric hepatopathy by some combination of TPE, blood transfusion, RBC exchange, cholestyramine, ursodeoxycholic acid and vitamin E is reasonable and can be guided by measuring plasma and erythrocyte protoporphyrin levels. Some combination of these treatments can also be used in patients with more chronic disease. These treatments are often used to bridge patients to orthotopic liver transplantation (OLT) (Connelly-Smith, et al., 2023).

Familial Hypercholesterolemia (Grade 1B): Familial hypercholesterolemia (FH) is a common genetic cause of premature atherosclerotic cardiovascular disease (ASCVD) and comprises mutations in the genes encoding LDL receptor (LDLR), apolipoprotein B, proprotein convertase subtilisin-kexin type 9 (PCSK9), or LDLR adaptor protein 1. Reducing lifetime cardiovascular risk associated with accumulating cholesterol burden is the fundamental rationale for multimodal lipid lowering treatment in FH, which comprises lifestyle counselling, dietary restrictions, escalating combination drug therapy including PCSK9-inhibitors. PP is effective but the availability of the selective removal systems and their superior efficacy in cholesterol removal makes its use uncommon. TPE may be the only option in small children where the extracorporeal volume of selective removal systems is too large. It has been recommended that apheresis begin by age 6 or 7 to prevent aortic stenosis that can occur in homozygous FH (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Hashimoto's Encephalopathy (HE); Steroid Responsive Encephalopathy Associated with Autoimmune Thyroiditis (Grade 2C): HE is a rare neuropsychiatric syndrome defined by encephalopathy of unknown etiology associated with the high titers of antithyroid antibodies in the absence of alternative diagnoses such as nervous system infection, tumor, or stroke. First-line therapy for this condition is high dose corticosteroids. For patients who fail initial therapy with steroids or relapse, secondary therapies had been proposed with variable efficacy (e.g., IVIG, azathioprine or cyclophospamide after steroid pulse therapy and rituximab). In the published cases to date, TPE has been tried, in both pediatric and adult cases and in patients who have failed to respond to steroids. Although few of the reported cases demonstrate removal of the anytithyroid antibodies, most demonstrate symptomatic improvement (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2016).

Lambert-Eaton Myasthenic Syndrome (LEMS) (Grade 2C): The primary goal of treatment for LEMS is to identify and treat any tumors or other underlying disorders. In some cases, prednisone or other medications that suppress the immune response may be used initially to improve symptoms. PP may be a useful adjunct for patients with severe or rapidly developing neurological deficit, in the case of patients who are too uncomfortable to wait for immunosuppressive or aminopyridine drugs to take effect, or who cannot tolerate treatment with IVIG (National Institutes of Health [NIH], 2024; Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; Smith, et al., 2003).

Multiple Sclerosis, Acute Attack/Relapse; Acute Central Nervous System Inflammatory Demyelinating Disease (Grade 1A): Multiple sclerosis (MS) is the most prevalent chronic inflammatory demyelinating disease of the central nervous system. Acute attacks of inflammatory demyelinating disease (e.g., acute attack secondary to multiple sclerosis) are most commonly treated with pharmacotherapy including intravenous high-dose corticosteroids. PP may be indicated for the treatment of those patients who do not respond to pharmacotherapy (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013; 2016; Weinshenker, 2001).

Mushroom Poisoning (Grade 2C): Mushroom poisoning occurs from ingestion of several types of mushrooms, including Inocybe, Clitocybe, and Amanita phalloides. Treatment is supportive in nature and focused on the removal of the toxin. Toxin-specific antidotes, induced emesis, gastric lavage, and oral administration of activated charcoal may be used. PP has been shown to decrease mortality in patients with mushroom poisoning by the removal of protein-bound toxins. The U. S. Food and Drug Administration (FDA) lists plasmapheresis as a treatment modality for amanita poisoning (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; FDA, 2012).

Myasthenia Gravis (long-term treatment) (Grade 2B): Myasthenia gravis (MG) is an autoimmune disease. In therapy refractory patients PP may represent an option for long-term management of myasthenia gravis (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019).

Myeloma Associated with Acute Renal Failure (Myeloma Cast Nephropathy) (Grade 2B): Therapy for this condition may include anti-myeloma chemotherapy, diuresis, dialysis, autologous bone marrow transplant, immune modulation and proteosome inhibition. PP has been used to acutely decrease monoclonal free light chain (FLCs), since early reduction in FLCs have been associated with better renal outcomes and overall survival (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; Smith, et al., 2003).

Neuromyelitis Optica Spectrum Disorders (NMSOD), Acute (Grade 1B): NMSOD is an inflammatory disease of the central nervous system with episodes of inflammation and damage to the myelin that most often affects the optic nerves causing temporary or permanent blindness. High-dose intravenous steroids are used to treat acute attacks. In patients who fail steroid therapy, PP is an established treatment modality for the removal of pathologic antibody, immune complexes, and inflammatory mediators (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Pediatric Postinfectious Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) (Grade 1B), Sydenham's chorea (SC) (III Grade 2B): PANDAS and SC are both pediatric post-infectious autoimmune neuropsychiatric disorders which typically follow Group-A beta-hemolytic streptococcus (GABHS) infection. PANDAS is a condition defined by five clinical characteristics – the presence of obsessive-compulsive disorder (OCD) and/or tic disorder, prepubertal age of onset, abrupt onset and relapsing-remitting symptom course, association with neurological abnormalities during exacerbations (adventitious movements

or motoric hyperactivity), and a temporal association between symptom exacerbations and a Group-A beta-hemolytic streptococcal infection. These five criteria have been used for the purpose of conducting research on PANDAS as well as studies of the pathophysiology of post-streptococcal OCD and tic disorders. SC, a neuropsychiatric manifestation of acute rheumatic fever, occurs in an estimated 10–50% of patients with acute rheumatic fever (Connelly-Smith, et al., 2023; National Institute of Mental Health, Revised 2019; Padmanabhan, et al., 2019; Schwartz, et al., 2016; Swedo et al., 2001).

The diagnosis and treatment of PANDAS remains a controversial issue. Studies are either recruiting or ongoing at this time to address the proper diagnosis and treatment of PANDAS. Preliminary results of certain studies suggest enlarging the spectrum of PANDAS to include attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) (Martino, et. al., 2009). Initial treatment for PANDAS typically includes cognitive behavioral therapy and/or anti-obsessional medications. Antibiotic administration is indicated in patients with tonsillo-pharyngitis and a positive Group-A beta-hemolytic streptococcus throat culture. Although PP for PANDAS is listed as category II, ASFA stated that the mechanism of the benefit of PP is not clear as there is a lack of relationship between therapeutic response and the rate of antibody removal. Studies investigating PP for PANDAS are few in number and have small patient populations with short-term follow-ups. There is a lack of well, designed randomized controlled trials with large patient populations to support the effectiveness of PP for the treatment of PANDAS (Padmanabhan, et al., 2019; Schwartz, et al., 2013; 2016).

Phytanic Acid Storage Disease (Refsum's Disease) (Grade 2C): The mainstay of therapy for Refsum's disease is to limit the daily intake of foods rich in phytanic acid. PP is indicated for acute attacks or exacerbations because of its ability to rapidly decrease the level of phytanic acid (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; Patterson, 2012).

Post-Transfusion Purpura (III Grade 2C): First-line treatment for post-transfusion purpura typically includes steroids. PP is a proposed option if severe thrombocytopenia persists. PP removes alloantibodies which results in a decrease in the antibody titer, removal of antigens, an increase in platelet count and cessation of bleeding (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; Wu and Snyder, 2013; Smith, et al., 2003).

