



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject Plasmapheresis

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INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA covers plasmapheresis as a medically necessary primary therapy for ANY of the following indications:

- acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome) when EITHER of the following is present:
 - severity grade 3–5 within four weeks of onset
 - severity grade 1–2 within two weeks of onset
- anti-glomerular basement membrane disease (Goodpasture's syndrome) for EITHER of the following:
 - individual is dialysis independent
 - individual has diffuse alveolar hemorrhage (DAH)

- chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- cryoglobulinemia
- recurrent focal segmental glomerulosclerosis
- hyperviscosity syndrome in monoclonal gammopathies (e.g., Waldenström's macroglobulinemia, multiple myeloma)
- myasthenia gravis in preparation for surgery OR with respiratory crisis
- paraproteinemic polyneuropathy associated with immunoglobulin G (IgG), immunoglobulin A (IgA) or immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance (e.g., MGUS)
- pediatric postinfectious autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and Sydenham's chorea (severe exacerbation)
- thrombotic microangiopathy (TMA) secondary to ticlopidine or clopidogrel
- thrombotic thrombocytopenic purpura (TTP)
- Wilson's disease presenting as fulminant hepatic failure with hemolysis

CIGNA covers plasmapheresis as a medically necessary adjunctive secondary therapy for the following conditions when the individual 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
- acquired pure red cell aplasia
- acute central nervous system inflammatory demyelinating disease
- acute disseminated encephalomyelitis (ADEM)
- anti-neutrophil cytoplasmic antibodies (ANCA)-associated rapidly progressive glomerulonephritis (RPGN) (e.g., Wegener's) for EITHER of the following:
 - individual is dialysis dependent
 - individual has diffuse alveolar hemorrhage (DAH)
- catastrophic antiphospholipid syndrome (CAPS)
- cold agglutinin disease (CAD), life-threatening
- hemolytic uremic syndrome (HUS), atypical
- kidney transplantation and EITHER of the following:
 - antibody mediated rejection (AMR)
 - elevated human leukocyte antigens (HLA)
- Lambert-Eaton myasthenic syndrome (LEMS)
- mushroom poisoning
- myeloma associated with acute renal failure (myeloma cast nephropathy)
- neuromyelitis optica (NMO; Devic's disease)
- phytanic acid storage disease (Refsum's disease)
- post-transfusion purpura
- Rasmussen's encephalitis (chronic focal encephalitis)
- red cell alloimmunization in pregnancy
- systemic lupus erythematosus, severe without nephritis

CIGNA does not cover plasmapheresis for ANY other indication, including, but not limited to the following, because it is considered experimental, investigational or unproven:

- ABO incompatible solid organ transplantation – liver
- acute liver failure
- amyloidosis, systemic
- amyotrophic lateral sclerosis
- aplastic anemia
- burn shock resuscitation
- cardiac allograft rejection
- coagulation factor inhibitors
- dermatomyositis or polymyositis

- dilated cardiomyopathy (DCM)
- hypertriglyceridemic pancreatitis
- idiopathic thrombocytopenic purpura (ITP)
- immune complex rapidly progressive glomerulonephritis (RPGN)
- inclusion body Myositis
- lupus nephritis
- multiple myeloma with polyneuropathy
- multiple sclerosis
- nephrogenic systemic fibrosis (NSF)
- overdose, venoms, and poisoning (compounds other than mushroom poisoning)
- paraneoplastic neurologic syndromes
- pemphigus vulgaris
- polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS)
- psoriasis
- rheumatoid arthritis
- rheumatoid vasculitis
- schizophrenia
- scleroderma (progressive systemic sclerosis)
- sepsis
- stiff-person syndrome
- thrombotic microangiopathy (TMA), drug- associated (except for ticlopidine or clopidogrel) or hematopoietic stem cell transplant-associated
- thyroid storm
- warm autoimmune hemolytic anemia (WAIHA)

General Background

Plasmapheresis (PP), apheresis, 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 10 treatments over a two- to ten-week period) depends upon the patient's condition and underlying disease.

Plasmapheresis is a recognized treatment modality for multiple conditions. The American Society for Apheresis (ASFA) (Szczepiorkowski, et al., 2010) 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. [Example: plasma exchange in Guillain-Barre´ syndrome as first-line standalone therapy; plasma exchange in myasthenia gravis as first-line in conjunction with immunosuppression and cholinesterase inhibition]"
- 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. [Example: plasma exchange as standalone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease]"
- Category III - "Optimum role of apheresis therapy is not established. Decision making should be individualized. [Example: extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multiorgan failure]"

- Category IV – “Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances. [Example: plasma exchange for active rheumatoid arthritis]”.

Category I Indications

The evidence in the published peer-reviewed literature and professional societies support the safety and effectiveness of PP as an established and acceptable primary treatment option for the following conditions:

- acute inflammatory demyelinating polyneuropathy (Guillain-Barré Syndrome) during the first two weeks of onset in patients with minor symptoms (grade 1) or patients that are able to walk without support (grade 2). PP may also be used within the first four weeks of onset if the patient is able to walk with the assistance of a cane, appliance or support (grade 3), is confined to bed or chair-bound (grade 4), or requires assisted ventilation (grade 5).
- anti-glomerular basement membrane disease (Anti-GBM) (Goodpasture’s syndrome) in dialysis independent patients or when diffuse alveolar hemorrhage (DAH) is present
- chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- cryoglobulinemia
- recurrent focal segmental glomerulosclerosis
- hyperviscosity syndrome in monoclonal gammopathies (e.g., Waldenström’s macroglobulinemia, multiple myeloma)
- myasthenia gravis in preparation for surgery or with respiratory crisis
- paraproteinemic polyneuropathy associated with immunoglobulin G (IgG), immunoglobulin A (IgA) or immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance (e.g., MGUS)
- pediatric postinfectious autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and severe exacerbation of Sydenham’s chorea
- thrombotic microangiopathy (TMA) secondary to ticlopidine or clopidogrel
- thrombotic thrombocytopenic purpura (TTP)
- Wilson’s disease presenting as fulminant hepatic failure with hemolysis

Category II Indications

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

ABO Incompatible Hematopoietic Progenitor Cell (HPC) Transplantation: 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 (Szczepiorkowski, et al., 2010).

