

**Subject: Plasmapheresis**  
**Number: 0153**

**Effective Date: 8/15/2006**  
**Revision Date: 10/15/2007**

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## **INSTRUCTIONS FOR USE**

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## **Plasmapheresis is considered medically necessary for ANY of the following conditions:**

- acute inflammatory demyelinating polyneuropathy (Guillain-Barré Syndrome) when ONE of the following is established:
  - severity grade 3–5 AND is within four weeks of onset
  - severity grade 1–2 AND is within two weeks of onset
- anti-glomerular basement membrane disease (Goodpasture's syndrome)
- chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- cryoglobulinemia
- hyperviscosity syndrome (e.g., Waldenström's macroglobulinemia, multiple myeloma)
- myasthenia gravis in preparation for surgery OR with respiratory crisis
- pediatric postinfectious autoimmune neuropsychiatric disorders (PANDAS) associated with streptococcal infections and Sydenham's chorea (severe exacerbation)
- paraproteinemic polyneuropathy associated with monoclonal gammopathies of undetermined significance (e.g., MGUS)
- thrombotic thrombocytopenic purpura (TTP)

## **Plasmapheresis is considered medically necessary adjunctive secondary therapy when the patient has failed to respond to conventional therapy (e.g., corticosteroids or intravenous immunoglobulins [IVIG]):**

- ABO incompatible hematopoietic progenitor cell transplantation
- ABO incompatible transplantation – kidney and infant heart
- acute central nervous system inflammatory demyelinating disease
- hemolytic uremic syndrome (HUS; atypical)
- kidney transplantation (antibody mediated rejection [AMR]) and human leukocyte antigens [HLA] desensitization)
- Lambert-Eaton myasthenic syndrome (LEMS)
- mushroom poisoning
- myeloma associated with acute renal failure with polyneuropathy
- phytanic acid storage disease (Refsum's disease)
- post-transfusion purpura
- rapidly progressive glomerulonephritis (RPGN) (e.g., Wegener's)
- Rasmussen's encephalitis
- red cell alloimmunization in pregnancy

**Plasmapheresis for the following conditions is considered experimental, investigational or unproven and not medically necessary (this list may not be all-inclusive):**

- ABO incompatible solid organ transplantation – liver
- acute disseminated encephalomyelitis
- acute liver failure
- amyloidosis, systemic
- amyotrophic lateral sclerosis
- autoimmune hemolytic anemia (warm autoimmune hemolytic anemia; cold agglutinin)
- catastrophic antiphospholipid syndrome
- coagulation factor inhibitors
- dermatomyositis or polymyositis
- focal segmental glomerulosclerosis
- heart transplant rejection
- hematopoietic stem cell disorders (aplastic anemia; pure red cell aplasia)
- hypertriglyceridemic pancreatitis
- idiopathic thrombocytopenic purpura
- inclusion body myositis
- multiple sclerosis
- overdose and poisoning (compounds other than mushroom poisoning)
- paraneoplastic neurologic syndromes
- pemphigus vulgaris
- polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS)
- psoriasis
- rheumatoid arthritis
- schizophrenia
- scleroderma (progressive systemic sclerosis)
- sepsis
- stiff-person syndrome
- systemic lupus erythematosus
- thyrotoxicosis

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## **General Background**

Plasma, the portion of blood that remains after red cells, leukocytes and platelets are removed, is comprised of water, salts, enzymes, antibodies and other proteins. Plasma proteins are involved in blood clotting, fighting diseases and other critical functions. Plasmapheresis (PP), plasma exchange (PE) or therapeutic plasma exchange (TPE) is a process by which whole blood is withdrawn from the body via a vein; plasma is removed via a cell separator and the red cells, white cells, platelets and 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 National Institutes of Health (NIH) states, “for TPE to be accepted as an effective therapy, relationships must be established between removal of some pathologic factor and reversal of morbidity or mortality” (NIH, 1986). The procedure takes 1–3 hours, and the number of treatments needed (e.g., six to 10 treatments over a two- to ten-week period) depends upon the patient’s condition and underlying disease. As a general rule, PP is an extremely safe procedure. Side effects may include: drop in blood pressure, which can be experienced as faintness, dizziness, blurred vision, coldness, sweating or abdominal cramps; allergic reaction to the solutions; and bleeding (NIH, 1986; American Academy of Neurology [AAN], 1996).

Plasmapheresis has evolved since the mid-1970s and is a recognized treatment modality for multiple conditions (e.g., myasthenia gravis and Guillain-Barré syndrome). The American Academy of Neurology

(AAN) published an assessment of the value of PP for the treatment of neurological conditions (AAN, 1996). The Hemapheresis Committee of the American Association of Blood Banks (AABB) developed indication categories for therapeutic apheresis (TA), which incorporated therapeutic indication categories established by the American Society for Apheresis (ASFA) (Smith, et al., 2003). In 2007, ASFA published an update of the indications for the use of PP (Szczepiorkowski, et al., 2007b).

The indication categories for therapeutic apheresis most recently published by the ASFA include (ASFA, 2007b):

- “Category I includes diseases for which TA is standard and acceptable, either as a primary therapy or a valuable first-line adjunct therapy. (The perception of efficacy in these disorders is usually based on well-designed randomized controlled trials or on a broad and non-controversial base of published experience.) Note that this designation need not imply that TA is mandatory in all cases.
- Category II denotes diseases for which TA is generally accepted but considered to be supportive or adjunctive to other, more definitive treatments, rather than a primary first-line therapy. (Randomized controlled studies are available for some of these disorders, but in others the literature contains only small series or informative case studies.)
- Category III diseases are those in which there is a suggestion of benefit for which existing evidence is insufficient, either to establish the efficacy of TA or to clarify the risk/benefit (or sometimes the cost/benefit) ratio associated with TA. Included are disorders in which controlled trials have produced conflicting results or for which anecdotal reports are too few or too variable to support an adequate consensus. Therapeutic apheresis may reasonably be used in such patients when conventional therapies do not produce an adequate response or as part of an IRB-approved research protocol.
- Category IV indicates disorders for which controlled trials have not shown benefit or anecdotal reports have been discouraging. TA for these disorders is discouraged and should be carried out only in the context of an IRB-approved research protocol.”

The NIH Consensus Statement lists selected conditions for which PP is an appropriate treatment modality (i.e., myasthenia gravis, Eaton-Lambert Syndrome, chronic inflammatory demyelinating polyneuropathy, and Guillain-Barré Syndrome), and conditions which were not improved by the use of PP (i.e., amyotrophic lateral sclerosis and multiple sclerosis). They state, “TPE is a promising new treatment modality for a limited number of neurologic diseases.” Its effects are relatively short-lived, which poses limitations in the management of chronic disease (NIH, 1986).

### **Category I and Category II Indications**

PP is considered an acceptable primary or adjunctive treatment for the treatment of conditions in categories I and II.

**Acute inflammatory demyelinating polyneuropathy (Guillain-Barré Syndrome):** Guillain-Barré Syndrome (GBS) consists of a group of autoimmune syndromes which causes inflammation and damage to the nerve cell and myelin sheath, resulting in muscle weakness, paralysis and sensory loss. The body's immune system attacks itself, specifically, the nerves outside of the brain and spinal cord (i.e., peripheral nerves). Conduction of impulses through the nerves is slowed. The damage can also denervate the axon part of the nerve cell, which stops nerve function entirely. Without the axon, messages cannot be transferred from one nerve cell to another. Most patients spontaneously recover, so supportive therapy (e.g., mechanical ventilation and physical therapy) is the goal of treatment. Some studies reported that PP can accelerate motor recovery, decrease ventilator time and enhance clinical improvement. Intravenous immune globulin (IVIG) may also be used to reduce the severity and duration of the disease (Szczepiorkowski, et al., 2007; NIH, Jan 24, 2006; Natarajan and Weinstein, 2005; AAFP, 2004; Raphaël, et al., 2004).