Systemic Lupus Erythematosus (SLE), Severe Complications without Nephritis (Grade 2C): SLE is a chronic inflammatory disease leading to cell and tissue injury. Corticosteroids or other immunosuppressive medications are often effective in reducing symptoms. PP has been shown to be effective in the treatment of severe SLE without nephritis. Studies have reported that when used in combination with pharmacotherapy PP has resulted in improvement and stabilization of the disease. TPE in lupus nephritis has previously been classified as category IV (Schwartz, et al., 2016) based on a RCT of PP plus prednisone and cyclophosphamide versus prednisone and cyclophosphamide that showed no benefit in the PP arm. Further smaller trials since then supported these findings. Plasma exchange is not currently among induction or maintenance therapy guidelines for treatment of lupus nephritis but is mentioned in current European guidelines as a treatment option in the setting of pregnancy or rapidly progressive glomerulonephritis (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; Smith, et al., 2003).

Thyroid Storm (Grade 2C): Thyroid storm, or accelerated hyperthyroidism is an extreme manifestation of thyrotoxicosis and is seen in Graves' disease and toxic multinodular goiter. Treatment depends upon the underlying cause and related symptoms and includes pharmacotherapy and supportive care. PP and emergency surgery have been used to treat thyroid storm in patients who respond poorly to first line therapeutic measures. PP is usually performed in

patients with thyroid storm with severe symptoms and when the patient does not improve with first-line therapies within 24-48 hours of treatment or when first-line therapies cannot be used due to toxicity. Since a portion of T3 and T4 is firmly bound to plasma proteins, PP should, in theory, efficiently reduce their circulating pool and result in a decrease in the hormone concentrations (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Transplantation, Kidney, ABO incompatible; Antibody Mediated Rejection/Humoral Rejection (Grade 1B): Major incompatibility refers to the presence of natural antibodies in the recipient against the donor's A or/and B blood group antigen. These antibodies may cause hyperacute/acute humoral rejection of the organ due to endothelial damage. ABO incompatible solid organ transplants involve PP-mediated removal of anti-A or anti-B antibodies in conjunction with immunosuppressive treatment with drugs and other immunotherapy (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Transplantation, Hematopoietic Stem Cell ABO Incompatible Major (Grade 1-2B): Depending on the severity of the incompatibility, the treatment of ABO incompatible HPC may include: high-dose erythropoietin, donor lymphocyte infusions, discontinuation of cyclosporine, and antithymocyte globulin. PP can be used to reduce the ABO antibodies responsible for hemolysis and pure red cell aplasia, especially in major incompatibility (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Vasculitis, Other (Hepatitis B Virus [HBV] Polyarteritis Nodosa [PAN]) (Grade 2C): Polyarteritis nodosa (PAN) is a form of vasculitis that mainly affects medium-sized arteries, frequently presenting with peripheral neuropathy, skin, renal, and other organ and system manifestations, some of these are non-specific: weight loss, fever, rash, myalgia, neuropathy, or abdominal ischemia. It can be idiopathic, or associated with infection such as hepatitis B virus (HBV). For HBV-PAN, treatment includes TPE, glucocorticoids and anti-viral medications. Because of the HBV vaccination, HBV-PAN is uncommonly seen (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2016).

Voltage Gated Potassium Channel Antibody-Related Diseases (Grade 1B): Voltage gated potassium channel (VGKC) antibody related diseases is also known as limbic encephalitis, neuromyotonia, and Morvan's syndrome. VGKCs are expressed by a wide range of cells, but are most important in the control of membrane excitability in the nervous system. The vast spectrum of clinical presentations makes differential diagnosis complex and many patients suffer from the delayed recognition of these conditions (in order of months to years). Treatment includes different immunotherapies and PP in addition to symptomatic treatment (e.g., antiseizure medication). Studies have reported that VGKC antibodies decrease with TPE, and this is associated with clinical improvement (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Category III and Category IV Indications

For conditions rated as a category III or IV by the American Society for Apheresis, scientific studies have reported inconsistent outcomes, and/or lack of consistent efficacy, and/or no benefit from PP as a treatment modality. Therefore, in these conditions, PP is not recommended as a treatment modality (Padmanabhan, et al., 2019; Schwartz, et al., 2013; 2016; Szczepiorkowski, et al., 2010; Shaz, et al., 2007).

Acquired Pure Red Cell Aplasia (PRCA) (III Grade 2C): Acquired PRCA is a hematopoietic stem cell disorder in which red blood cell precursors in the bone marrow are nearly absent. PRCA can occur in patients with underlying thymoma, lymphoproliferative disorders, systemic lupus erythematosus (SLE), autoimmune disorders, or following an ABO mismatched allogeneic

hematopoietic stem cell transplant. Management of the disease includes corticosteroids and treatment of the underlying disease if present. PP may be used for the treatment of acquired PRCA to remove serum antibodies and/or inhibitory activities (Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Acute Liver Failure (ALF) (III Grade 2B): One of the most common causes of ALF is viral hepatitis, but it may also occur as a result of acetaminophen and other drug toxicity, autoimmune hepatitis, and Wilson disease. Treatment includes supportive therapy until the patient can receive a liver transplant. The use of PP has been proposed to lower the level of bilirubin and hepatic enzymes and remove toxins, but there is insufficient evidence supporting PP as a treatment option for ALF. High volume PP is being performed to treat ALF outside of the United States. At this time, high volume PP is not available in the United States (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; O'Grady, 2005).

Acute Toxins, Venoms, and Poisoning (Envenomation; Other: drug overdose, poisoning, mechanical hemolysis and methemoglobinemia) (III Grade 2C): Envenomation, drug overdose (accidental, intentional, or iatrogenic), poisoning, hemolysis, and methemoglobinemia can result from exposure to agents or toxins that cause tissue injury and/or organ dysfunction. Common routes of exposure for drugs and poisons include ingestion, inhalation, and injection. Envenomation occurs from snakes, spiders, scorpions, or venomous stinging insects. Initial treatment focuses on supportive care and removal of the toxic agent by antidotes, lavage, inducted vomiting and other methods of toxic desensitization. Dialysis may also be indicated. To aid in the removal of protein-bound toxins, PP has been proposed as an alternate therapy to dialysis or hemoperfusion, but for PP to be effective, toxic agents must not be lipid soluble, bound to tissue, or be present in large volume outside of the bloodstream. There is insufficient evidence in the published clinical trials supporting the efficacy of PP for overdosing, envenomation and poisoning by compounds other than mushroom poisoning (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Alzheimer's Disease (III Grade 2A)
Alzheimer's disease (AD) is the most common cause of dementia and is characterized by progressive cognitive impairment, with psychiatric manifestations of depression, delusions, or agitation. There is no effective treatment to slow or reverse the progression of AD. PP has been proposed as a treatment for alzheimer's disease, but has not been proven to be an effective therapy (Connelly-Smith, et al., 2023).

Amyloidosis, Systemic, Dialysis Related (IV Grade 2C): Systemic amyloidosis is a metabolic storage disease in which protein is deposited throughout the body, resulting in an insoluble matrix in a variety of tissue. Treatment depends upon which organs are involved and is aimed at preventing overproduction of the precursor proteins, further tissue deposition and fibril formation. Chemotherapy and stem cell transplantation may be included in the treatment. PP has been proposed as a treatment for amyloidosis, but has not been proven to be an effective therapy (Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; Shaz, et al, 2007; Muller, et al., 2006; Brunt, et al., 2004; Drew, 2002).

Amyotrophic Lateral Sclerosis (ALS) (IV Grade 1C): ALS, or Lou Gehrig's disease, is a rapidly progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. Treatment is supportive in nature and may include supportive devices, pharmacotherapy, physical therapy, and occupational therapy. Small clinical trials (n=3–7) have been conducted to determine the effect of PP in the treatment of ALS, but the studies reported no benefit of PP for the treatment of the disease (Padmanabhan, et al., 2019; Schwartz, et al., 2013; Shaz, et al., 2007).