ABO Incompatible Transplantation – Kidney and Infant Heart: Typically, ABO incompatibility is treated with enhanced immunosuppression and intravenous immune globulin (IVIG). 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., 2010; Kaufman, 2005; Reid, et al., 2005; Smith, et al., 2003).

Acquired Pure Red Cell Aplasia (PRCA): 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 (Szczepiorkowski, et al., 2010).

Acute Central Nervous System (CNS) Inflammatory Demyelinating Disease: Acute attacks of inflammatory demyelinating disease 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 (Szczepiorkowski, et al., 2010; Pike and Noseworthy, 2003; Weinshenker, 2001).

Acute Disseminated Encephalomyelitis (ADEM): ADEM is an acute inflammatory monophasic demyelinating neurologic disease causing inflammation of the brain and spinal cord. The standard therapy is corticosteroids and IVIG. PP has been proposed for the removal of offending antibodies, but there is insufficient evidence to support the efficacy of PP for the treatment of ADEM (Szczepiorkowski, et al., 2010; Rust, 2009; National Institute of Neurological Disorders and Stroke [NINDS], 2010).

Anti-neutrophil cytoplasmic antibodies (ANCA)-Associated Rapidly Progressive Glomerulonephritis (RPGN) (e.g., Wegener's): ANCA-associated RPGN is one form of RPGN that involves minimal immune deposits in the kidney, anti-neutrophil antibodies in the serum, and can lead to rapid loss of renal function. The management of ANCA-associated RPGN includes corticosteroids, cytotoxic immunosuppressive drugs and other pharmacotherapy. PP may be used as an adjunctive treatment modality for a subgroup of patients with life-threatening situations when there is severe small and medium vessel vasculitis of the kidney. Results of clinical trials indicated that PP was most beneficial in patients who were on dialysis and/or had diffuse alveolar hemorrhage (Szczepiorkowski, et al., 2010).

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. Therapy focuses on treating the underlying cause, preventing and controlling thrombosis, and suppression of excessive cytokine production. PP is used to remove antiphospholipid antibodies, cytokines, and tumor necrosis factor alpha (Szczepiorkowski, 2010).

Cold Agglutinin Disease [CAD], Life-Threatening: 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 life-threatening cases involving fulminate hemolysis, PP is used in combination with immunosuppressive therapy to remove/reduce circulating autoantibodies (Szczepiorkowski, et al., 2010; Berentsen, et al., 2007).

Hemolytic Uremic Syndrome, Atypical (aHUS): The 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. In the presence of renal failure, extracorporeal immunoadsorption therapy may be used as an adjunctive therapy. 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 (Szczepiorkowski, et al., 2010; McCrae, 2005; Kaplan, 2004).

Kidney Transplantation and Antibody Mediated Rejection [AMR] or Elevated Human Leukocyte Antigens [HLA] Desensitization): Desensitization using immunosuppressant therapy and/or intravenous immune globulin (IVIG) may be the initial treatment options for rejection. PP with low dose IVIG prior to transplantation may be performed to allow these patients to accept a donor kidney that would otherwise be avoided. When used PP is typically continued following transplantation (Szczepiorkowski, et al., 2010).

Lambert-Eaton Myasthenic Syndrome (LEMS): 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 (Szczepiorkowski, et al., 2010; NIH, Sep 2008; Smith, et al., 2003).

Mushroom Poisoning: 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 (Szczepiorkowski, et al., 2010; FDA, 2009; Merck, 2007).

Myeloma Associated with Acute Renal Failure (Myeloma Cast Nephropathy): Therapy for this condition may include anti-myeloma chemotherapy, diuresis, dialysis, autologous bone marrow transplant, immune

modulation and proteasome inhibition. The American Society for Apheresis (ASAF) (2010) 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 (Szczepiorkowski, et al., 2010; Smith, et al., 2003).

Neuromyelitis Optica (NMO) (Devic’s Disease): NMO 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.

Phytanic Acid Storage Disease (Refsum’s Disease): 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 (Szczepiorkowski, et al., 2010; National Institute of Neurological Disorders and Stroke [NINDS], 2007a; NINDS, 2007b; Rowland, 2005).

Post-Transfusion Purpura: First-line treatment for post-transfusion purpura typically includes intravenous immune globulin (IVIG) and steroids. PP is a proposed option 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., 2010; Wu and Snyder, 2005; Smith, et al., 2003).

Rasmussen’s Encephalitis (Chronic Focal Encephalitis): Primary treatment of Rasmussen’s encephalitis includes the use of anti-epileptic drugs, corticosteroids, IVIG, 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 (Szczepiorkowski, et al., 2010; National Institute of Neurological Disorders and Stroke [NINDS], Feb 2008).