The severity of the syndrome is graded according to the following Hughes scale:

- Grade 1 - minor symptoms
- Grade 2 - able to walk without support

- Grade 3 - able to walk with assistance of a cane, appliance or support
- Grade 4 - confined to bed or chair-bound
- Grade 5 - requires assisted ventilation.

The American Academy of Family Physicians (AAFP) states that “plasma exchange is the only treatment that is superior to supportive treatment alone. Furthermore, plasma exchange is most effective for ambulant patients when initiated within two weeks of disease onset but is still beneficial in nonambulant patients up to 30 days after onset” (AAFP, 2004).

The AAN issued a practice parameter guideline on immunotherapy for GBS which states that “Plasma exchange (PE) is recommended in nonambulant patients within four weeks of onset and for ambulant patients within two weeks of onset. The effects of PE and intravenous immunoglobulin (IVIg) are equivalent. Sequential treatment with PE followed by IVIg or immunoabsorption followed by IVIg is not recommended” (Hughes, et al., 2003).

**Anti-glomerular basement membrane disease (Anti-GBM):** Anti-GBM disease (Goodpasture’s syndrome) is considered one type of rapidly progressive glomerulonephritis (RPGN) and accounts for about 15% of RPGN cases. Anti-GBM is an autoimmune disorder caused by an antibody response against a certain type of protein (collagen) which is present in the alveoli of the lungs and in the glomeruli of the kidneys. These antibodies are called anti-glomerular basement membrane antibodies (or anti-GBM antibodies). Goodpasture’s syndrome is defined by the presence of a triad of glomerulonephritis, pulmonary hemorrhage and anti-GBM antibodies. Most patients present with rapidly progressive RPGN; therefore, an early and precise diagnosis is extremely important for preserving renal function and preventing death. The main goal is to decrease or remove the circulating antibodies by PP. Immunosuppression with high-dose steroids and oral cyclophosphamide, together with PP, is the current treatment of this disease (Szczeplorkowski, et al., 2007; NIH/NLM, 2004; Smith, et al., 2003).

**Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP):** CIDP is a neurological disorder characterized by progressive weakness and impaired sensory function in the legs and arms. The disorder, also known as chronic relapsing polyneuropathy, is caused by damage to the myelin sheath of the peripheral nerves. CIDP presents with symptoms that include tingling or numbness, weakness of the arms and legs, loss of deep tendon reflexes, fatigue and abnormal sensations. CIDP is closely related to GB syndrome and is considered to be the chronic counterpart of that acute disease. Effective treatments include the use of corticosteroids, PP and IVIG, which all have similar outcomes. Because CIDP is presumed to be the result of an autoimmune attack on the peripheral nerves, treatment is aimed at modulation of the abnormal immune response (Szczeplorkowski, et al., 2007; Shields, et al., 2003; Smith, et al., 2003).

The NIH consensus statement states that PP “may be useful in patients with CIDP, particularly those who have failed to respond to corticosteroids and ISDT. Repeated courses of PE may be required to sustain benefits” (NIH, 1986; updated 1992).

According to the AAN, “A randomized controlled trial performed by Dyck et al. showed that a significant proportion of patients with chronic inflammatory demyelinating polyneuropathy improved following PP. Thus, PP is a useful modality of therapy in this group of patients, who may also benefit from oral prednisone and intravenous human immune globulin. Which of these therapies is best will depend on a number of factors, and to factors that have been reviewed recently. PP is considered established for this disorder” (AAN, 1996).

**Cryoglobulinemia:** Cryoglobulinemia is the presence of an abnormal protein (i.e., cryoglobulin) in the blood, which thickens and becomes gel-like when exposed to cold. There are three types of cryoglobulinemia. Type I is often associated with lymphoma, while types II (mixed cryoglobulin) and III are often associated with lymphomas, autoimmune disorders (e.g., lupus, scleroderma, rheumatoid arthritis) and infectious diseases (e.g., hepatitis A, B, or C, and Epstein-Barr virus). Cryoglobulinemia may be classified based upon the cryoglobulin composition or upon the underlying, associated disease process. It is basically driven by four classes of disease (i.e., liver disease, infectious disease, connective tissue disease, lymphoproliferative disorders). Presenting symptoms and severity of the condition depend upon the type of cryoglobulinemia. Common signs and symptoms due to systemic vasculitis include: weakness,

rash, leg ulcers, edema, bruising, arthritis, and nerve damage. Laboratory studies will be conducted to test for the presence and type of serum cryoglobulin. Treatment is symptom-based and includes avoidance of the cold, pharmacotherapy with nonsteroidal anti-inflammatory drugs (NSAID) and immunosuppressants. PP may be used in all types of cryoglobulinemia to remove cryoglobulins. It is most often used in active to severe episodes with renal impairment, neuropathy, vasculitis and ulcerating purpura. It may be used alone or in conjunction with steroids or cytotoxic agents (Szczepiorkowski, et al., 2007; Tricot, 2005; Dispenzieri and Gerta, 2004).

**Hyperviscosity Syndrome (e.g., Waldenstrom's macroglobulinemia, multiple myeloma):**

Hyperviscosity syndrome usually results from increased serum immunoglobulins, causing increased resistance to blood flow. Symptoms include: bleeding, visual changes and neurologic manifestations (i.e., Bing-Neel syndrome), such as mental status changes, headache, dizziness, vertigo, stupor and coma. Peripheral neuropathies and myelopathies are the result of occlusive changes in small vessels. Complications of hyperviscosity syndrome include: Raynaud's phenomenon, livedo reticularis, palpable purpura, eruptive spider nevus-like lesions, digital infarcts and peripheral gangrene. Symptoms are not usually seen before the viscosity reaches four units, and hyperviscosity syndrome usually presents with a serum viscosity greater than five units. Hyperviscosity syndrome is associated with multiple myeloma, a plasma cell dyscrasia, and Waldenström macroglobulinemia, which is a rare chronic cancer of the B lymphocytes. PP is used to control the symptoms of Waldenström's macroglobulinemia due to the hyperviscosity of the blood. Hyperviscosity syndrome responds at least transiently to plasmapheresis as the circulating M-protein is removed. Alkylating agents, corticosteroids and transplants may be used for long-term treatment (Szczepiorkowski, et al., 2007; Hemingway, 2006; Smith, et al., 2003).

**Myasthenia Gravis (MG):** MG is a chronic autoimmune neuromuscular disease characterized by varying degrees of weakness of the skeletal muscles of the body. The hallmark of MG is muscle weakness that increases during periods of activity and improves after periods of rest. MG is caused by a defect in the transmission of nerve impulses to muscles. Antibodies produced by the body's immune system block, alter, or destroy the neurotransmitter substance, acetylcholine. Presenting clinical symptoms include ptosis, diplopia, dysarthria, extremity weakness and respiratory difficulty. The clinical course is variable, with remission alternating with exacerbation. A myasthenic crisis is a state of acute symptom-worsening and mechanical ventilation is often needed. Progressive deterioration is most likely in the first three years. Treatment options include: anticholinesterase drugs, thymectomy, immunosuppressive drugs and PP, which removes circulating antibodies. PP is especially useful during a myasthenic crisis, preoperatively for thymectomy or as an adjunctive therapy (Szczepiorkowski, et al., 2007; National Institute of Neurological Disorders and Stroke [NINDS], Jan 24, 2006; Romi, et al., 2005; Smith, et al., 2003).