Anti-neutrophil Cytoplasmic Antibodies (ANCA)-Associated Rapidly Progressive Glomerulonephritis (RPGN) (granulomatosis with polyangiitis [e.g., Wegner's] and microscopic polyangiitis [MPA) (III Grade 2C): Clinical trials suggest that PP is most beneficial in patients with dialysis-dependency (at presentation) and offers no benefit over immunosuppression in milder disease (i.e., dialysis independence) (Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Anti-Glomerular Basement Membrane Disease (Anti-GBM) (Goodpasture's syndrome) (III Grade 2B): The likelihood of a response to PP in the dialysis-dependent patient and no diffuse alveolar hemorrhage (DAH) is very low (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Aplastic Anemia (III Grade 2C): Aplastic anemia (AA) is one form of hematopoietic stem cell disorders characterized by the lack of production of red blood cells, white blood cells and plates by the bone marrow. Treatment depends upon the etiology of the disease (e.g., malignancy, infection), and may include administration of immunosuppressant therapy, surgical resection, or transplantation. PP has been proposed for removal of serum antibodies and/or by inhibitory activity, but its effectiveness has not been proven (Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Atopic (Neuro-) Dermatitis (Atopic Eczema), Recalcitrant (III Grade 2C): The treatment of atopic dermatitis (AD) involves a systematic, multifaceted approach that incorporates skin hydration, topical anti-inflammatory therapy (including tacrolimus), identification, and elimination of flare factors (especially foods), and, if necessary, systemic therapy. In refractory disease phototherapy (UVA-1, UVB, or PUVA) are proposed. Proposed treatments for third-line or under investigation are interferon-g, omalizumab, allergen immunotherapy, probiotics, Chinese herbal medications, and antimetabolites. PP has been proposed to reduce IgE and immune complexes from patients' blood, but its effectiveness has not been proven (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2016).

Autoimmune dysautonomia (III Grade 2C): Autoimmune dysautonomia refers to syndromes with symptoms related to the autonomous nervous system. Autoimmune autonomic ganglionopathy (AAG) is characterized by various symptoms such as central nervous system involvement, peripheral sensory neuropathy, endocrinopathy, as well as autonomic dysfunction. Typical autonomic symptoms of AAG are severe orthostatic hypotension, constipation, and urinary disturbances. Small fiber neuropathy (SFN) is the result of damage to peripheral nerves and patients can present with autonomic and/or somatic symptoms. Postural orthostatic tachycardia syndrome (POTS) is the most prevalent chronic cardiovascular dysautonomia. In adults, POTS is characterized by a sustained heart rate increment of ≥30 beats/min within 10 minutes of standing or head-up tilt without orthostatic hypotension. Interventions to treat Standard orthostatic intolerance include patient education and behavioral conditioning, increased sodium and water intake, physical counter-maneuvers to increase mean arterial pressure, use of support garments, graded exercise training, and tailored pharmacotherapy with fludrocortisone, midodrine, droxidopa, beta-adrenergic blockers, and/or pyridostigmine. PP has been proposed to remove the autoantibodies and therefor improve autoimmune dysautonomia symptoms, but its effectiveness has not been proven (Connelly-Smith, et al., 2023).

Burn Shock Resuscitation (III Grade 2B): Burn injury including more than 25% of the body results in increased capillary permeability and intravascular volume deficits that may lead to cellular shock. Aggressive intravenous fluid resuscitation is the mainstay of therapy. It has been proposed that the removal of inflammatory mediators or toxic humoral substances in exchange for fresh frozen plasma and albumin could decrease capillary permeability and improve intravascular oncotic pressure, improving the body's response to fluid resuscitation. However, the limited

number of studies reported inconsistent outcomes and one randomized controlled trial concluded that PP did not alter the course of burn shock (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; Pham, et al., 2008).

According to the American Burn Association (Pham et al., 2008), PP "does not abate the humorally-mediated systemic inflammation" and cannot be recommended outside the context of clinical trials.

Cardiac Neonatal Lupus (III Grade 2C): Congenital lupus affecting the cardiovascular system can result in congenital heart block (CHB) and cardiomyopathy. CHB is an acquired immune-mediated disease caused by placental transfer of maternal antibodies beginning at 12 week gestational age (GA). The current recommendation is for pregnant women with positive antibodies to have fetal cardiac evaluation every 2–3 week from 18 to 28 wk GA to evaluate cardiac rhythm and function. Treatment is either prophylactic, when a mother has had a previously affected fetus/neonate, or as treatment when CHB is detected. The proposed mainstay of maternal treatment is fluorinated steroids and b-agonists; adjuvant therapies include IVIG, TPE, hydroxychloroquine, and other immunosuppressive agents. Since CHB is caused by antibodies, removal of the antibodies by TPE may potentially prevent or reverse the disease (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2016).

Cardiac Transplantation, Antibody-Mediated (AMR) (III Grade 2C): The four types of cardiac allograft rejection include hyperacute in cases of ABO or major human leukocyte antigen (HLA) incompatibility, acute cellular (ACR), acute antibody-mediated (AMR) or chronic rejection (allograft vasculopathy). ACR is the most common form of rejection and is mediated by T cells. Rejection is treated by immunosuppression. Steroids are used for episodes of rejection. If AMR progresses, rituximab and TPE are considered. Many past studies focusing on desensitization were performed with older medical regimens. Newer agents, such as bortezomib, are now used for desensitization. Extracorporeal photopheresis (ECP) may be used to treat cellular rejection and allograft vasculopathy. PP has been proposed as a treatment modality during the acute rejection period to remove donor-specific antibodies and/or inflammatory mediators in AMR. However, the evidence is primarily in the form of case series, case reports and retrospective reviews. The clinical benefit of PP for cardiac allograft rejection has not been established (Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Chronic Acquired Demyelinating Polyneuropathies (CADP); Anti-MAG Neuropathy (III Grade 1C): Chronic acquired demyelinating polyneuropathies (CADP), includes a variety of neuromuscular disorders resulting from immune-mediated demyelination including neuropathy associated with monoclonal IgM antibodies to myelin-associated glycoprotein (MAG; anti-MAG neuropathy), and other neuropathic syndromes associated with monoclonal gammopathy. The detection of anti-MAG in IgM monoclonal gammopathy associated neuropathy establishes the diagnosis of anti-MAG neuropathy. Optimal treatment is unknown and response to immunopressive drugs varies. For anti-MAG neuropathy, steroids have not been shown to be effective, and treatment effect of IVIG or TPE is often transient (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2016).

Coagulation Factor Deficiency and Inhibitors (CFI) (III Grade 2C): Blood coagulation factor inhibitors interfere with the normal clotting mechanism of the blood as seen in conditions such as hemophilia. Treatment depends on the etiology and aims to accomplish cessation of bleeding and suppression of inhibitor production. This may be accomplished by replacing the factor or bypassing it. Inhibitor suppression may be accomplished by the administration of high dose corticosteroids and IVIG. It has been proposed that PP may be useful in the removal of inhibitors, but its effectiveness has not been proven (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Complex Regional Pain Syndrome (CRPS) (III Grade 2C): The pathophysiological mechanisms of complex regional pain syndrome (CRPS) are not fully understood. Presently there is no standard testing or diagnostic modality. CRPS remains a clinical diagnosis with the exclusion of other causes. Chronic or severe CRPS is challenging to manage requiring a multidisciplinary approach. Multiple therapeutic agents have been used with variable and often partial effects including bisphosphonates, gabapentin, calcitonin, intravenous ketamine, free radical scavengers, oral corticosteroids, and spinal cord stimulation. Due to the suspected auto-immune nature of the disease in a subset of patients steroids, IVIG, and rituximab have been tried and shown to have variable responses. It has been proposed that TPE can remove auto-antibodies to b2-adrenergic, a1-adrenergic, and muscarinic M2 receptors (and possibly cytokines), and thus relieve localized and systemic symptoms. The effect may be transient so maintenance TPEs may be required, in combination with other therapies. The clinical benefit of PP for CRPS has not been established (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2016).

Hemolysis, Elevated Liver Enzymes and Low Platelets (HELLP Syndrome), Postpartum and Antepartum (III/IV Grade 2C): The HELLP syndrome (Hemolysis, Elevated Liver Enzymes and Low Platelets) typically presents in the 3rd trimester of pregnancy but up to 1/4 of patients may present post-partum. In 70–80% of cases, HELLP coexists with pre-eclampsia but can also occur in the absence of hypertension or proteinuria. Patients with severe HELLP may develop DIC and multi-organ failure. The definitive treatment for HELLP is prompt delivery by cesarean section. TPE is proposed to remove circulating protein bound platelet aggregating and procoagulant factors released from both activated platelets and endothelial cells. The clinical benefit of PP for HELLP has not been established (Padmanabhan, et al., 2019; Schwartz, et al., 2016).