Red Cell Alloimmunization in Pregnancy: Management of red 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. PP of the mother removes the maternal red cell alloantibody, reduces the maternal antibody titer, and protects the fetus from hemolytic disease (Szczepiorkowski, et al., 2010; Ruma, et al., 2007).

Systemic Lupus Erythematosus (SLE), Severe without Nephritis: 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 (Szczepiorkowski, et al., 2010; Smith, et al., 2003).

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 (Szczepiorkowski, et al., 2010; Shaz, et al., 2007).

ABO Incompatible Solid Organ Transplantation – Liver (III): 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, intravenous immune globulin (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 efficacy of PP for liver transplantation rejection (Szczepiorkowski, et al., 2010; National Institute of Diabetes and Digestive and Kidney Disease [NIDDK], 2010).

Acute Liver Failure (ALF) (III): 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's 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 (Szczepiorkowski, 2010; O'Grady, 2005).

Amyloidosis, Systemic (IV): 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 (Shaz, et al, 2007; Muller, et al., 2006; Brunt, et al., 2004; Drew, 2002).

Amyotrophic Lateral Sclerosis (ALS) (IV): 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 (Szczepiorkowski, et al., 2010; NINDS, 2010; Shaz, et al., 2007).

Aplastic Anemia (III): 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 intravenous immune globulin (IVIG), 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 (Szczepiorkowski, et al., 2010).

Burn Shock Resuscitation (IV): 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 (Szczepiorkowski, et al., 2010; 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 Allograft Rejection (III): 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 (allograft vasculopathy). ACR is the most common form of rejection and is mediated by T cells. Maintenance immunosuppression therapy includes calcineurin-inhibitor (cyclosporine or tacrolimus), antiproliferative agent (mycophenolate mofetil or azathioprine) and corticosteroids. 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 (Szczepiorkowski, 2010).

Coagulation Factor Inhibitors (CFI) (III): Blood coagulation factor inhibitors interfere with the normal clotting mechanism of the blood as seen in conditions such as hemophilia. 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. 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 (Szczepiorkowski, 2010).

Dermatomyositis and Polymyositis (IV): Dermatomyositis and polymyositis (idiopathic inflammatory myositis) are the major inflammatory myopathies believed to develop in response to an immune system disturbance. Treatment includes immunosuppressive agents, corticosteroids, heat, exercise, physical therapy, and assistive devices (Szczepiorkowski, et al., 2010; NINDS, 2010; Iorizzo and Jorizzo, 2008; Shaz, et al., 2007; Choy, 2005).

Studies have been primarily in the form of case series and retrospective reviews (n=3–35) and have reported mixed results or no improvement in outcomes in patients treated with PP. The American Society for Apheresis reported that “early anecdotal reports” in pediatric patients, as well as two retrospective large case series described improvement when PP was used in conjunction with oral immunosuppressives, but that a randomized sham-controlled trial (n=33) utilizing PP and leukocytapheresis reported no significant differences in outcomes between the three therapies (Shaz, et al., 2007).

Dilated Cardiomyopathy (DCM) (III): DCM involves cardiac enlargement with impaired ventricular systolic function and 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 (Szczepiorkowski, et al., 2010).

Hypertriglyceridemic Pancreatitis (III): 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. Proponents of PP hypothesize that it may be indicated for the reduction of triglyceride levels, but there is insufficient evidence supporting the efficacy of PP for this condition (Szczepiorkowski, et al., 2007).

Idiopathic Thrombocytopenic Purpura (ITP) (IV): ITP is an autoimmune disease that occurs when the lymphocytes produce antibodies against platelets. Initial treatment may include the use of corticosteroids, 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 extracorporeal immunoadsorption therapy. Some patients may require a splenectomy to control the effects of ITP (National Heart, Lung and Blood Institute, 2009).

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

Immune Complex Rapidly Progressive Glomerulonephritis (RPGN) (III): Immune complex RPGN is one type of RPGN which is treated with pharmacotherapy including high-dose corticosteroid (e.g., methylprednisolone) and cytotoxic immunosuppressive drug (e.g., cyclophosphamide or azathioprine). Studies investigating PP for the treatment of immune RPGN are lacking. Clinical trials that have included immune-complex RPGN and pauci-immune RPGN have shown no benefits of PP over pharmacotherapy. The role of PP in the treatment of this condition has not been established (Szczepiorkowski, et al., 2010).

Inclusion Body Myositis (IV): 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.

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 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.

Lupus Nephritis (IV): Lupus nephritis, inflammation of the kidney, is a complication of systemic lupus erythematosus and has a high mortality rate. Treatment includes immunosuppressants and dialysis. Studies evaluating PP for the treatment of lupus nephritis have reported no clinical benefit following therapy (Szczepiorkowski, et al., 2010).

Multiple Myeloma with Polyneuropathy (III): 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 (American Cancer Society, 2010; Szczepiorkowski, et al., 2010).

Multiple Sclerosis (MS) (III): 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 and progressive MS (NINDS, 2010; Szczepiorkowski, et al., 2010; Smith, et al., 2003).

In their 2008 guideline on current therapeutic recommendations for the treatment of MS, the Multiple Sclerosis Therapy Consensus Group states that the evidence on the efficacy of PP for the treatment of MS is still limited. PP cannot be recommended as a “permanent disease-modifying therapy strategy in MS patients”.

Nephrogenic Systemic Fibrosis (NSF) (III): NSF is a systemic disorder with acute or chronic renal failure that occurs following the administration of gadolinium (Gd) containing contrast agents, in hepatorenal syndrome, 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 (Szczepiorkowski, et al., 2010).