**Pediatric Postinfectious Autoimmune Neuropsychiatric Disorders (PANDAS) Associated with Streptococcal Infections and Sydenham's Chorea (SC):** PANDAS is used to describe a subset of children who have obsessive compulsive disorder (OCD) and/or tic disorders such as Tourette's syndrome, and in whom symptoms typically worsen following streptococcal infections such as streptococcal throat infection or scarlet fever. PANDAS is characterized by abrupt onset and dramatic exacerbation of symptoms. In PANDAS, it is theorized that the body's antibodies produced to fight infection attack the part of the brain responsible for movement and behavior, and therefore tics and/or OCD are caused. SC is a movement disorder associated with rheumatic fever. The movements are involuntary, jerky, and purposeless. They lack rhythm and occur sporadically in different muscle groups. Fine motor control becomes difficult, and handwriting may change dramatically. Treatment of PANDAS includes antibiotics, cognitive behavioral therapy (CBT) and/or anti-obsessional medications. SC is treated with antibiotics to prevent rheumatic carditis. It has been proposed that streptococcal antigens induce antineuronal antibodies, and PP is indicated in both conditions with severe exacerbation for antibody removal. PP may reduce the severity of the symptoms and shorten the course of the disease. IVIG is also a treatment option for these children (Szczepiorkowski, et al., 2007; National Institute of Mental Health [NIMH], Aug 1, 2004; Kurlan and Kaplan, 2004; Smith, et al., 2003).

**Paraproteinemic Polyneuropathy Associated with Monoclonal Gammopathies of Undetermined Significance (e.g., MGUS):** Patients with MGUS have an M-protein in the serum without symptoms or findings of multiple myeloma, macroglobulinemia, amyloidosis, or lymphoma. Most patients remain asymptomatic. However, in some patients, MGUS may develop into a serious condition, such as multiple myeloma or lymphoma. Treatment should be directed at reducing the tumor cell burden and reversing

any complications of disease, such as renal failure, infection, hyperviscosity, or hypercalcemia. The MGUS polyneuropathies associated with immunoglobulin (Ig) G and IgA conform to a sensorimotor polyneuropathy that shares many of the same clinical features as chronic inflammatory demyelinating polyneuropathy (CIDP), such as predominant proximal weakness. However, sensory symptoms are usually more prominent, the initial phase of the disorder progresses much slower, and the course of the disease is less cyclical or relapsing. PP is also indicated in the treatment of polyneuropathy with IgM (e.g., Waldenström's macroglobulinemia). Treatment may include the use of corticosteroids, cyclosporins, immunoglobulins and PP. PP assists in the removal of monoclonal proteins, stabilizing the patient and improving neurological symptoms (Szczepiorkowski, et al., 2007; Shields, et al., 2003).

The AAN states, "A randomized controlled trial (Dyck, et al., 1991) has shown that patients with polyneuropathy associated with IgA and IgG monoclonal gammopathies of undetermined significance (MGUS) improve following therapy with PP. Those with IgM MGUS and polyneuropathy did not improve. The patients entering this study were heterogeneous and included those with both demyelinating and axonal polyneuropathies. Patients in the IgM MGUS group may have included those with anti-myelin-associated glycoprotein antibodies. Because of continuing controversy concerning the exact relationship of the monoclonal protein to the neuropathy, treatment decisions in IgM patients remain individualized. PP may be considered possibly useful for these disorders. For those with IgA and IgG, Class I evidence would indicate that PP is established." The AAN summary states that the use of PP for IgM patients is considered investigational (AAN, 1996).

**Thrombotic Thrombocytopenic Purpura (TTP):** TTP is a blood disorder characterized by low platelets and red blood cell count, abnormal kidney function and neurological abnormalities. TTP is a thrombotic microangiopathy condition in which there is a high incidence of severe deficiency of the von Willebrand factor (VWF) cleaving protease, an enzyme called A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13 (ADAMTS13), in patients with clinically diagnosed TTP. (Kaplan, 2004; McCrae, 2005). The resulting effects can be organ ischemia, thrombocytopenia, and erythrocyte fragmentation. The lining of the kidneys, brain, heart, pancreas, spleen, and adrenal glands are especially vulnerable to TTP. Other organs may be affected to a lesser degree. Refractory cases have been treated with vincristine or cyclosporine A. According to the ASFA, PP is a "life-saving therapy" because it is proposed that PP may remove the anti-ADAMTS13 autoantibody and restore the ADAMTS 13 protease activity (Szczepiorkowski, et al., 2007; Silverman, 2005; Symonette, 2005).

The NIH states that PP is the treatment option for TTP, and if patients fail PP, splenectomy or corticosteroids may be indicated (NIH, July, 2005).

**ABO Incompatible Hematopoietic Progenitor Cell Transplantation:** There are two types of incompatibility, major and minor. Major incompatibility occurs when there is a presence of natural antibodies in the recipient against the donor's ABO blood group. The incompatibility may cause hemolysis of red blood cells in the transplanted product. In minor incompatibility, the donor product has antibodies against the recipient's ABO blood type, which may cause a fatal hemolytic transfusion reaction. PP can be used to reduce the ABO antibodies responsible for hemolysis and pure red cell aplasia, especially in major incompatibility. Red cell exchange with group O red cells may be used to deplete recipient type red cells in minor incompatibility (Szczepiorkowski, et al., 2007).

**ABO Incompatible Transplantation – Kidney and Infant Heart:** Historically, ABO compatibility between donor antigens and recipient antibodies has been critical for successful transplantation. ABO incompatible grafts are at high risk for rejection, and transplantation against ABO barriers has been generally contraindicated. Highly sensitized patients are reactive to a broad panel of non-self human antigens, particularly those of the human leukocyte antigen (HLA) system and may wait years for a cadaver allograft in the absence of an available compatible living donor. Major incompatibility in solid organ transplantation occurs in the presence of natural antibodies in the recipient against the donor's ABO blood group. This incompatibility may lead to hyperacute/acute humoral rejection of the organ. However, improvements in immunosuppressant regimens and anti-microbial prophylaxis to prevent graft rejection, especially in those who are highly sensitive, have been positive. Studies are showing benefits in short-term outcomes of transplants across the ABO blood group barrier (Gloor, et al., 2003; Jordon, et al., 2003; Lorber, 2004; Magee, et al., 2004). Development of treatment regimens including PP, enhanced immunosuppression and IVIG has increased the success rate of solid organ transplants. Peri-transplant

PP may be used to lower the antibody titer for ABO-mismatched solid organ transplant preventing hyperacute rejection and improving graft survival. PP can also be used to reduce high titer antibodies responsible for humoral rejection (Szczepiorkowski, et al., 2007; Kaufman, 2005; Reid, et al., 2005; Smith, et al., 2003).

**Acute Central Nervous System Inflammatory (CNS) Demyelinating Disease:** Acute CNS inflammatory demyelinating disease is often associated with acute fulminant attacks of various types of multiple sclerosis (MS) (e.g., Marburg's variant of MS, Balo's concentric sclerosis). Sudden onset of acute attacks or exacerbations result in worsening of symptoms or onset of new symptoms, and last for at least 24 hours and sometimes up to several weeks. The attacks involve destruction of the myelin (i.e., demyelination). Acute attacks are most commonly treated with intravenous high-dose corticosteroids. PP may be indicated for the treatment of those patients who do not respond to steroid therapy. The National Multiple Sclerosis Society (NMSS) states that it has been reported that 90% of patients experiencing a severe attack respond to high-dose steroids, but for the 10% who do not, PP may "offer an important and beneficial treatment option" (Szczepiorkowski, et al., 2007; NMSS, 2006; NMSS, 2005; Pike and Noseworthy, 2003; Weinshenker, 2001; Weinshenker, 1999).