Hemophagocytic Lymphohistiocytosis (HLH); Hemophagocytic Syndrome (HS); Macrophage Activating Syndrome: (III Grade 2C): Hemophagocytic syndrome (HS) or hemophagocytic lymphohistiocytosis (HLH) is an immune-mediated life-threatening disease. Treatment of HS consists of supportive intensive care according to the standards for similar life threatening diseases, the elimination of the trigger (for example, rituximab in EBV associated HS after HSCT) and the suppression of inflammatory response and cell proliferation or both with immunsuppressive and cytotoxic drugs (cyclosporin, corticoids, etoposide, IVIG, alemtuzumab). The rational for TPE are organ failure, especially hepatic organ failure, or suppression of the hyperinflammatory syndrome, the excess of cytokines ("cytokine storm") and the coagulopathy. The use of TPE is not supported in large controlled trials (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2016).

Henoch-Schonlein Purpura, IgA Vasculitis (IgAV); IgA Vasculitis with Nephropathy (IgAVN) (III Grade 2C): Henoch-Schonlein purpura (HSP) is the most common systemic vasculitis in childhood with 95% of cases occurring in this age group, but is less common in adults. Treatment is predominantly supportive care. In patients with severe kidney involvement (i.e., crescentic glomerulonephritis) or severe symptoms of vasculitis, treatment also includes pharmacotherapy. If end stage renal disease develops, kidney transplantation may be necessary. PP is proposed for removal of IgA-containing immune complexes or IgG autoantibodies. However, the evidence is primarily in the form of case series and case reports. The clinical benefit of PP for Henoch Schonlein purpura has not been established (Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Heparin Induced Thrombocytopenia and Thrombosis (HIT/HITT) (III Grade 2C): HIT is a major cause of morbidity and mortality in patients receiving heparin. After recognizing a possible case of HIT, all heparins are generally discontinued. Because of the continued risk of thrombosis after heparin cessation, all patients with confirmed HIT are therapeutically anticoagulated with an alternative agent. In the setting of urgent need for surgery during active HIT, or with persistent

HIT antibodies, PP is considered as an alternative to using a direct thrombin inhibitor during cardiopulmonary bypass. PP has also been proposed in the setting of life-or-limb threatening thrombosisor progressive thrombosis in HIT patients. The evidence is TPE protocols used in this setting have been heterogeneous (1–5 treatments) and have utilized different laboratory tests for serological monitoring of the HIT antibody to optimize treatment regimen. Some of these case reports have utilized TPE in conjunction with non-unfractionated heparin anticoagulation while others have used TPE alone. The clinical benefit of PP for HIT has not been established (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Hypertriglyceridemic Pancreatitis, severe and prevention of relapse (III Grade 1C/2C): Elevations in lipoproteins responsible for triglyceride transport are responsible for the development of hypertriglyceridemic (HTG) pancreatitis. Lipoatrophy is a rare form of HTG. Treatment includes lowering of lipids by diet and medication. When associated pancreatitis occurs, total parenteral nutrition and limited oral and caloric intake are indicated. The 2020 Endocrine Society clinical practice guideline on lipid management in patients with endocrine disorders states that plasmapheresis may be useful in those who do not respond to conventional methods of lowering triglycerides, such as individuals who have extraordinarily elevated triglyceride levels (eg, over 10,000 mg/dL [112.9 mmol/L]) or in extremely high-risk situations, such as pregnancy (Newman, et al., 2020). The European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidemias state that plasmapheresis is able to rapidly lower TG levels in the acute setting (Mach, et al., 2019). The American Society for Apheresis (ASFA) report that TPE has not consistently increased the rate of triglyceride (TG) clearance compared to insulin (Connelly-Smith, et al., 2023).

Idiopathic Dilated Cardiomyopathy, NYHA II-IV (iDCM) (III Grade 2C): Dilated cardiomyopathy (DCM) involves cardiac enlargement with impaired ventricular systolic function. Fifty percent of cases have no identifiable cause and are idiopathic (iDCM). iDCM is typically treated with pharmacotherapy (e.g., angiotensin converting inhibitors, angiotensin receptor blockers, diuretics, digitalis, beta-blockers). PP is proposed to remove the circulating autoantibodies found in 80% of patients. In a case series of nine patients, PP resulted in improved left ventricular ejection fraction (LVEF), decline in IgG deposition, and improved the quality of life and functional class. Large randomized controlled trials are needed to validate the results of this study (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Idiopathic Inflammatory Myopathies (III Grade 2B): Idiopathic inflammatory myopathy or myositis (IIM) designates a rare and heterogeneous group of acquired autoimmune diseases comprising dermatomyositis, polymyositis, inclusion body myositis, anti-synthetase syndrome (ASyS), and immune-mediated necrotizing myopathies (IMNM). Treatment for IIM consists of high-dose steroids as first line pharmacological therapy that should be tapered within six months. Additional combination pharmacological treatment includes methotrexate, azathioprine, mycophenolate mofetil, or calcineurin inhibitors. PP has been proposed to rapidly decrease putatively pathogenic circulating antibodies, cytokines, and immune complexes to achieve clinical improvement, however its efficacy has not been established (Connelly-Smith, et al., 2023).

Immune checkpoint inhibitors, immune-related adverse events (III Grade 2C): Immune checkpoint inhibitors (ICIs) are oncologic drugs that target immune checkpoint proteins and can result in immune-related adverse events (irAEs). ICI-induced irAEs affect multiple organ systems including immune (cytokine release syndrome), neurologic (myasthenia gravis [MG]), endocrine (diabetes, thyroiditis), hepatic (acute liver failure), pulmonary (pneumonitis), cardiovascular (myocarditis), musculoskeletal (myositis), and hematologic systems (thrombotic thrombocytopenic purpura (TTP) or other thrombotic microangiopathy). Current treatment includes stopping the ICI and starting corticosteroids based on severity of the adverse event. PP

has been proposed to remove the monoclonal IgG antibodies to decrease systemic effects, however its efficacy has not been established (Connelly-Smith, et al., 2023).

Immune Thrombocytopenic (ITP) (III Grade 2C): ITP is an autoimmune disease that occurs when the lymphocytes produce antibodies against platelets. Initial treatment may include the use of corticosteroids and anti-(Rh) D immunoglobulin. Other treatments may include platelet transfusions, stopping medications that can cause bleeding (e.g., aspirin, ibuprofen, anti-coagulants) and extracorporeal immunoadsorption therapy. Some patients may require a splenectomy to control the effects of ITP. The American Society for Apheresis (2016) stated that case reports and small case series have reported a potential benefit of PP when used in combination with prednisone, splenectomy, IVIG and cytotoxic agents for the treatment of thrombocytopenic ITP, but responses were transient (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Immunoglobulin A (IgA) nephropathy (Berger's Disease) (III Grade 2B-C): IGA nephropathy is the most common form of glomerulonephritis. It is frequently asymptomatic but there are reports of slow progression to ESRD in up to 50% of patients. Roughly 10% of patients present as rapidly progressive crescentic glomerulonephritis. Therapy consists of nonspecific blood pressure control and control of proteinuria with pharmacotherapy. PP is proposed for use in IGA nephropathy to remove circulating pathologic IgA molecules and related immune complexes. The majority of published trials have examined the treatment of the rapidly progressive glomerulonephritis form of the disease and not the chronic progressive disease. The evidence consists of case series and case reports. PP may improve function during therapy and delay the time to dialysis-dependence but does not halt disease progression. The role of PP in the treatment of IgA nephropathy has not been established (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Inclusion Body Myositis (IV Grade 2C): Inclusion body myositis (IBM) is an inflammatory myopathy characterized by chronic muscle inflammation and muscle weakness. There is no standard treatment or cure for the disease. Physical therapy and supportive care may be helpful. IVIG may produce short-term effects. Corticosteroids and immunosuppressive drugs are generally ineffective (Schwartz, et al., 2013)

The American Society for Apheresis (Shaz, et al., 2007) reported on studies using PP for the treatment of inclusion body myositis. The studies included a single case report, an uncontrolled study of 35 patients with idiopathic inflammatory myopathy nonresponsive to treatment. Improvement following PP was reported, but the patients were treated in conjunction with either cyclophosphamide or chlorambucil. The diagnosis of IBM was not specified and the role of PP was undetermined.