Overdose, Venoms, and Poisoning (Compounds Other than Mushroom Poisoning) (III): Excessive exposure to drugs and poisoning by ingestion, inhalation, injection, or snake bites can lead to tissue injury and/or organ dysfunction. Initial treatment focuses on supportive care and removal of the toxic agent by antidotes, lavage, induced 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 and poisoning by compounds other than mushroom poisoning (Szczepiorkowski, et al., 2010).

Paraneoplastic Neurologic Syndromes (III): 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, intravenous immune globulin (IVIG) 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 (Szczepiorkowski, et al., 2010; NINDS, Mar 2009).

Pemphigus Vulgaris (PV) (III): 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 (Szczepiorkowski, et al., 2010; Martin, et al., 2009; Bickle, et al., 2002).

In guidelines for the management of pemphigus vulgaris, the British Association of Dermatologists (Harman, et al., 2003) stated, “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) (IV): 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, 2009; Kuwabara, 2008; 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.

Psoriasis (IV): 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 (Szczepiorkowski, et al., 2010; Shaz, et al., 2007; American Academy of Dermatology [AAD], 2009).

Rheumatoid Arthritis (RA) (IV): 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 (Shaz, et al., 2007; Seror, 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 (NIH, 2010; Vasculitis Foundation, 2006). PP has been proposed as a treatment option for renal vasculitis, but its effectiveness remains unproven.

Schizophrenia (IV): 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 (Shaz, et al., 2007).

Scleroderma (Progressive Systemic Sclerosis) (III): Scleroderma is a chronic multisystem disorder characterized by an accumulation of connective tissue and involvement of the gastrointestinal tract, lungs, heart and kidney. 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., 2010; National Institute of Arthritis and Musculoskeletal and Skin Diseases [NIAMS], 2010).

Sepsis (III): 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 (Szczepiorkowski, et al., 2010).

Stiff-Person Syndrome (III): 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 and intravenous immune globulin (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., 2010; NINDS, 2009).

Thrombotic Microangiopathy (TMA) – Drug-Associated (Except for Ticlopidine or Clopidogrel) or Hematopoietic Stem Cell Transplant-Associated (III): Thrombotic microangiopathy (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 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 (Szczepiorkowski, et al., 2010).

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.

Thyroid Storm (III): 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. In theory, PP was proposed to decrease the amount of T₃ and T₄ 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., 2010).

Warm Autoimmune Hemolytic Anemia (WAIHA) (III): 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, immunosuppressive/immunomodulatory therapy, and in severe cases splenectomy. The role of PP in the treatment of WAIHA has not been established (Szczepiorkowski, et al., 2010).

Summary

Plasmapheresis (PP), or plasma exchange (PE), has been proposed for the treatment of multiple conditions. Its use for some conditions is uniformly supported by the evidence in the published peer-reviewed scientific literature and professional societies as a primary or adjunctive therapy in appropriate conditions.

Due to the limited number of studies, small patient populations, short-term follow-ups and lack of comparisons to established conventional therapies, PP has not been supported in the published peer-reviewed scientific literature to be a beneficial treatment modality in various other conditions.

Coding/Billing Information

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

Covered when medically necessary as the primary therapy for the following conditions:

CPT [®] * Codes	Description
36514	Therapeutic apheresis for plasmapheresis

ICD-9-CM Diagnosis	Description
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Codes	
273.1	Monoclonal paraproteinemia
273.2	Other paraproteinemias
273.3	Macroglobulinemia
275.1	Disorders of copper metabolism
357.0	Acute infective polyneuritis
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
392.0-392.9	Rheumatic chorea
446.21	Goodpasture's syndrome
446.6 [†]	Thrombotic microangiopathy
581.1	Nephrotic syndrome with lesion of membranous glomerulonephritis
580.4	Acute glomerulonephritis with lesion of rapidly progressive glomerulonephritis??
582.4	Chronic glomerulonephritis with lesion of rapidly progressive glomerulonephritis??
996.81	Complications of transplanted kidney

[†]**Note:** Coverage is limited to thrombotic microangiopathy (TMA) secondary to Ticlopidine or Clopidogral.

Covered when medically necessary as an adjunctive secondary therapy for the following conditions when the individual has failed to respond to conventional therapy:

ICD-9-CM Diagnosis Codes	Description
283.0 [†]	Autoimmune hemolytic anemias
283.11	Hemolytic-uremic syndrome
284.81	Red cell aplasia (acquired) (adult) (with thymoma)
284.89	Other specified aplastic anemias
287.4	Secondary Thrombocytopenia
323.61	Infectious acute disseminated encephalomyelitis (ADEM)
323.81	Other causes of encephalitis and encephalomyelitis
341.0	Neuromyelitis optica
356.3	Refsum's disease
357.89	Other inflammatory and toxic neuropathy
358.00	Myasthenia gravis without (acute) exacerbation
358.01	Myasthenia gravis with (acute) exacerbation
358.1	Myasthenic syndromes in diseases classified elsewhere
446.4	Wegener's granulomatosis
583.4	Nephritis and nephropathy, not specified as acute or chronic, with lesion of rapidly progressive glomerulonephritis
656.1	Rhesus isoimmunization
710.0	Systemic lupus erythematosus
988.1	Toxic effect of mushrooms
V42.0	Kidney replaced by transplant
V42.1	Heart replaced by transplant
V42.82	Peripheral stem cells replaced by transplant

[†]**Note:** Coverage is limited to life-threatening cold agglutinin disease (CAD).