**Hemolytic Uremic Syndrome (HUS):** HUS is a thrombotic microangiopathy blood disorder characterized by low platelets and red blood cell count primarily affecting kidney function. In HUS, the defining feature is renal involvement that results in microthrombi confined to the kidneys. On gross examination, the kidneys are swollen and pale, with small surface hemorrhages. Diarrhea and upper respiratory infection are the most common precipitating factors. It most often occurs after a gastrointestinal infection, typically caused by *Escherichia coli*, accompanied by bloody diarrhea, vomiting and fever (NIH, 2007; Kaplan, 2004; McCrae, 2005). The two types of HUS are diarrhea-associated HUS or typical HUS and non-diarrhea-associated-HUS or atypical HUS. Management of HUS consists of early dialysis for acute renal failure, blood transfusion, and general supportive care. Refractory cases have been treated with vincristine or cyclosporine A. If the patient is unresponsive to conventional therapy, PP may be used as a treatment option for atypical HUS to remove antibodies from the blood. In the presence of renal failure, extracorporeal immunoadsorption (ECI) therapy may be used as an adjunctive therapy (Szczepiorkowski, et al., 2007; Silverman, 2005; Symonette, 2005).

The NIH and the National Kidney Foundation (NKF) state that PP may be a necessary form of treatment for HUS when conventional therapy is ineffective (NIH, Apr, 2007; NKF, 2006).

**Kidney Transplantation (Antibody Mediated Rejection [AMR]) and Human Leukocyte Antigens [HLA] Desensitization:** Two barriers to successful kidney transplantation are recipient HLA and ABO incompatibility with the donor. Recipients with elevated antibodies have difficulty finding a compatible donor. Desensitization using IVIG or PP with low dose IVIG prior to transplantation is performed to allow these patients to accept a donor kidney that would otherwise be avoided. PP is typically continued following transplantation. Immunosuppressive drugs, cyclosporine, tacrolimus, mycophenolat mofetil and tacrolimus are also prescribed after the transplant to prevent rejection. In antibody-mediated rejection, PP is used to remove donor-specific antibodies (Szczepiorkowski, et al., 2007).

**Lambert-Eaton Myasthenic Syndrome (LEMS):** LEMS is a disorder with symptoms very similar to those of MG. There is muscle weakness associated with disturbed communication between nerves and muscles. In MG, the neurotransmitter acetylcholine (i.e., the chemical that transmits impulses between nerves and muscles) is blocked by antibodies to its receptor. In LEMS syndrome, however, the signal distortion is caused by an insufficient release of neurotransmitter by the nerve cell. The disorder may be associated with small-cell carcinoma of the lung and other malignancies such as paraneoplastic syndrome or with autoimmune disorders. The primary goal of treatment is to identify and treat any tumors or other underlying disorders. Prednisone or other medications that suppress the immune response may improve symptoms in some cases. PP may be a useful adjunct for patients with severe or rapidly developing neurological deficit, or for patients too uncomfortable to wait for drugs to take effect (Szczepiorkowski, et al., 2007; NIH, Jul 2004; Smith, et al., 2003).

The NIH consensus statement indicates that although only a small number of patients with LEMS have been treated with PP, the "preliminary data, taken in conjunction with the antibody-mediated pathogenesis of the disease, persuade the panel that PE may well have a role in the treatment of this

syndrome. Short-term improvement in muscular weakness can be effected by PE. This is particularly useful in those patients with small cell carcinoma of the lung” (NIH, 1986).

The AAN states that “While no controlled trials exist on the use of PP in LEMS, a case series has suggested a benefit. The rationale is similar to that in myasthenia; that is, patient strength should be improved by the removal of the pathogenic antibody to the voltage-gated calcium channel. In most cases, patients are treated long-term with a combination of corticosteroids and immunosuppressant drugs,” and “PP would be considered promising for LEMS” (AAN, 1996).

**Mushroom Poisoning:** Mushroom poisoning occurs from ingestion of several types of mushrooms, including *Inocybe*, *Clitocybe*, and *Amanita phalloides*. Depending upon the type of mushroom ingested, symptoms may include: nausea, vomiting, abdominal pain and cramping, diarrhea, dizziness, confusion, seizures, coma, kidney and liver damage, and even death if untreated. Treatment is supportive in nature and focused on removal of the toxin. PP has been shown to decrease mortality in patients with mushroom poisoning by the removal of protein-bound toxins. The FDA lists plasmapheresis as a treatment modality for amanita poisoning (Szczepiorkowski, et al., 2007; Merck, 2003; FDA, 1992).

**Myeloma Associated with Acute Renal Failure with Polyneuropathy:** Multiple myeloma is a common primary cancer of the bones in adults. It is formed by malignant plasma cells that typically produce tumors in the bone marrow. The multiple myeloma cell clones produce an excess of monoclonal (M-proteins) and free light chain proteins. The light chain proteins deposit in organs, producing damage. The organ most commonly affected is the kidney. Myeloma kidney results from toxicity to the distal nephron caused by an inflammatory response around the cast. Myeloma patients may acquire coagulation abnormalities related to the high level of paraproteins or associated hyperviscosity (DeVita, et al., 2005). There are various treatments for patients with multiple myeloma depending upon the course of the disease and associated disease processes. Therapy may include anti-myeloma chemotherapy, diuresis, dialysis, autologous bone marrow transplant, immune modulation and proteasome inhibition. The American Society for Apheresis (ASAF) states that in acute renal failure, PP “may be used to decrease the delivery of light chains delivered to the renal glomerulus for filtration.” In other conditions associated with myeloma, PP may be used to remove cryoglobulins or decrease hyperviscosity. The American Cancer Society (ACS) states that plasmapheresis is “helpful when accumulation of certain myeloma proteins thickens the blood and interferes with circulation” (Szczepiorkowski, et al., 2007; ACS, 2006; Smith, et al., 2003).

**Phytanic Acid Storage Disease (Refsum’s Disease):** Refsum’s disease is a genetic disorder that involves damage to the white matter of the brain and affects motor movements. It is one of an inherited disorder called leukodystrophies. The disorder involves a genetic defect that prevents the body from breaking down phytanic acid, a substance commonly found in foods. As a result, toxic levels of phytanic acid build up in the brain, blood, and other tissues. There is adult Refsum’s disease (ARD) and infant Refsum’s disease (IRD). ARD and IRD are separate disorders caused by different biomechanisms involved in the breakdown of phytanic acid. Symptoms of IRD begin in infancy with a visual impairment that may progress to blindness and a hearing impairment that may progress to deafness by early childhood. Other symptoms may include: nystagmus, hypotonia, ataxia, mental and growth retardation, dysmorphia, hepatomegaly, hypocholesterolemia, retinitis pigmentosa, loss of the sense of smell, deafness, ataxia, weakness, numbness, dry and scaly skin, and cardiac arrhythmias. Some individuals will have shortened bones in their fingers or toes or a noticeably shortened fourth toe. The mainstay of therapy is to limit the daily intake of foods rich in phytanic acid. PP rapidly decreases the level of phytanic acid which is indicated for acute attacks or exacerbations (Szczepiorkowski, et al., 2007; NIH, 2006; Rowland, 2005)

**Post-Transfusion Purpura:** Post-transfusion purpura is a rare disorder characterized by acute thrombocytopenia, occurring about one week after a blood transfusion in patients lacking a specific platelet antigen. The patient often has a history of sensitization with prior transfusions or pregnancies. After resensitization by the transfusion or additional pregnancy, patients develop potent antibodies against the platelet-specific antigen that they are lacking but which are present on donor platelets. Treatment includes IVIG and steroids. PP should only be used if IVIG is not effective and 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 (Szczepiorkowski, et al., 2007; Smith, et al., 2003; Wu and Snyder, 2005).