Multiple Myeloma with Polyneuropathy (III Grade 2C): Multiple myeloma is a systemic cancer of plasma cells which are immunoglobulin-producing cells. The plasma cells grow out of control and produce multiple plasma cell tumors causing anemia, thrombocytopenia, and leukopenia. Multiple myeloma can also be accompanied by polyneuropathy. Treatment includes pharmacotherapy, chemotherapy, and stem cell transplantation. PP has been proposed for the removal of the abnormal proteins from the blood, but there is insufficient evidence to support PP for this indication (Padmanabhan, et al., 2019; American Cancer Society, 2018; Schwartz, et al., 2013, 2016).

Multiple Sclerosis (MS) (III Grade 2B): MS is a demyelinating disease of the central nervous system that follows a variable course. Although a variety of treatments, including pharmacologic therapy, are used in an attempt to control the disease, there is presently no known cure. PP is not recommended for the treatment of relapsing/remitting, secondary progressive or chronic

progressive forms of MS (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; Smith, et al., 2003).

Nephrogenic Systemic Fibrosis (NSF) (III Grade 2C): NSF is a systemic disorder with acute or chronic renal failure that occurs in hepatorenal syndrome, following the administration of gadolinium (Gd) containing contrast agents, or following liver transplantation. Treatment includes pharmacotherapy (e.g., steroids) and renal transplantation. PP has been proposed as a treatment modality because of the high failure rate of other therapies. However, there is insufficient evidence to support PP for this condition (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Neuromyelitis Optica Spectrum Disorders (NMSOD), Maintenance (III Grade 2C): NMSOD is an inflammatory disease of the central nervous system with episodes of inflammation and damage to the myelin that most often affects the optic nerves causing temporary or permanent blindness. Approximately 80% of patients with NMO have relapsing course, which has a poor prognosis: 50% of patients become legally blind or wheelchair bound and 30% die with respiratory failure within 5 years. There is not a progressive phase like Multiple Sclerosis; the disease worsens by incomplete recovery with each acute attack. Prophylaxis to prevent further acute attacks includes immunosuppressive medications and immunomodulation. There is insufficient evidence supporting the efficacy of PP as maintenance therapy for NMO (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Paraneoplastic Autoimmune Retinopathies (III Grade 2C): Paraneoplastic autoimmune retinopathy (PNAR) is characterized by inflammatory processes that affect the retina which leads to photoreceptor dysfunction, visual field defects, scotoma, and acute or subacute vision loss and can be in association with the presence of anti-retinal antibodies. Paraneoplastic retinopathy can be characterized as cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), or bilateral diffuse uveal melanocytic proliferation (BDUMP). Current treatment and management varies by the condition. PP has been proposed for the management, however its efficacy has not been established (Connelly-Smith, et al., 2023).

Paraneoplastic Neurologic Syndromes (III Grade 2C): Paraneoplastic syndromes are a group of rare degenerative disorders triggered by a person's immune system in response to a neoplasm or cancerous tumor. Therapy is focused on treatment of the underlying cancer and decreasing the autoimmune response by administration of steroids, or irradiation. The use of PP is proposed for the removal of antibodies, but there is insufficient evidence supporting the clinical benefit of PP for this condition (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Pemphigus Vulgaris (PV) (III Grade 2B): Pemphigus is a group of autoimmune skin diseases, of which PV is the most common. Treatment includes the use of corticosteroids and immunosuppressive medications. In severe cases, PP has been proposed for the reduction of autoantibodies in the bloodstream. There is insufficient evidence supporting the efficacy of PP for PV (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; Martin, et al., 2009; Bickle, et al., 2002).

Martin et al. (2011) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of interventions for the treatment of pemphigus vulgaris and pemphigus foliaceus. Treatment interventions included pharmacotherapy, PP, and traditional Chinese medicine. Eleven randomized controlled trials met inclusion criteria and only one evaluated PP (n=40). The effect of PP on all reported outcomes (i.e., death, disease control, antibody titer and withdrawal due to adverse events) was inconclusive.

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) (IV Grade 1C): POEMS is a multisystem paraneoplastic syndrome associated with an underlying plasma proliferative disorder and is associated with a bilateral polyneuropathy involving motor and sensory nerves, distally and proximally. Treatment is based upon the underlying plasma cell disorder and may include the use of corticosteroids, low-dose alkylators, chemotherapy, radiation therapy and peripheral blood stem cell transplantation. The efficacy of PP has not been proven to produce clinical benefits (Chan, 2020; Padmanabhan, et al., 2019; Schwartz, et al. 2013; Kuwabara, 2012; Dispenzieri, 2005).

According to the American Society of Apheresis (Shaz, et al., 2007), TPE was initially used as a treatment for POEMS because it was diagnosed as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) or monoclonal gammopathy of undetermined significance (MGUS). The number of scientific studies are limited and included small patient populations (n=1–30). There were no reported differences in the outcomes with the use of PP and corticosteroids compared to steroid therapy alone. PP is considered ineffective for this condition.

Progressive Multifocal Leukoenchephalopathy (PML) associated with Natalizumab (NTZ) (III Grade 1C): PML is a rare central nervous system (CNS) demyelinating disorder typically seen in patients with impaired cell-immunity. Prevention of PML development with risk stratification approaches are warranted. Immune reconstitution is the only intervention with demonstrated efficacy for PML. For NTZ-PML, management includes discontinuation of the drug (temporary or permanent) and consideration for initiation of TPE to accelerate clearance, especially if the drug is recently infused. Both will increase number and function of leukocytes migration to the CNS. Rapid immune reconstitution may precipitate an extreme immune response called Immune Reconstitution Inflammatory Syndrome (IRIS), which associated with neurological status deterioration, often life threatening. IRIS usually develops 2-6 weeks after TPE (versus 3 months after drug discontinuation) in almost all patients. Retrospective studies had major limitations including containing small number of patients and potential differences in baseline characteristics between the groups received TPE and the group did not. Thus, the benefits of immune reconstitution in patients with severe NTZ-PML may outweigh the risk of IRIS and although the role of TPE is not yet optimized in this condition and that the benefits of TPE are conjectural, and have not been proven rigorously, it can be considered in selected group of patients (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019).

Pruritus due to Hepatobiliary Diseases (III Grade 1C): Chronic pruritus can present in patients with a variety of hepatobiliary disorders. Medication is the first line of therapy. For patients unresponsive to medications, other measures have been proposed: (1) nasobiliary and transcutaneous drainage or external biliary diversion to remove the pruritogen(s) from the enterohepatic cycle, (2) anion absorption, TPE, or extracorporeal albumin dialysis to remove the potential pruritogen(s) from the systemic circulation, and (3) liver transplantation. TPE has been proposed to remove the potential pruritogen(s) from the systemic circulation. There is insufficient evidence supporting the efficacy of PP for pruritus due to hepatobiliary diseases (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2016).

Psoriasis (IV Grade 2C): Psoriasis is a chronic skin condition in which plaques and papules form as a result of hyperproliferation and abnormal differentiation of the epidermis. Treatment options include: topical steroids, methotrexates, cyclosporin, ultraviolet light therapy, and/or injectable biological agents. The studies that have been conducted to determine if patients would benefit from PP as a treatment modality for psoriasis concluded that PP offers no treatment benefit for this condition (American Academy of Dermatology [AAD], 2025; Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; Shaz, et al., 2007).