Experimental/Investigational/Unproven/Not covered for any of the following indications:

ICD-9-CM	Description
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Diagnosis Codes	
242.01	Toxic diffuse goiter with mention of thyrotoxic crisis or storm
242.11	Toxic uninodular goiter with mention of thyrotoxic crisis or storm
242.21	Toxic multinodular goiter with mention of thyrotoxic crisis or storm
242.31	Toxic nodular goiter, unspecified with mention of thyrotoxic crisis or storm
242.41	Thyrotoxicosis from ectopic thyroid nodule with mention of thyrotoxic crisis or storm
242.81	Thyrotoxicosis of other specified origin with mention of thyrotoxic crisis or storm
242.91	Thyrotoxicosis without mention of goiter or other cause with mention of thyrotoxic crisis or storm
277.30	Amyloidosis, unspecified
284.01-284.2, 284.9	Aplastic anemia and other bone marrow failure syndromes
286.0-286.9	Coagulation defects
287.31	Immune thrombocytopenic purpura
295.00-295.95	Schizophrenic disorders
323.81	Other causes of encephalitis and encephalomyelitis
333.91	Stiff-man syndrome
335.20	Amyotrophic lateral sclerosis
340	Multiple sclerosis
359.71	Inclusion body myositis
570	Acute and subacute necrosis of liver
581.1	Nephrotic syndrome with lesion of membranous glomerulonephritis
588.9	Unspecified disorder resulting from impaired renal function
694.4	Pemphigus
696.1	Other psoriasis
710.1	Systemic sclerosis
710.3	Dermatomyositis
710.4	Polymyositis
714.0-714.8	Rheumatoid arthritis
995.91	Sepsis
948.20-948.99	Burns classified according to the extent of body surface involved
960.0-979.9	Poisoning by drug, medicinal and biological substances
980.0-987.9	Toxic effects of substances chiefly nonmedicinal as to source
988.0	Toxic effect of fish and shellfish
988.2-988.9	Toxic effect of noxious substances eaten as food
989.0-989.9	Toxic effect of other substances, chiefly nonmedicinal as to source
996.83	Complications of transplanted heart
	All other codes

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References

1. American Academy of Dermatology (AAD). Psoriasis and psoriatic arthritis. 2009. Accessed Sept 1, 2010. Available at URL address: http://www.aad.org/public/publications/pamphlets/common_psoriasis.html
2. American Academy of Family Physicians (AAFP). Guillain-Barré Syndrome. May 15, 2004. Accessed Sept 1, 2010. Available at URL address: <http://www.aafp.org/afp/20040515/2405.html>

3. American Academy of Neurology (AAN). Assessment of plasmapheresis. 1996. Accessed Sept 1, 2010. Available at URL address: http://aan.com/professionals/practice/pdfs/pdf_1995_thru_1998/1996.47.840.pdf
4. American Cancer Society. Multiple myeloma. Aug 5, 2010. Accessed Sept 8, 2010. Available at URL address: <http://www.cancer.org/>
5. Appel GB. Glomerular disorders. Arend WP, Armitage JO, Drazen JM, Gill GN, Griggs RC, Powell DW, et al., editors. In: Goldman: Cecil textbook of medicine. St. Louis, MO: W.B.Saunders Co. 2004.p.729-31.
6. Ariceta G, Besbas N, Johnson S, Karpman D, Landau D, Licht C, Loirat C, Pecoraro C, Taylor CM, Van de Kar N, Vandewalle J, Zimmerhackl LB; European Paediatric Study Group for HUS. Guideline for the investigation and initial therapy of diarrhea-negative hemolytic uremic syndrome. *Pediatr Nephrol*. 2009 Apr;24(4):687-96.
7. Bayraktaroglu Z, Demirci F, Balat O, Kutlar I, Okan V, Ugur G. Plasma exchange therapy in HELLP syndrome: A single-center experience. *Turk J Gastroenterol*. 2006 Jun;17(2):99-102.
8. Berentsen S, Beiske K, Tjønnfjord GE. Primary chronic cold agglutinin disease: an update on pathogenesis, clinical features and therapy. *Hematology*. 2007 Oct;12(5):361-70.
9. Bickle KM, Roark TR, Hsu S. Autoimmune bullous dermatoses. A review. *Am Fam Physician*. 2002 May 1;65(9):1861-70.
10. Brunskill SJ, Tusold A, Benjamin S, Stanworth SJ, Murphy MF. A systematic review of randomized controlled trials for plasma exchange in the treatment of thrombotic thrombocytopenic purpura. *Transfus Med*. 2007 Feb;17(1):17-35.
11. Brunt EM, Tiniakos DG. Metabolic storage diseases: amyloidosis. *Clin Liver Dis*. 2004 Nov;8(4):915-30,
12. Chan JL. eMedicine. POEMS. Sep 25, 2009. Accessed Sept 1, 2010. Available at URL address: <http://www.emedicine.com/derm/topic771.htm>
13. Choy EH, Hoogendijk JE, Lecky B, Winer JB. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. *Cochrane Database Syst Rev*. 2005 Jul 20;(3):CD003643.
14. Choy EH, Isenberg DA. Treatment of dermatomyositis and polymyositis. *Rheumatology (Oxford)*. 2002 Jan;41(1):7-13.
15. DeVita VT, Perella A, Perella J, Hellman S, Rosenberg SA, editors. Plasma cell neoplasms. In: *Cancer principles and practice of oncology*. Philadelphia, PA: Lippincott Williams & Wilkins. 2005.
16. Dispenzieri A. POEMS Syndrome. *Hematology Am Soc Hematol Educ Program*. 2005;360-7.
17. Drew MJ. Plasmapheresis in the dysproteinemias. *Ther Apher*. 2002 Feb;6(1):45-52.
18. Eser B, Guven M, Unal A, Coskun R, Altuntas F, Sungur M, Serin IS, Sari I, Cetin M. The role of plasma exchange in HELLP syndrome. *Clin Appl Thromb Hemost*. 2005 Apr;11(2):211-7.
19. George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, Blanchette VS, Bussel JB, Cines DB, Kelton JG, Lichtin AE, McMillan R, Okerbloom JA, Regan DH, Warrier I. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood*. 1996 Jul 1;88(1):3-40.
20. Gloor JM, DeGoey SR, Pineda AA, Moore SB, Prieto M, Nyberg SL, et al. Overcoming a positive cross-match in living-donor kidney transplant. *Am J Transplant*. 2003;3:1017-23.