**Rapidly Progressive Glomerulonephritis (RPGN) (e.g., Wegener's):** RPGN is a form of kidney disease that causes inflammation and damage to the internal structures of the kidneys with rapid loss of function which can lead to renal failure and end-stage disease. RPGN is characterized by glomerular inflammation with formation of crescent-shaped abnormalities found upon biopsy. RPGN includes renal diseases with different causes, pathogeneses, and clinical presentations. Patients with primary RPGN have been divided into three patterns defined by immunologic pathogenesis:

- type I: with anti-glomerular basement membrane (GBM) disease (e.g., Goodpasture's syndrome)
- type II, with immune complex deposition (e.g., systemic lupus erythematosus [SLE], poststreptococcal)
- type III, pauci-immune; without immune deposits or anti-GBM antibodies. Most are categorized as antineutrophil cytoplasmic antibody-positive (ANCA-positive) RPGN (e.g., Wegener's granulomatosis and Churg-Strauss syndrome) (Appel, 2004; NIH, Sep 13, 2005).

The treatment varies depending on the suspected cause. Treatment goals may be cure of the causative disorder, the control of symptoms, or the treatment of renal failure. Corticosteroids or immunosuppressive agents, including cyclophosphamide, azathioprine and others, may be used to relieve the symptoms depending on the cause of the disorder. In fulminating cases, PP is utilized to remove the antibodies and reduce kidney tissue inflammation and in some cases, may relieve the symptoms (Szczepiorkowski, et al., 2007; Smith, et al., 2003; NIH, Sept 13, 2005; NIH/NLM, Dec 2004).

**Rasmussen's Encephalitis:** Rasmussen's encephalitis is a chronic inflammatory disease that typically affects only one hemisphere of the brain, occurs in children under age 10, and is characterized by frequent, severe seizures, loss of motor skills and speech, hemiparesis, encephalitis, and mental deterioration. It is proposed to be associated with Epstein-Barr virus, herpes simplex, enterovirus or cytomegalovirus; etiology is unknown. Treatment includes the use of anti-epileptic drugs, corticosteroids, IVIG, or tacrolimus. In unrefractory cases, surgery (e.g., functional hemispherectomy and hemispherotomy) may be performed to control seizures. PP would be indicated to remove autoantibodies and to delay or forego surgery. NINDS does not discuss PP as a treatment option (Szczepiorkowski, et al., 2007; NINDS, Feb 2007).

**Red Cell Alloimmunization in Pregnancy:** Red cell alloimmunization in pregnancy, hemolytic disease of the fetus and newborn, is a hemolytic disorder that occurs when maternal plasma contains an alloantibody against a red cell antigen carried by the fetus. The maternal IgG crosses the placenta, causing hemolysis of red blood cells in the fetus, fetal anemia and even fetal death. Sensitization to the red cell antigens typically occurs following hemorrhage during pregnancy or delivery, or through previous red cell transfusion. Management 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, with IVIG and/or PP as alternate therapies. TPE removes the maternal red cell alloantibody, reducing the maternal antibody titer, and protecting the fetus from hemolytic disease of the fetus and newborn (Szczepiorkowski, et al., 2007).

#### **Category III and Category IV Indications**

For conditions rated as a category III or IV, scientific studies have reported inconsistent outcomes, and/or lack of consistent efficacy, and/or no benefit for the use of plasma exchange as a treatment modality. Therefore, in these conditions, PP is not recommended as a treatment modality (Szczepiorkowski, et al., 2007; Shaz, et al., 2007).

**ABO Incompatible Transplantation – Liver:** Ideally, liver transplantation is not undergone until an ABO identical liver is available. In emergency situations, an ABO-incompatible organ may be used, increasing the risk of rejection. Rejection is typically treated with immunosuppressants, steroids, IVIG and antithymocyte globulins. It has been proposed that PP may help prevent hyperacute rejection after ABO-incompatible liver transplantation by removal of preformed antibodies. However, there is a lack of data to support the use of PP for liver transplantation rejection in this setting (Szczepiorkowski, et al., 2007; National Institute of Diabetes and Digestive and Kidney Disease [NIDDK], 2003).

**Acute Disseminated Encephalomyelitis (ADEM):** ADEM is an acute inflammatory monophasic demyelinating neurologic disease causing inflammation of the brain and spinal cord, and thought to be due to an autoimmune response following a viral infection or immunization. The disease is associated with a change in mental status, ataxia, weakness, dysarthria and dysphagia. ADEM shares clinical and pathological resemblance to multiple sclerosis and GB. The standard therapy is corticosteroids and IVIG for patients nonresponsive to corticosteroids. PP has been proposed for the removal of offending antibodies (Szczepiorkowski, et al., 2007; Rust, 2007; National Institute of Neurological Disorders and Stroke [NINDS], Jan 2006). In a discussion of the treatment of MS, AAN reports, based upon a single small Class I study, that it is possible that plasma exchange may be helpful in the treatment of severe, acute episodes of demyelination in previously non-disabled individuals (Goodin, et al., 2002).

**Acute Liver Failure (ALF):** In the United States, the most common cause of ALF is viral hepatitis, but it may also occur as a result of acetaminophen and other drug toxicity, autoimmune hepatitis, and Wilson's disease. It can occur in a normal liver (i.e., fulminant hepatic failure) or in chronic liver disease. Treatment includes supportive therapy until the patient can receive a liver transplant. ALF patients receive 30% of liver transplantations. The use of PP has been proposed to lower the level of bilirubin and hepatic enzymes and remove toxins (Szczepiorkowski, 2007; O'Grady, 2005).

**Amyloidosis, Systemic:** 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. The two major types of systemic amyloidosis are AL, primary amyloidosis or myeloma-associated amyloidosis, and AA, secondary or reactive amyloid. Organ dysfunction occurs as a result of the presence of amyloid fibrils, disruption to the architecture and function of the organ, and the presence of cytotoxicity. The disease is categorized as primary (etiology unknown) or secondary. Primary disease has no local disorder and may affect the nerves, skin, tongue, joints, heart, and liver. Secondary amyloidosis demonstrates a local inflammation and affects the spleen, kidneys, liver, and adrenal glands. The disease is generally progressive and fatal. Patients may present with nephrotic renal insufficiency, congestive heart failure, or peripheral neuropathy. 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. The NIH does not discuss PP as a treatment option for amyloidosis (Shaz, et al, 2007; NIH, Feb 2007; Muller, et al., 2006; December, 2006; Brunt, et al., 2005; Drew, 2002).

Shaz et al. (2007) review of the literature revealed small case series and case reports regarding the use of PP for the treatment of amyloidosis. PP was used in two patients as an adjunct to dialysis. No scientific data exists that supports the use of PP for this condition.

**Amyotrophic Lateral Sclerosis:** Amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, is a rapidly progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. The disease leads to deterioration and death of motor neurons. When the motor neurons die, the ability of the brain to initiate and control muscle movement is lost. The onset of symptoms is very subtle and often goes unnoticed. The earliest symptoms may include twitching, cramping, stiffness of muscles, muscle weakness affecting an arm or a leg, slurred speech, and/or difficulty chewing or swallowing. Patients in the later stages of the disease may become totally paralyzed and eventually die. Treatment is supportive in nature and may include supportive devices, pharmacotherapy, physical therapy, and occupational therapy. In the late 1970s and early 1980s small trials (n=3-7) were 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. The NINDS does not discuss PP as a treatment option (Shaz, et al., 2007; NIH, Jun 2007; ALS Association, 2004; Flaum, et al., 1979).

**Autoimmune Hemolytic Anemia (AIHA) (Warm Autoimmune Hemolytic Anemia; Cold Agglutinin Disease):** AIHA is a group of disorders in which autoantibodies mediate either intravascular red cell destruction by the terminal lytic complex or by extravascular destruction in the spleen by the macrophage-phagocytic system. Autoimmune hemolytic anemia is caused by autoantibodies that react with RBCs at temperatures  $\geq 37$  degrees Celsius (C) (warm antibody hemolytic anemia) or  $< 37$  degrees C (cold agglutinin disease). Warm autoantibodies consist of IgG hemolysins directed primarily against the red cell Rh

antigens. Cold agglutinin disease (CAD) consists of IgM autoantibodies directed against red cell antigens. Treatment depends upon the type of anemia and may include prednisone, splenectomy, IVIG, and immunomodulatory agents. Autoantibody removal by PP has been proposed for severe cases. The National Heart, Lung and Blood Institute (NHLBI) includes plasmapheresis as a treatment modality for AIHA (Szczepiorkowski, 2007; NHLBI; Merck, 2005).