Rasmussen Encephalitis (Chronic Focal Encephalitis) (III Grade 2C): Primary treatment of Rasmussen encephalitis includes the use of anti-epileptic drugs, corticosteroids or tacrolimus. In refractory cases, surgery (e.g., functional hemispherectomy and hemispherotomy) may be performed to control seizures. PP is proposed to remove autoantibodies and to delay or forego surgery (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013; 2016).

Red Blood Cell Alloimmunization in Pregnancy, gestational age < 20 weeks (III Grade 2C): Management of red blood cell alloimmunization includes assessing the phenotype of the father and performing maternal antibody titers. Depending upon the titer level, ultrasound and/or amniocentesis may be performed. Ongoing assessment of the status of the fetus may also be indicated. If the fetus is determined as being high risk for hydrops fetalis, intrauterine transfusion is the primary therapy. Treatment of the mother with IVIG and/or PP may be used as an adjunct therapy if there is a high risk of fetal demise or signs of hydrops at <20 weeks gestational age, especially in a mother with a previously affected pregnancy. PP of the mother removes the maternal red call alloantibody, reduces the maternal antibody titer, and protects the fetus from hemolytic disease (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; Ruma, et al., 2007).

Rheumatoid Arthritis (RA) (IV Grade 1B): RA is a chronic inflammatory autoimmune disorder of unknown cause that can affect most joints and is characterized by symmetrical erosive synovitis that can progress to joint destruction and significant disability. Therapy may include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), and/or low doses of steroids. Physical and occupational therapy may also be helpful (Schwartz, et al., 2013; Seror, 2007; Shaz, et al., 2007; Szczepiorkowski, et al., 2007; Smith, et al., 2003).

PP has been proposed for the treatment of RA in an attempt to remove circulating immune complexes and rheumatoid factors. Two controlled trials reported no benefit from the use of PP (Shaz, et al., 2007). Seror et al. (2007) conducted a systematic review of the literature and reported on two studies that used PP for the treatment of RA. The patient populations were small (n=19 and 20), and improvement was shown in the control group, as well as the study group, but values returned to baseline within eight weeks.

Rheumatoid Vasculitis: Rheumatoid vasculitis is an inflammatory disease that occurs in small and medium-sized blood vessels and can involve the nerves in the hands and feet, as well as blood vessels in the heart, eyes, fingers, and toes. Treatment may include pharmacotherapy and surgical intervention for severely affected joints. PP has been proposed as a treatment option for renal vasculitis, but its effectiveness remains unproven.

Schizophrenia (IV Grade 1A): Schizophrenia is a chronic, disabling psychiatric disorder characterized by acute and chronic psychosis and deterioration in function. The mainstay of treatment is antipsychotic medication and adjunctive supportive psychosocial therapies targeted at both the effected individual and their families. Data is limited and, based upon one randomized trial, the American Society for Apheresis states PP offers no benefit in the treatment of schizophrenia (Schwartz, et al., 2016; Shaz, et al., 2007).

Sepsis with Multi-Organ Failure (III Grade 2B): Sepsis is a systematic inflammatory response to infection and a common cause of death due to organ dysfunction and hypotension. Treatment includes controlling the underlying infection and providing hemodynamic stability and support. Corticosteroids and other medications may be used to treat inflammation. PP is proposed for the treatment of sepsis because of its ability to remove toxins from the bloodstream, but the available data is limited, with conflicting outcomes (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Stiff-Person Syndrome (III Grade 2C): Stiff-person syndrome is a chronic disorder with features of an autoimmune disease involving painful muscle spasms and rigidity. Diazepam is administered to decrease rigidity and spasms. Anti-convulsants may be used to relieve symptoms. PP has been proposed as an adjunct to pharmacotherapy in patients who are refractory to other therapies but the data from clinical trials is limited to case reports, with conflicting results (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Pagano, et al., 2014; Schwartz, et al., 2013, 2016).

Sudden Sensorineural Hearing Loss (SSHL) (III Grade2A): Sudden sensorineural hearing loss (SSHL) is hearing loss of at least 30 dB in three sequential frequencies on standard pure tone audiogram occurring over < 3 days. Treatment is focused on decreasing inflammation and improving blood flow with various pharmacotherapy regimens. The use of PP is proposed for the treatment of SSHL, but there is insufficient evidence supporting the clinical benefit of PP for this condition (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Systemic Sclerosis (III Grade 2C): Systemic sclerosis (SSc) is a connective tissue disease characterized by an accumulation of collagen and other proteins and involvement of the gastrointestinal tract, lungs, heart, skin, blood vessels, musculoskeletal system, and kidney. Prominent symptoms are skin fibrosis and Raynaud's phenomenon. The two forms of SSc are diffuse cutaneous systemic sclerosis (dcSSc) and limited cutaneous systemic sclerosis (lcSSc). lcSSc presents with features of CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), has slower disease progression but does have progression of disability and disfigurement over time. dcSSc is characterized by thickening of the skin (scleroderma) and progressive visceral organ dysfunction due to fibrosis, typically with rapid onset and decreased survival. Antinuclear antibodies are present in more than 95% of patients with SSc. SSc is not curable, and treatment is aimed at relieving symptoms and improving function. Systemic therapies such as hydroxychloroquine, methotrexate, mycophenolate mofetil and cyclophosphamide, may be part of the treatment. Lung transplantation may be indicated in some cases. According to the ASAF, there is conflicting data which lends little support for the use of PP for the treatment of this condition (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016; National Institute of Arthritis and Musculoskeletal and Skin Diseases [NIAMS], 2019).

Thrombotic Microangiopathy (TMA), Coagulation Mediated (III Grade 2C): Thrombotic microangiopathy (TMA) refers to the histopathologic findings of arteriolar microthrombi with associated intimal swelling and fibrinoid necrosis of the vessel wall. A variety of etiologies for this syndrome are now classified. Atypical hemolytic uremic syndrome (aHUS) is now known to be mainly due to genetic mutations of complement and complement regulatory molecules leading to uncontrolled activation of the alternative complement pathway. Genetic mutations in proteins of the coagulation cascade appear to be implicated in the clinical syndrome of aHUS. This may be because underlying HUS pathophysiology is due to small vessel thrombosis; thus, genetic mutations of the coagulation proteins may increase the risk TMA. Thrombomodulin, THBD, is a thrombin cofactor that acts as an anticoagulant and also decreases factor I (CFI)-induced inactivation of C3b. The benefit for TPE is not consistent in these patient groupings (Connelly-Smith, et al., 2023; Schwartz, et al., 2016).

Thrombotic Microangiopathy (TMA), Complement Mediated (Except for Factor H Antibodies) (III Grade 2C): Atypical hemolytic syndrome (aHUS) is caused by uncontrolled activation of the alternative complement system, now called complement-mediated thrombotic microangiopathy (TMA). Many affected patients are children. A growing list of genetic mutations and polymorphisms are now known to predispose to complement-mediated TMA, primarily

involving complement regulatory proteins, leading to complement-mediated endothelial injury. Empiric plasma therapy in all forms of complement-mediated TMA is recommended, pending testing. It has been reported that in contrast to TPE, the use of eculizumab not only can lead to recovery of hematological parameters, but can also lead to renal function recovery. Kidney transplantation may be considered but risks recurrence of the disease process in the allograft; graft loss are common. The availability of eculizumab may also reduce the need for kidney transplantation. The rationale for TPE use is that it has been reported to remove the autoantibody or mutated circulating complement regulators while replacing absent or defective complement regulators. With the current understanding of the pathological mechanism and extensive use of eculizumab in this condition, use of TPE becomes somewhat limited. Before a firm diagnosis can be made, it is still considered as standard care to initiate TPE when idiopathic thrombotic thrombocytopenic purpura is suspected. When eculizumab is not available, TPE remains an alternative treatment option, although the evidence suggests a more robust effect with eculizumab. TPE may not work for patients with membrane cofactor protein mutations, as the factor does not circulate and plasma therapy has in general not been shown to influence patient outcomes (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2016).