21. Goodin DS, Frohmn EM, Garmany GP, Halper J, Likosky WH, Lublin FD. 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. *Neurology*. 2002 Jan 22;58(2):169-78.
22. Harman KE, Albert S, Black MM. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003 Nov;149(5):926-37. Accessed Sept 1, 2010. Available at URL address: <http://www.bad.org.uk/site/622/default.aspx>
23. Hughes RA, Wijdicks EF, Barohn R, Benson E, Cornblath DR, Hahn AF, Meythaler JM, Miller RG, Sladky JT, Stevens JC. Practice parameter: immunotherapy for Guillain-Barre syndrome: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2003 Sep 23;61(6):736-40. Accessed Sept 7, 2010. Available at URL address: <http://www.guideline.gov/content.aspx?id=4110>
24. Iorizzo LJ 3rd, Jorizzo JL. The treatment and prognosis of dermatomyositis: an updated review. *J Am Acad Dermatol*. 2008 Jul;59(1):99-112. Epub 2008 Apr 18.
25. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, Mirapeix E, Savage CO, Sinico RA, Stegeman CA, Westman KW, van der Woude FJ, de Lind van Wijngaarden RA, Pusey CD; European Vasculitis Study Group. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol*. 2007 Jul;18(7):2180-8.
26. Jordan S, Cunningham-Rundles C, McEwan R. Utility of intravenous immune globulin in kidney transplant: efficacy, safety and cost implications. *Am J Transplant*. 2003;3:653-4.
27. Kaplan RN, Bussel JB. Differential diagnosis and management of thrombocytopenia in childhood. *Pediatr Clin N Am*. 2004;51:1109-40.
28. Kaufman RM, Ritz J, Dzik WH. Transfusion medicine in hematopoietic stem cell and solid organ transplant. Hoffman R, Benz EJ, Shattill SJ, Furie B, Cohen HJ, Silberstein LE, editors. In: Hoffman: *hematology: basic principles and practice*. Orlando, FL: WB Saunders. 2005. p. 2549.
29. Kurlan R, Kaplan EL. The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) etiology for tics and obsessive-compulsive symptoms: hypothesis or entity? Practical considerations for the clinician. *Pediatrics*. 2004 Apr;113(4):883-6.
30. Kuwabara S, Dispenzieri A, Arimura K, Misawa S. Treatment for POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD006828. DOI: 10.1002/14651858.CD006828.pub2.
31. Lorber M. What's new in general surgery: Transplantation. *J Am Coll Surg*. 2004;198(3):424-30.
32. Magee CC, Pascual M. Update in renal transplant. *Arch Intern Med*. 2004;164:1373-88.
33. Martin LK, Agero AL, Werth V, Villanueva E, Segall J, Murrell DF. Interventions for pemphigus vulgaris and pemphigus foliaceus. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD006263. DOI:10.1002/14651858.CD006263.pub2.
34. Martin JN Jr, Rose CH, Briery CM. Understanding and managing HELLP syndrome: the integral role of aggressive glucocorticoids for mother and child. *Am J Obstet Gynecol*. 2006 Oct;195(4):914-34.
35. McCrae KR, Sadler JE, Cines D. Thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome. In: Hoffman: *Hematology: Basic Principles and Practice*, 4th ed. 2005 Churchill Livingstone. P. 2289-2296.