**Catastrophic Antiphospholipid Syndrome (CAPS):** CAPS is a condition in which there is acute onset of multiple thromboses in three or more organs, systems and/or tissue (e.g., kidneys, lungs, brain, heart and skin) with evidence of antiphospholipid antibodies. The syndrome can be accompanied by multiple organ failure, respiratory distress, pulmonary embolism, purpura, cerebral infarct and occlusion, and systemic inflammatory response syndrome. It may also be associated with the presence of systemic lupus. Therapy focuses on treating the underlying cause, preventing and controlling thrombosis, and suppression of excessive cytokine production. The most commonly employed therapies include anticoagulation, corticosteroids, PP and IVIG. PP has been proposed for removal of antiphospholipid antibodies, cytokines, and tumor necrosis factor alpha (Szczepiorkowski, 2007; Rare Thrombotic Disease Consortium).

**Coagulation Factor Inhibitors (CFI):** Blood coagulation factor inhibitors interfere with the normal clotting mechanism of the blood, can be a congenital or an acquired condition, and patients can develop inhibitors, alloantibodies to the inhibitor factors. This condition is seen in patients with hemophilia and von Willebrand's disease. CFI can be associated with an autoimmune disease, infection and malignancy. Treatment depends upon 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. It has been proposed that PP may be useful in the removal of inhibitors (Szczepiorkowski, 2007).

**Dermatomyositis and Polymyositis:** Dermatomyositis and polymyositis (idiopathic inflammatory myositis) are the major inflammatory myopathies believed to develop in response to an immune system disturbance. In these conditions, voluntary muscles undergo degenerative changes leading to muscle weakness and wasting. Weakness begins in the large muscles, and excessive fatigue is noticed. The cardinal symptom of dermatomyositis is a patchy, bluish-purple or red rash that precedes and/or accompanies the muscle weakness. The rash appears on eyelids, face, neck, shoulders, chest, back, knuckles, elbows, heels and toes, and may be accompanied by swelling. Calcium deposits develop under the skin or in the muscle. Dermatomyositis may be associated with collagen, vascular or autoimmune diseases, such as lupus. The disease is not curable. Polymyositis slowly progresses and is hard to distinguish from muscular dystrophy. Treatment includes immunosuppressive agents, corticosteroids, heat, exercise, physical therapy, and assistive devices (Shaz, et al., 2007; NIH, 2007; Muscular Dystrophy Association [MDA], 2005; Choy, 2002).

Since idiopathic inflammatory myositis is associated with the production of autoantibodies, PP has been tried for the treatment of refractory cases. In a review article, Choy and Isenberg report that early studies by Dau (1981) (n=35) and Clark et al. (1988) (n=3) reported a benefit from the use of PP. The Dau study used PP in conjunction with cyclophosphamide or chlorambucil and prednisone, and the effects of PP could not be disassociated from the use of the immunosuppressant drugs (Shaz, et al., 2007). A randomized controlled trial by Miller et al. (1992) included 39 patients with polymyositis or dermatomyositis who were treated with PP, leukapheresis or sham therapy. There were no significant differences in the outcomes of all three groups. PP was no more effective than sham.

The MDA states that PP is not well-established for the treatment of dermatomyositis and polymyositis. (MDA, 2005).

**Focal Segmental Glomerulosclerosis (FSGS):** FSGS refers to scarring in one part of the glomerulus and a minority of the glomeruli and may be idiopathic or result from a system disorder. It can be primary or secondary to obesity, reflux nephropathy, HIV or heroin use. The most common symptom is proteinuria. No universal treatment regimen has been identified. Steroids, immunosuppressants, angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) may be prescribed. The goal of treatment is to control blood pressure, blood cholesterol level and factors that may cause kidney scarring. Fifty percent of these patients may progress to the need for a kidney transplantation. PP has been proposed for treatment of patients with FSGS prior to or following kidney

transplantation to save the graft. NIH does not discuss PP as a treatment option (Szczepiorkowski, 2007; National Kidney and Urologic Diseases [NKUDIC]; Apr 2006; NKUDIC, 2005)

**Heart Transplant Rejection:** The most common form of heart transplant rejection is cellular rejection mediated by T cells. Humoral rejection occurs less frequently but is accompanied by increased graft loss, mortality and vasculopathy. Mainstream therapy for rejection includes cyclosporine, mycophenolate mofetil and corticosteroids. Extracorporeal photopheresis (ECP) may be used to treat cellular rejection and allograft vasculopathy. Some propose that PP may be used to treat acute humoral rejection in an attempt to remove antibodies and/or inflammatory mediators (Szczepiorkowski, 2007).

**Hematopoietic Stem Cell Disorders (Aplastic Anemia; Pure Red Cell Aplasia):** Hematopoietic stem cells (HSCs) are the cells that form blood and immune cells. HSCs are isolated from blood and bone marrow, can renew themselves, differentiate to a variety of specialized cells, mobilize out of the bone marrow into circulating blood, and undergo programmed cell death (i.e., apoptosis—a process by which cells that are detrimental or unneeded self-destruct). They are responsible for the constant renewal of billions of new blood cells that occur on a daily basis. Aplastic anemia (AA) and pure red cell aplasia (PRCA) are two forms of hematopoietic stem cell disorders. AA exists in the presence of marked pancytopenia in the peripheral blood and hypocellular bone marrow in the absence of clonal hemtopoiesis, abnormal cellular infiltration of increased reticulin fibrosis. PRCA is characterized by normochromic normocytic anemia, reticulopenia and absence of marrow erythroblasts with normal platelet and leukocyte counts. The disease may be primary (idiopathic) or secondary, acquired or inherited. PRCA may be seen in patients with chronic infection and lysis of erythroid progenitors such as seen in AIDS patients, and may occur after a major ABO mismatched hemtopoietic progenitor cell transplant. Treatment depends upon the etiology of the disease (e.g., malignancy, infection), and may include administration of IVIG, immunosuppressant therapy, surgical resection, or transplantation. PP has been proposed for removal of serum antibodies and/or by inhibitory activity (Szczepiorkowski, et al., 2007;NIH, 2006).

**Hypertriglyceridemic Pancreatitis;** Elevations in lipoproteins responsible for triglyceride transport are responsible for the development of hypertriglyceridemic (HTG) pancreatitis. Primary etiology is genetic mutation, and secondary causes include diabetes mellitus, hypothyroidism, pregnancy, and medication usage. 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. Proponents of PP hypothesize that it may be indicated for the reduction of triglyceride levels (Szczepiorkowski, et al., 2007).

**Idiopathic Thrombocytopenic Purpura (ITP):** Idiopathic thrombocytopenia purpura (ITP) is an autoimmune disease that occurs when the lymphocytes produce antibodies against platelets. The etiology of this disease is unknown. There are two types of ITP, acute and chronic. Acute generally lasts about six months, mainly occurs in children, across both genders, and is the most common form of ITP. Acute ITP may spontaneously resolve without the need for treatment. Chronic ITP lasts longer than six months and usually affects adults, although it has been found in teenagers. Women of childbearing age are affected 2–3 times more than men. Initial treatment may include the use of corticosteroids, intravenous immunoglobulin (IVIG) and anti-(Rh) D immunoglobulin. Other treatments may include platelet transfusions, stopping medications that can cause bleeding (e.g., aspirin, ibuprofen, anti-coagulants) and ECI. Some patients may require a splenectomy to control the effects of ITP (NIH, Jul 29, 2005).