Thrombotic Microangiopathy (TMA), Drug-Associated (Except for Ticlopidine) or Hematopoietic Stem Cell Transplant-Associated (III/IV Grade 2B-C): Thrombotic microangiography (TMA) involves the histopathological appearance of arteriolar microthrombi with swelling and necrosis of the vessel wall which presents with microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and renal dysfunction. Certain drugs can cause TMA including clopidogrel, calcineurin inhibitors (CNIs), estrogen/progesterone, gemcitabine, interferon, mitomycin,cyclosporine, tacrolimus, gemcitabine, and quinine. Treatment includes cessation of the drug if medically appropriate or reduction in dosage and supportive care. Although PP has been proposed as a treatment option for TMA to remove plasma protein bound drugs, therapeutic benefit has not been defined.

TMA following allogeneic hematopoietic stem cell transplantation, also known as transplant associated (TA)-TMA may be caused by endothelial cell injury due to chemotherapy, irradiation, graft-versus-host disease (GVHD), calcineurin inhibitor drugs and infections. Management of TA-TMA includes reduction or discontinuation of certain medications, as well as treatment of underlying graft-versus-host disease (GVHD), and infections. PP has been proposed as a treatment option for TA-TMA but available studies have reported no improvement following therapy (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Thrombotic Microangiopathy (TMA), Infection Associated; Hemolytic Uremic Syndrome (HUS) Shiga Toxin Mediated (STEC-HUS, severe), Streptococcus pneumoniae (pHUS) (III Grade 2C): The most common TMA, hemolytic uremic syndrome (HUS), is a potentially life-threatening condition characterized by TMA that typically targets the kidney causing renal failure. In the majority (90%) of patients with HUS, the cause is due to the action of Shiga-like toxin (Stx) on the renovascular endothelium and is often referred to as STEC-HUS (D1HUS). Another infection-induced HUS that usually occurs in children <2 years is due to sepsis, pneumonia, or meningitis caused by Streptococcus pneumoniae (pHUS). Stx binds to multiple cells in the kidney and causes a spectrum of renal injury. Brain endothelial and neuronal cells are also targeted. The severity of acute illness, particularly central nervous system impairment and the need for dialysis is strongly associated with a worse long-term prognosis. replacement therapy. There is no robust evidence from the available literature that TPE benefits patients with STEC-HUS. TPE may reduce concentrations of various cytokines, von Willebrand factor multimers, and Stx that damage the endothelium however there is limited data to support this. Free Stx has not been detected in the serum, and how it transits from the GI tract to target organs remains unclear. For pHUS, TPE would remove antibodies directed against the exposed T-antigen, as well as circulating bacterial

neuraminidase. There evidence for treating pHUS with PP is limited without reported adverse effects (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2016).

Thrombotic Microangiopathy (TMA), Pregnancy Associated (III, Grade 2C): Thrombotic microangiopathy (TMA) is a pattern of endothelial injury that results in the clinical triad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and organ injury. In pregnancy, TMA is diagnosed based on thrombocytopenia (platelets $<100 \times 10^9$/L), MAHA (hemoglobin<10 g/dL, lactate dehydrogenase (LDH) 1.5x upper limit of normal, undetectable haptoglobin, schistocytes on peripheral smear) and evidence of organ injury (kidney, heart, neurological). The differential diagnosis of TMA in the setting of pregnancy includes coagulation mediated TMA, complement mediated TMA (also referred to as atypical hemolytic uremic syndrome (aHUS)), drug associated TMA, infection associated TMA, thrombotic thrombocytopenic purpura (TTP; see separate fact sheets), pre-eclampsia and HELLP syndrome. The most common causes of TMA in pregnancy are pre-eclampsia and HELLP syndrome. Treatment for pre-eclampsia and HELLP syndrome is the delivery of the baby, usually by cesarean section. "Currently, TPE is recommended in patients with suspected pre-eclampsia/HELLP who have severe thrombocytopenia and life-threatening neurological or cardiac signs (seizures, coma, altered mental status, elevated troponins) until TTP is ruled out with an ADAMTS-13 level of greater than 20%. TPE can be considered in other patients whose thrombocytopenia, hemolysis and kidney function fail to improve 24 to 72 hours after delivery until diagnostic workup is completed, including ADAMTS-13 level and sFlt-1/ PlGF ratio drawn before plasma is exchanged. Once all alternative diagnoses are excluded, treatment for complement mediated TMA/aHUS with an anti-C5 agent such is eculizumab is recommended (Fakhouri, 2020). Antepartum TPE for suspected HELLP remains a category IV indication as described in the JCA 2019 Special Edition, as prompt delivery is the definitive treatment" (Connelly-Smith, et al., 2023).

Toxic Epidermal Necrolysis (TEN) (III Grade 2B): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), also called Lyell syndrome, are severe idiosyncratic reactions with medications being the most common trigger. They are characterized by mucocutaneous lesions leading to necrosis and sloughing of the epidermis. For medication-induced SJS/TEN, the causative medication is immediately withdrawn. Beyond supportive care, there are no universally accepted therapies for this disease. Removal of a toxin, such as a drug/drug metabolite, or other mediators of keratinocyte cytotoxicity are proposed as rationale for PP treatment. PP has not been used in patients with SJS. There is insufficient evidence supporting the clinical benefit of PP for TEN (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Transplantation, Hematopoietic Stem Cell, HLA desensitization (III Grade 2C): Hematopoietic stem cell transplantation (HSCT) is currently a key treatment modality in a number of diseases including but not limited to hematological malignancies. Current strategies are aimed at identifying and defining HLA antibodies present in the recipient and to use this information to avoid selection of allogeneic donors with cognate antigens. Due to the role of donor-specific antibody in engraftment failure, elimination/reduction of these antibodies peritransplant may result in improved outcomes. Additional, larger studies are needed to fully establish the impact of TPE on engraftment in donor-specific antibody positive allogeneic HSCTs (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2016).

Transplantation, Intestine; Antibody Mediated Rejection and Desensitization (III Grade 2C): Rejection in intestinal transplantation (ITx) can be acute (humoral and/or cellular) or chronic. The cause of acute rejection is likely a combination of both antibody-mediated and T-cell mediated processes. PP along with other immunosuppressive medications have been used for treatment of antibody mediated rejection and in desensitization protocols. It has been proposed that PP can remove existing alloantibodies, such as de novo donor-specific antibodies, but that it

needs to be used in conjunction with other immunosuppressive therapies to prevent their formation (Connelly-Smith, et al., 2023).

Transplantation, Kidney, ABO Compatible and Elevated Panel Reactive Antibodies (PRA) Desensitization, Deceased Donor (III Grade 2C): Use of immunologically incompatible kidneys is growing due to organ shortage and sensitized candidates. PP is now used in many transplant centers, to broaden access to transplantation to patients with high PRA and in need of deceased donor and thus must lower their Human Leukocyte Antigens antibody titer. Recipients at higher risk of antibody-mediated rejection include those with previous transplant and high PRA. PP-based regimens appear to be effective only for those awaiting living donor transplants (Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Transplantation, Liver, ABO Incompatible; Deceased Donor; Antibody Mediated Rejection/Humoral Rejection (III Grade 2C): Major incompatibility refers to the presence of natural antibodies in the recipient against the donor's A or/and B blood group antigen. These antibodies may cause hyperacute/acute humoral rejection of the organ due to endothelial damage. There is a paucity of evidence that PP, in combination with enhanced immunosuppression may be effective in reversing humoral rejection in the liver allograft. In the deceased donor liver transplant setting. PP is typically instituted immediately before and sometimes both before and after transplantation in an attempt to prevent hyperacute rejection and acute antibody medicated rejection (AMR). In deceased donor liver transplant, PP procedures are often utilized in the urgent/emergent setting after a deceased ABO incompatible allograft has been identified, making a thorough analysis of PP efficacy challenging. The clinical benefit of PP for ABO incompatible deceased donor liver transplant has not been established (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Transplantation, Lung, Antibody Mediated Rejection/Allograft, Rejection; Desensitization (III Grade 2C): Recent case reports and series suggest that antibody mediated rejection; (AMR) should be considered a potential cause of graft dysfunction, particularly when resistance to corticosteroid therapy is encountered. Formal criteria for the diagnosis of pulmonary AMR have now been put forth by the the International Society for Heart and Lung Transplantation. Both anti-HLA and antiendothelial antibodies have been proposed in mediating AMR. Recent reports suggest that PP may be efficacious in treating AMR, but the evidence is insufficient to support PP for this indication. In the area of desensitization of highly alloimmunized lung transplant waitlisted patients, use of a multimodal desensitization protocol including TPE, steroids, rituximab, and bortezomib in a small cohort of patients (n=8) did not appear to significantly reduce pretransplant HLA antibodies and survival among the treated group was comparable to untreated cohort. (Connelly-Smith, et al., 2023; Schwartz, et al., 2013, 2016; Snyder, et al., 2014).