36. Merck Manual. Autoimmune hemolytic anemia. Feb 2009. Accessed Sept 1, 2010. Available at URL address: <http://www.merck.com/mmpe/print/sec11/ch131/ch131b.html>
37. Merck Manual. Chemical food poisoning. Sep 2007. Accessed Sept 1, 2010. Available at URL address: <http://www.merck.com/mmhe/sec09/ch122/ch122f.html#sec09-ch122-ch122f-361>
38. Muller AM, Geibel A, Neumann HP, Kuhnemund A, Schmitt-Graff A, Bohm J, Engelhardt M. Primary (AL) amyloidosis in plasma cell disorders. *Oncologist*. 2006 Jul-Aug;11(7):824-30.
39. Multiple Sclerosis Therapy Consensus Group (MSTCG), Wiendl H, Toyka KV, Rieckmann P, Gold R, Hartung HP, Hohlfeld R. Basic and escalating immunomodulatory treatments in multiple sclerosis: current therapeutic recommendations. *J Neurol*. 2008 Oct;255(10):1449-63.
40. Natarajan N, Weinstein R. Therapeutic apheresis in neurology critical care. *J Intensive Care Med*. 2005 Jul-Aug;20(4):212-25.
41. National Cancer Institute (NCI). Multiple myeloma and other plasma cell neoplasms treatment (PDQ®). Nov 18, 2009. Accessed Sept 1, 2010. Available at URL address: <http://www.cancer.gov/cancertopics/pdq/treatment/myeloma/Patient/page4#Keypoint31>
42. National Cancer Institute (NCI). Waldenström macroglobulinemia: questions and answers. Sep 25, 2007. Accessed Sept 1, 2010. Available at URL address: <http://www.cancer.gov/cancertopics/factsheet/Sites-Types/MM>
43. National Heart, Lung and Blood Institute (NHLBI). Hemolytic anemia. 2009. Accessed Sept 1, 2010. Available at URL address: http://www.nhlbi.nih.gov/health/dci/Diseases/ha/ha_all.html
44. National Heart, Lung and Blood Institute (NHLBI). Idiopathic thrombocytopenia purpura. Jun 2009. Accessed Sept 1, 2010. Available at URL address: http://www.nhlbi.nih.gov/health/dci/Diseases/Itp/ITP_WhatIs.html
45. National Institute of Arthritis and Musculoskeletal and Skin Diseases. Scleroderma. May 2010. Accessed Sept 1, 2010. Available at URL address: http://www.niams.nih.gov/Health_Info/Scleroderma/default.asp
46. National Institute of Diabetes and Digestive and Kidney Disease (NIDDK). What I need to know about liver transplantation. Jun 2010. Accessed Sept 1, 2010. Available at URL address: http://digestive.niddk.nih.gov/ddiseases/pubs/livertransplant_ez/livertrans.pdf
47. National Institutes of Health (NIH). National Library of Medicine. Medical Encyclopedia. Lambert-Eaton Syndrome. Sep 16, 2008. Accessed Sept 1, 2010. Available at URL address: <http://www.nlm.nih.gov/medlineplus/ency/article/000710.htm>
48. National Institutes of Health (NIH). National Library of Medicine. Medical encyclopedia. Rheumatoid arthritis. Feb 7, 2010. Accessed Sept 1, 2010. Available at URL address: <http://www.nlm.nih.gov/medlineplus/ency/article/000431.htm>
49. National Institute of Neurological Disorders and Stroke (NINDS). Acute disseminated encephalomyelitis information page. May 2010. Accessed Sept 1, 2010. Available at URL address: http://www.ninds.nih.gov/disorders/acute_encephalomyelitis/acute_encephalomyelitis.htm
50. National Institute of Neurological Disorders and Stroke (NINDS). Amyotrophic Lateral Sclerosis Fact Sheet. Aug 13, 2010. Accessed Sept 1, 2010. Available at URL address: http://www.ninds.nih.gov/disorders/amyotrophiclateralsclerosis/detail_amyotrophiclateralsclerosis.htm

51. National Institute of Neurological Disorders and Stroke (NINDS). NINDS Dermatomyositis Information Page. May 27, 2010. Accessed Sept 1, 2010. Available at URL address: <http://www.ninds.nih.gov/disorders/dermatomyositis/dermatomyositis.htm>
52. National Institute of Neurological Disorders and Stroke (NINDS). Infantile Refsum disease page. Feb 14, 2007a. Accessed Sept 1, 2010. Available at URL address: http://www.ninds.nih.gov/disorders/refsum_infantile/refsum_infantile.htm
53. National Institute of Neurological Disorders and Stroke (NINDS). Multiple sclerosis: hope through research. Aug 7, 2009. Accessed Sept 1, 2010. Available at URL address: http://www.ninds.nih.gov/disorders/multiple_sclerosis/detail_multiple_sclerosis.htm
54. National Institute of Neurological Disorders and Stroke (NINDS). Paraneoplastic Syndromes information page. Mar 12, 2009. Accessed Sept 1, 2010. Available at URL address: <http://www.ninds.nih.gov/disorders/paraneoplastic/paraneoplastic.htm>
55. National Institute of Neurological Disorders and Stroke (NINDS). Rasmussen's encephalitis information page. Feb 7, 2008. Accessed Sept 1, 2010. Available at URL address: <http://www.ninds.nih.gov/disorders/rasmussen/rasmussen.htm>
56. National Institute of Neurological Disorders and Stroke (NINDS). Refsum Disease information page. Feb 14, 2007b. Accessed Sept 1, 2010. Available at URL address: <http://www.ninds.nih.gov/disorders/refsum/refsum.htm>
57. National Institute of Neurological Disorders and Stroke (NINDS). NINDS Stiff-Person Syndrome information page. Oct 6, 2009. Accessed Sept 1, 2010. Available at URL address: <http://www.ninds.nih.gov/disorders/stiffperson/stiffperson.htm>
58. National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). Glomerular disease. Apr 2006. Accessed Sept 1, 2010. Available at URL address: <http://kidney.niddk.nih.gov/kudiseases/pubs/glomerular/>
59. National Multiple Sclerosis Society. Plasmapheresis. Accessed Sept 1, 2010. Available at URL address: <http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/exacerbations/index.aspx>
60. O'Grady JG.. Acute liver failure. *Postgrad Med J.* 2005 Mar;81(953):148-54.
61. Pham TN, Cancio LC, Gibran NS; American Burn Association. American Burn Association practice guidelines burn shock resuscitation. *Burn Care Res.* 2008 Jan-Feb;29(1):257-66.
62. Pirko I, Noseworthy JH. Chapter 48 – Demyelinating disorders of the central nervous system. Multiple sclerosis. In: Goetz: *Textbook of Clinical Neurology*, 2nd ed. St. Louis: W.B. Sanders; 2003.
63. Raphaël JC, Chevret S, Hughes RAC, Annane D. Plasma exchange for Guillain-Barré syndrome. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD001798. DOI: 10.1002/14651858.CD001798.
64. Reid ME, Olsson ML. Human blood group antigens and antibodies. Hoffman R, Benz EJ, Shattill SJ, Furie B, Cohen HJ, Silberstein LE, editors. In: Hoffman: *Hematology: basic principles and practice*. Orlando, FL: WB Saunders. 2005. p. 2378.
65. Romi F, Gilhus NE, Aarli JA. Myasthenia gravis: clinical, immunological, and therapeutic advances. *Acta Neurol Scand.* 2005 Feb;111(2):134-41.
66. Rowland RP. Refsum disease. In: Merritt's *Neurology*. 11th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 657-8.