The ASAF states 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 ITP, but responses were transient. Studies were small (n=5–12) and reported no differences in patients treated with PP (Shaz, et al., 2007),

The Canadian Apheresis Group states that “there is no significant data to support the use of PE for ITP.” The National Heart, Lung and Blood Institute (NHLBI) does not discuss PP as a treatment option for ITP (NHLBI, 2006). Practice guidelines by the American Society of Hematology (ASH) do not include PP as a treatment modality for patients with ITP (George, et al. 1996).

**Inclusion Body Myositis:** Inclusion body myositis (IBM) is an inflammatory myopathy characterized by chronic muscle inflammation and muscle weakness. The onset is gradual and affects proximal and distal muscles and may be unilateral. Symptoms begin in the finger and wrist muscles and progress to the forearm and quadriceps. Difficulty swallowing may develop along with muscle atrophy. There is no standard treatment or cure for the disease. Physical therapy and supportive care are helpful. IVIG may produce short-term effects. Corticosteroids and immunosuppressive drugs are generally ineffective. NINDS does not discuss PP as a treatment option for this condition (NINDS, May2007).

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 ITP 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 Sclerosis (MS):** MS is a demyelinating disease of the central nervous system that follows a variable course. The cause of MS is unknown, although the pathogenesis of the disease is thought to result from an autoimmune process with both humoral and cellular components. The humoral response is thought to produce autoantibodies directed against protein targets in the patient's own myelin. Cellular response appears to be activated through the auto-reactive T-lymphocytes that release immune-regulating cytokines. Manifestations may include paresthesias, transitory abnormal sensory feelings such as numbness, prickling, or "pins and needles" sensations, speech impediments, tremors, and dizziness. Some individuals may experience pain and occasionally there may be hearing loss. Approximately half of all individuals with MS experience cognitive impairments such as difficulties with concentration, attention, memory, and poor judgment. Although a variety of treatments, including pharmacologic therapy, are used in an attempt to control the disease, there is presently no cure (NINDS, Jan 4, 2006). PP is not recommended for the treatment of relapsing/remitting and progressive MS (Szczepiorkowski, et al., 2007; Smith, et al., 2003).

In the clinical guideline "Disease Modifying Therapies in Multiple Sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines," AAN states, "On the basis of consistent Class I, II, and III studies, plasma exchange is of little or no value in the treatment of progressive MS" (Goodin, et al., 2002).

**Overdose and Poisoning (Compounds Other than Mushroom Poisoning):** Excessive exposure to drugs and poisoning by ingestion, inhalation or injection can lead to tissue injury and/or organ dysfunction. Unfortunately, many incidents are accidental and involve children. Damage may result at the site of entry and may lead to systemic effects, causing toxicity and metabolic injury. Initial treatment focuses on supportive care and removal of the toxic agent by antidotes, lavage, induced vomiting and other methods of toxic desensitization. Whole-bowel irrigation, ECP, and/or 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 (Szczepiorkowski, et al., 2007).

**Paraneoplastic Neurologic Syndromes:** Paraneoplastic syndromes are a group of rare degenerative disorders triggered by a person's immune system in response to a neoplasm or cancerous tumor. Paraneoplastic neurologic syndromes are proposed to occur as the result of cancer-fighting antibodies or white blood cells (i.e., T cells) attacking normal cells in the nervous system. These disorders are most commonly associated with lung, ovarian, lymphatic, or breast cancer. Syndromes are classified according to the involved area of the central nervous system. The neurologic syndromes include paraneoplastic cerebellar degeneration (PCD), paraneoplastic encephalomyelitis (PEM), paraneoplastic opsoclonus/myoclonus (POM), paraneoplastic stiff-person syndrome, and cancer-associated retinopathy (CAR). Neurologic symptoms typically occur prior to the diagnosis of cancer in 50% of cases. Symptoms may include: difficulty walking, dysphagia, loss of muscle tone and fine motor coordination, slurred speech, memory loss, vision and sleep disturbances, dementia, seizures, sensory loss in the limbs, and vertigo. Therapy is focused on treatment of the underlying cancer and decreasing the autoimmune response by administration of steroids, IVIG or irradiation. The use of PP is proposed for the removal of antibodies (Szczepiorkowski, et al., 2007; NINDS, Feb 2007).

**Pemphigus Vulgaris (PV):** Pemphigus is a group of autoimmune skin diseases, of which PV is the most common. Antibodies produce a reaction that leads to blistering of the outer layer of the skin and mucous membranes. Blisters usually develop first in the mouth and then progress to the scalp, face and trunk. The blisters are relatively asymptomatic, but the lesions become widespread and complications develop rapidly and may be debilitating or fatal. Although it may be seen in children and the elderly, the mean age of onset is between ages 40 and 60. PV is also more common in persons of Jewish and Mediterranean descent. Researchers hypothesize that circulating IgG autoantibodies are the cause of PV. Sometimes PV appears in reaction to medications, although this is rare. Treatment includes the use of corticosteroids and immunosuppressive medications. In severe cases, PP has been proposed for the reduction of autoantibodies in the bloodstream (Szczepiorkowski, et al., 2007; Bickle, et al., 2002; NIH, July 2, 2004).

In guidelines for the management of pemphigus vulgaris, Harman et al. (2003) state, “plasma exchange cannot be recommended as a routine treatment option in newly presenting patients with PV.” Although the evidence is poor, they suggest that PP “could be considered in difficult cases if combined with systemic corticosteroids (CS) and immunosuppressant drugs.”

**Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS):** POEMS is a multisystem paraneoplastic syndrome associated with an underlying plasma proliferative disorder, and diagnosis is made when patients have three of the five features. POEMS is associated with a bilateral polyneuropathy involving motor and sensory nerves, distally and proximally. Demyelination and axonal degeneration occur. The major clinical feature is chronic progressive polyneuropathy with a precominant motor disability. Enlargement of the lymph nodes and spleen are consistent with Castleman disease. Multiple endocrinopathies (e.g., diabetes mellitus, hypothyroidism, hyperprolactinemia and hypoparathyroidism) are associated with the disease. 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. IVIG and PP do not produce clinical benefits (NINDS, 2006; Chan, 2006; Dispenzieri, 2005).

TPE was initially used as a treatment for POEMS because it was diagnosed as CIDP or MGUS. The number of scientific studies are limited and include small patient populations (n=1–30). There was no reported difference in the outcomes with the use of PP and corticosteroids compared to steroid therapy alone. PP is considered ineffective for this condition (Shaz, et al., 2007).

**Psoriasis:** Psoriasis is a chronic skin condition in which plaques and papules form as a result of hyperproliferation and abnormal differentiation of the epidermis. The patient experiences dry, itch, scaly red skin. The elbows and knees are the most commonly affected areas, but psoriasis may appear on other areas of the body as well. Treatment options include: topical steroids, methotrexates, cyclosporin, ultraviolet light therapy, and/or injectable biological agents. Small studies have been conducted to determine if patients would benefit from PP as a treatment modality for psoriasis. The studies concluded that PP offers no benefit as a treatment for this disease (Shaz, et al., 2007; American Academy of Dermatology [AAD]; AAFP, 2006).

**Rheumatoid Arthritis (RA):** RA is a chronic inflammatory autoimmune disorder of unknown cause that can affect most joints. It is characterized by symmetrical erosive synovitis that can progress to joint destruction and significant disability. Although joints are the principal body parts affected by RA, inflammation can develop in other organs as well. The clinical features of the disease include: symmetrical joint swelling and tenderness commonly involving the hands, wrists and feet; morning stiffness lasting an hour or longer; subcutaneous nodules; and fever. The goals of treatment are to minimize symptoms and disability, reduce inflammation, protection of articular surfaces, control systemic involvement, and healing of bone erosion. 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 (Shaz, et al., 2007; Seror, 2007; Szczepiorkowski, et al., 2007; American College of Rheumatology, 2004; 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 small 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.