Vaccine-Induced Immune Thrombotic Thrombocytopenia (III Grade 2C): Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare complication that can occur after adenoviral vector-based vaccinations and was first described after the ChAdOx-1 (AstraZeneca) COVID-19 vaccine in February 2021. Other terms used to describe it were thrombotic thrombocytopenic syndrome (TTS), vaccine-associated thrombosis and thrombocytopenia (VATT), and vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). VITT is characterized by the formation of anti-platelet factor 4 (PF4) IgG antibodies which cause cause hemostatic derangement and thromboembolism. Thrombosis can occur at any site with VITT, with atypical and/or multi-site thrombosis common (e.g., cerebral, abdominopelvic, arterial). Current treatment of VITT consists of therapeutic anticoagulation and antibody inhibition. PP has been proposed to directly remove the pathologic antibodies wen unresponsive to first-line treatment. There evidence for treating VITT with PP is limited and needs further study (Connelly-Smith, et al., 2023).

Vasculitis, Antineutrophil Cytoplasmic Antibody (ANCA)-Associated: Microscopic polyangiitis (III Grade 1B), Granulomatosis with polyangiitis (III Grade 1B), Eosinophilic Granulomatosis with Polyangiitis (**EGPA) (III Grade 2C):** Prior to 2020, the AFSA had categorized plasmapheresis as a category I (Padmanabhan, et al., 2019; Schwartz, et al., 2016). Based on a RCT (Walsh, et al.2020), the society downgraded to a category III for this indication. This RCT was the largest to conclude that PP did not reduce the incidence of death or ESKD for this condition. However, additional studies are needed to validate these findings.

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). These diseases affect small- and medium-sized vessels. It is characterized by multisystem organ involvement, typically affecting the kidneys (rapidly progressive glomerulonephritis [RPGN] with high risk of end stage kidney disease [ESKD]), lungs (from asymptomatic pulmonary lesions to life-threatening diffuse alveolar hemorrhage [DAH]), ear-nose-throat, joints, skin and nerves. GPA is characterized by necrotizing granulomatous inflammation and is typically associated with cytoplasmic ANCA and antibodies to proteinase 3. MPA is characterized by vasculitis without granulomatous inflammation, and is most commonly associated with perinuclear ANCA and antibodies to myeloperoxidase. EGPA is rarely associated with RPGN or DAH. Mainstay of therapy for all AAV subtypes is high-dose glucocorticoids with either cyclophosphamide or rituximab. TPE and granulocyte and monocyte adsorption apheresis have also been tried with some success (Padmanabhan, et al., 2019; Schwartz, et al., 2016). The role of PP in the treatment of GPA, MPA, and EGPA vasulitis has not demonstrated an improvement in ESKD or mortality (Connelly-Smith, et al., 2023).

Walsh et al. (2020) conducted a randomized control trial (n=704) to evaluate the use of plasma exchange and two regimens of oral glucocorticoids in patients with severe ANCA-associated vasculitis (AAV). Primary composite outcome was end-stage kidney disease (ESKD) or death. Patients with AAV with an eGFR<50 ml/min or with diffuse alveolar hemorrhage (DAH) were given pulse steroids and cyclophosphamide or rituximab. They were then randomized to receive plasma exchange (n=352) (seven plasma exchanges within 14 days) or no plasma exchange (n=352) (control). Patients were also randomized to receive either a standard-dose regimen or a reduced-dose regimen of oral glucocorticoids. Median follow-up was 2.9 years. Death from ESKD or any cause occurred in 28.4% (n=100/352) of patients in the plasma-exchange group and in 31% (n=109/352) patients in the control group (p=0.27). In this study, the authors concluded that the use of plasma exchange did not reduce the incidence of death or ESKD in patients with ANCA-associated vasculitis. Additional studies are needed to confirm these findings.

Vasculitis, IgA: Crescentic Rapidly Progressive Glomerulonephritis, Severe Extra-Renal Manifestations (III Grade 2C): The most common systemic vasculitis in childhood is Henoch-Schönlein purpura (HSP), now know as IgA vasculitis (IgAV), or IgA vasculitis with nephropathy (IgAVN) and in severe cases, crescent IgAVN (CreIgAVN). It is usually a self-limiting, systemic small vessel vasculitis with initial presentation of arthralgia/arthritis, abdominal pain, kidney disease, and palpable purpura in the absence of thrombocytopenia or coagulopathy. Supportive care is the mainstay of treatment including hydration, rest, and pain control. Treatment for those with kidney involvement includes corticosteroids with or without immunosuppressants such as cyclophosphamide, azathioprine, or cyclosporine and IVIG. Kidney transplantation may be necessary if ESKD develops. PP has been proposed to remove the IgA1- containing immune complexes or IgG autoantibodies. PP may benefit those with severe disease, but there is insufficient evidence in the published literature to support its use at this time (Connelly-Smith, et al., 2023).

Vasculitis, Other: Kawasaki Disease, Multisystem Inflammatory Syndrome in Children (III Grade 2C), Behcet's Disease (BD) (Grade III 2C): Behcet's disease (BD) is a rare

immune-mediated systemic vasculitis that can involve blood vessels of all sizes and can affect both the arterial and venous vessels. Current management of BD includes topical medication, systemic steroids, antibiotics, and immunosuppressive and anti-inflammatory agents. TPE and granulocyte and monocyte adsorption apheresis have also been tried with some success. The role of PP in the treatment of BD vasulitis has not been established (Padmanabhan, et al., 2019; Schwartz, et al., 2016). Kawasaki disease (KD) is an acute febrile illness of childhood associated with systemic vasculitis mainly of medium-sized arteries with a predilection for coronary arteries. Treatment for KD includes the administration of a single high dose IVIG (2 gm/kg) and aspirin. Alternate therapies for IVIG-resistant patients include intravenous methylprednisolone, infliximab, cyclosporine, ulinastatin, and PP. Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe hyperinflammatory disease. It can occur 2–6 weeks after a COVID-19 infection and is characterized by severe abdominal pain, shock, cardiac dysfunction, neurologic and respiratory findings, and lymphopenia. MIS-C can lead to cardiovascular collapse and multiorgan failure. Treatment for MIS-C includes immunomodulation (IVIG and/or corticosteroids), anticoagulation, and management of shock. There is insufficient evidence in the published literature to support the use of PP for KD or MIS-C at this time (Connelly-Smith, et al., 2023).

Warm Autoimmune Hemolytic Anemia (WAIHA), Severe (III Grade 2C): WAIHA is one type of autoimmune hemolytic anemia (AIHA) in which autoantibodies attach to and destroy the red blood cells at temperatures ≥ 37 degrees Celsius. Treatment includes steroids, immunosuppessive/immunomodulatory therapy, and in severe cases spleenectomy. The role of PP in the treatment of WAIHA has not been established (Connelly-Smith, et al., 2023; Padmanabhan, et al., 2019; Schwartz, et al., 2013, 2016).

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Apheresis (Therapeutic Pheresis) (110.14)	7/30/1992
LCD		No Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
36514	Therapeutic apheresis for plasma pheresis

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Revision Details

Type of Revision	Summary of Changes	Date
Annual review	• No clinical policy statement changes.	6/15/2025
Annual review	• No clinical policy statement changes.	6/15/2024