67. Ruma MS, Moise KJ Jr, Kim E, Murtha AP, Prutsman WJ, Hassan SS, Lubarsky SL. Combined plasmapheresis and intravenous immune globulin for the treatment of severe maternal red cell alloimmunization. *Am J Obstet Gynecol.* 2007 Feb;196(2):138.e1-6.
68. Rust Jr. RS. Acute Disseminated Encephalomyelitis. Sep 3, 2009. Accessed Sept 1, 2010. Available at URL address: <http://www.emedicine.com/NEURO/topic500.htm>
69. Seror R, Pagnoux C, Guillevin L. Plasma exchange for rheumatoid arthritis. *Transfus Apher Sci.* 2007 Apr;36(2):195-9.
70. Shaz BH, Linenberger ML, Bandarenko N, Winters JL, Kim HC, Marques MB, Sarode R, Schwartz J, Weinstein R, Wirk A, Szczepiorkowski ZM. Category IV indications for therapeutic apheresis-ASFA fourth special issue. *J Clin Apher.* 2007 Mar 21;22(3):176-180.
71. Shields RW Jr, Wilbourn AJ. Demyelinating disorders of the peripheral nervous system. Goetz CG, editor. In: Goetz: textbook of clinical neurology. St.Louis, MO: W.B. Saunders. 2003. p.1083-93.
72. Smith JW, Weinstein R, For The AABB Hemapheresis Committee KL; AABB Hemapheresis Committee; American Society for Apheresis. Therapeutic apheresis: a summary of current indication categories endorsed by the AABB and the American Society for Apheresis. *Transfusion.* 2003 Jun;43(6):820-2.
73. Szczepiorkowski ZM, Bandarenko N, Kim HC, Linenberger ML, Marques MB, Sarode R, Schwartz J, Shaz BH, Weinstein R, Wirk A, Winters JL. Guidelines on the use of therapeutic apheresis in clinical practice-Evidence-based approach from the apheresis applications committee of the American society for apheresis. *Clin Apher.* 2007a Mar 29;22(3):106-175.
74. Szczepiorkowski ZM, Shaz BH, Bandarenko N, Winters JL. The new approach to assignment of ASFA categories-Introduction to the fourth special issue: Clinical applications of therapeutic apheresis. *J Clin Apher.* 2007b Mar 29;22(3):96-105.
75. Szczepiorkowski ZM, Winters JL, Bandarenko N, Kim HC, Linenberger ML, Marques MB, Sarode R, Schwartz J, Weinstein R, Shaz BH; Apheresis Applications Committee of the American Society for Apheresis. Guidelines on the use of therapeutic apheresis in clinical practice--evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. *J Clin Apher.* 2010;25(3):83-177.
76. Tricot G. Cryoglobulinemia. In: Hoffman R, Benz E, Shattil S, Furie B, Cohen HJ, Silberstein LE, McGlave P, editors. *Hoffman: hematology: basic principles and practice*, 4th ed. Philadelphia: W.B. Saunders; 2004. p. 1525-7.
77. U.S. Food and Drug Administration (FDA). BBB –mushroom toxins. May 5, 2009. Accessed Sept 1, 2010. Available at URL address: <http://www.fda.gov/Food/FoodSafety/FoodborneIllness/FoodborneIllnessFoodbornePathogensNaturalToxins/BadBugBook/ucm070853.htm>
78. Vasculitis Foundation. Rheumatoid vasculitis. 2006. Accessed Sept 1, 2010. Available at URL address: <http://www.vasculitisfoundation.org/rheumatoidvasculitis>
79. Walters G, Willis NS, Craig JC. Interventions for renal vasculitis in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD003232. DOI: 10.1002/14651858.CD003232.pub2.
80. Weinshenker BG. Plasma exchange for severe attacks of inflammatory demyelinating diseases of the central nervous system. *J Clin Apher.* 2001;16(1):39-42.

81. Wu YY, Snyder EL. Transfusion reactions. Hoffman R, Benz EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, et al., editors. In: Hoffman: hematology: basic principles and practice. Orlando, FL: W.B. Saunders. 2005. p. 2515.
82. Yu X, Ma J, Tian J, Jiang S, Xu P, Han H, Wang L. A controlled study of double filtration plasmapheresis in the treatment of active rheumatoid arthritis. J Clin Rheumatol. 2007 Aug;13(4):193-8.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	10/15/2008	0153	Plasmapheresis
Great-West Healthcare	4/23/07	95.286.05	Plasmapheresis, Plasma Exchange, Therapeutic Apheresis

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.