The American College of Rheumatology (ACR) has issued a guideline on the management of RA which includes a multidisciplinary approach. They do not discuss the use of PP for the treatment of RA in the guideline (ACR, 2002).

**Schizophrenia:** Schizophrenia is a chronic, disabling psychiatric disorder characterized by acute and chronic psychosis and deterioration in function. Persons with schizophrenia may have a flat or markedly inappropriate affect, auditory hallucinations, disorganization of thought and/or delusions. People with this disorder can become agitated and difficult to manage, particularly during periods of acute exacerbation of psychosis. As a result of deteriorated function, some individuals may not be able to function independently or care for themselves. The mainstay of treatment for schizophrenia 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 ASFA states PP offers no benefit in the treatment of schizophrenia (Shaz, et al., 2007; NIMH, 2007).

**Scleroderma (Progressive Systemic Sclerosis):** Scleroderma is a chronic multisystem disorder of unknown etiology. It is characterized by an accumulation of connective tissue and involvement of the gastrointestinal tract, lungs, heart and kidney. Microvascular abnormalities are present, and Raynaud's phenomenon is an initial symptom of scleroderma. Patients with limited cutaneous scleroderma present with calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and teleangiectasia (CREST). Scleroderma is not curable, and treatment is aimed at relieving symptoms and improving function. D-Penicillamine, corticosteroids, immunosuppressants, and other pharmacotherapy 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 (Szczepiorkowski, et al., 2007; National Institute of Arthritis and Musculoskeletal and Skin Diseases [NIAMS] Jun 2006).

**Sepsis:** Sepsis is a systematic inflammatory response to infection and a common cause of death. Symptoms include fever, tachycardia, hyperventilation, leukocytosis or leucopenia. If the condition progresses organ dysfunction and hypotension can develop. 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 (Szczepiorkowski, et al., 2007).

**Stiff-Person Syndrome:** Stiff-person syndrome is a chronic disorder with features of an autoimmune disease involving painful muscle spasms and rigidity. It is associated with autoimmune endocrinopathies such as Graves' disease and diabetes mellitus. Diazepam is administered to decrease rigidity and spasms. Anti-convulsants and IVIG may also be used to relieve symptoms. PP has been proposed as an adjunct to pharmacotherapy in patients who are refractory to other therapies and to IVIG, but the data from clinical trials is limited to case reports, with conflicting results (Szczepiorkowski, et al., 2007; NINDS, Feb 2007).

**Systemic Lupus Erythematosus (SLE):** SLE is a chronic inflammatory disease leading to cell and tissue injury. Circulating autoantibodies, immune complexes and complement deposition can affect any organ. Lupus nephritis (LN) occurs when complexes of these antibodies accumulate in the kidneys and result in an inflammatory response. LN is the major cause of renal failure and mortality. At present, there is no cure for SLE; however, symptoms can be controlled with appropriate therapy in most patients. Corticosteroids or other immunosuppressive medications are often effective in reducing symptoms. PP is proposed under the theory that a reduction in autoantibody concentration would slow the rate of progression of the disease. PP should not be used to treat SLE with nephritis because it has not been shown to be beneficial (Szczepiorkowski, et al., 2007; Smith, et al., 2003).

The AAN considers the use of PP for central nervous system SLE investigational based on Class III evidence (i.e., evidence provided by expert opinion, nonrandomized historical controls, or case reports) (AAN, 1996).

Hayes (1999) conducted several reviews of the literature (from 1993 to September 2004) on PP for renal conditions and concluded that “When used concomitantly with standard drug therapy in nonrandomized trials, plasmapheresis provided no additional benefit in patients with lupus nephritis.”

**Thyrotoxicosis:** Thyrotoxicosis develops from an excess of thyroid hormone from hyperthyroidism, inflammation of the thyroid gland, ingestion of excess iodine, medication, Graves’ disease, toxic multinodular goiter or toxic adenomas. Patients can experience a thyroid crisis, and decompensation of one or more organ systems may occur as exhibited by weakness, tachycardia, palpitations, sweating, increased appetite, fatigue, restlessness, heat intolerance and tremors. Treatment depends upon the underlying cause and related symptoms. Antithyroid medications, radioactive iodine, beta-blockers and/or thyroidectomy are included in the treatment regimen. In theory, PP was proposed to decrease the amount of T<sub>3</sub> and T<sub>4</sub> bound to plasma proteins or to decrease the level of a drug in the system, but results of clinical trials are conflicting and provide limited data (Szczepiorkowski, et al., 2007; NIH, Aug 2006).

**Other Indications:**

The AAN considers the use of PP investigational for the following conditions: acquired neuromyotonia, stiff-man syndrome, central nervous system systemic lupus, acute disseminated encephalomyelitis, ALS, and paraneoplastic neurologic syndromes with circulating antibodies (ANA, 1996).

In a review of the literature, Hayes concluded that the peer-reviewed, scientific literature is not sufficient to support the safety and efficacy of treatment with PP for the following conditions: central pontine myelinolysis, severe late left ventricular failure, cardiac transplantation, post-transplant cardiomyopathy, advanced HIV infection, Raynaud’s phenomenon, and sepsis syndrome (Hayes, 2001; updated 2005).

**Summary**

Plasmapheresis (PP), or plasma exchange (PE), is a therapeutic process in which blood is withdrawn from the body, filtered through a cell separator to remove plasma from the blood, and returned to the body with a plasma substitute. The intent of the process is to remove toxins or harmful elements from the blood and improve the patient’s condition.

PP has been proposed for the treatment of multiple conditions. Its use for some conditions is uniformly supported by the National Institutes of Health (NIH), American Academy of Neurology (AAN), the American Association of Blood Banks (AABB) and the American Society for Apheresis (ASAF), and it may be used as a primary or adjunctive therapy in appropriate diseases. For other conditions, PP has not been demonstrated by clinical trials published in the peer-reviewed literature to be a beneficial treatment modality.

**Coding/Billing Information**

**Note:** This list of codes may not be all-inclusive.

**When medically necessary:**

CPT®*	Description
36514	Therapeutic apheresis for plasmapheresis

HCPCS Codes	Description
	No specific codes

ICD-9-CM Diagnosis Codes	Description
273.1	Monoclonal paraproteinemia

273.2	Other paraproteinemias
273.3	Macroglobulinemia (Waldentrom's macroglobulinemia)
283.11	Hemolytic-uremic syndrome
287.4	Secondary Thrombocytopenia (posttransfusion purpura)
323.81	Other causes of encephalitis and encephalomyelitis
356.3	Refsum's disease
357.0	Acute infective polyneuritis (Guillain-Barre' syndrome)
357.81	Chronic inflammatory demyelinating polyneuritis
358.00	Myasthenia gravis without (acute) exacerbation
358.01	Myasthenia gravis with (acute) exacerbation
358.1	Myasthenic syndromes in diseases classified elsewhere
446.21	Goodpasture's syndrome
446.4	Wegener's granulomatosis
446.6	Thrombotic microangiopathy (thrombotic thrombocytopenic purpura)
580.4	Acute glomerulonephritis with lesion of rapidly progressive glomerulonephritis
582.4	Chronic glomerulonephritis with lesion of rapidly progressive glomerulonephritis
583.4	Nephritis and nephropathy, not specified as acute or chronic, with lesion of rapidly progressive glomerulonephritis
996.81	Complications of transplanted kidney

**Experimental/Investigational/Unproven/Not medically necessary:**

ICD-9-CM Diagnosis Codes	Description
	Multiple/varied

**\*Current Procedural Terminology (CPT®) © 2006 American Medical Association: Chicago, IL.**

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