



Cigna Medical Coverage Policy

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Subject **Plasmapheresis**

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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)
- kidney transplantation with antibody mediated rejection (AMR)
- myasthenia gravis in preparation for surgery OR for moderate to severe exacerbation OR respiratory crisis
- paraproteinemic polyneuropathy associated with immunoglobulin G (IgG), immunoglobulin A (IgA) or immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance (e.g., MGUS)

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- 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 (e.g., acute attack of multiple sclerosis)
- 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 with 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, chronic progressive
- nephrogenic systemic fibrosis (NSF)
- overdose, venoms, and poisoning (compounds other than mushroom poisoning)

- pediatric postinfectious autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
 - 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 ten 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 scientific literature and/or professional societies support PP as an established 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)
- kidney transplantation and antibody mediated rejection (AMR)
- myasthenia gravis in preparation for surgery or for moderate to severe exacerbation 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)
- 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

In their 2011 guidelines for plasmapheresis for neurologic disorders, the American Academy of Neurology (AAN) reported that PP is an established, effective therapy and should be offered in the treatment of acute inflammatory demyelinating polyneuropathy (AIDP)/Guillain-Barré syndrome (GBS) that is "severe enough to impair independent walking or to require mechanical ventilation." AAN also stated that PP should be considered in the treatment of milder clinical presentations of AIDP/GBS (i.e., stand unaided or walk five meters without assistance). According to AAN, there is insufficient evidence to demonstrate superiority of IV immunoglobulin (IVIG) compared to PP or PP over IVIG.

Additional AAN recommendations included:

- PP is an established, short-term treatment option and recommends its use for CIDP.
- PP is probably effective for IgA and IgG-MGUS-associated polyneuropathy, but probably not effective for polyneuropathy with IgM-MGUS.
- There is inadequate data in randomized controlled trials with masked outcomes to support or refute PP for the treatment of myasthenia gravis crisis or prethymectomy

AAN noted that PP is used by many medical centers for the above indications.

The European Federation of Neurological Societies (EFNS) (Skeie, et al., 2010) recommended PP "as a short-term treatment for myasthenia gravis, especially in severe cases to induce remission and in preparation for surgery." EFNS noted that IVIG and PP are equally effective for treatment exacerbations. Regarding CIDP, EFNS recommended PP when IVIG and corticosteroids are ineffective (Van den Bergh, et al., 2010). PP is also recommended as a consideration for the treatment of IgM paraproteinemic demyelinating neuropathies "especially in patients with rapid worsening or clinically similar to typical CIDP, although any benefit may be only short term and repeated treatments may be required" (Hadden, et al., 2010).

Pediatric Postinfectious Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS): PANDAS is a condition defined by five clinical characteristics – the presence of obsessive compulsive disorder (OCD) and/or tic disorder, prepubertal age of onset, abrupt onset and relapsing-remitting symptom course, association with neurological abnormalities during exacerbations (adventitious movements or motoric hyperactivity), and a temporal association between symptom exacerbations and a Group-A beta-hemolytic streptococcal infection. These five criteria have been used for the purpose of conducting research on PANDAS as well as studies of the pathophysiology of post-streptococcal OCD and tic disorders (National Institute of Mental Health, 2012; Swedo et. al., 2001).

The diagnosis and treatment of PANDAS remains a controversial issue. Studies are either recruiting or ongoing at this time to address the proper diagnosis and treatment of PANDAS. Preliminary results of certain studies suggest enlarging the spectrum of PANDAS to include attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) (Martino, et. al., 2009). Initial treatment for PANDAS typically includes cognitive

behavioral therapy and/or anti-obsessional medications. Antibiotic administration is indicated in patients with tonsillo-pharyngitis and a positive Group-A beta-hemolytic streptococcus throat culture. Although PP for PANDAS is listed as category I, ASFA stated that the mechanism of the benefit of PP is not clear. Studies investigating PP for PANDAS are few in number and have small patient populations with short-term follow-ups. There is a lack of well, designed randomized controlled trials with large patient populations to support the effectiveness of PP for the treatment of PANDAS (Szczeplorkowski, et al., 2010).

In their 2011 guidelines for plasmapheresis for neurologic disorders, the American Academy of Neurology (AAN) reported that there was insufficient evidence to support or refute PP for the treatment of PANDAS.

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 (Szczeplorkowski, 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 (Szczeplorkowski, 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 (Szczeplorkowski, et al., 2010).

Acute Central Nervous System (CNS) Inflammatory Demyelinating Disease: Acute attacks of inflammatory demyelinating disease (e.g., acute attack secondary to multiple sclerosis) are most commonly treated with pharmacotherapy including intravenous high-dose corticosteroids. PP may be indicated for the treatment of those patients who do not respond to pharmacotherapy (Szczeplorkowski, et al., 2010; Pike and Noseworthy, 2003; Weinshenker, 2001).

Regarding central nervous system (CNS) chronic inflammatory demyelinating disease, AAN (2011) stated that PP is “possibly effective” for acute fulminant CNS demyelinating diseases for patients who fail to respond to high-dose corticosteroid treatment.

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 is utilized for the removal of offending antibodies when the patient is unresponsive to standard therapy (Szczeplorkowski, et al., 2010; Rust, 2010; National Institute of Neurological Disorders and Stroke [NINDS], 2012).

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 (i.e., renal vasculitis). Results of clinical trials indicated that PP was most beneficial in patients who were on dialysis and/or had diffuse alveolar hemorrhage (Walsh, et al., 2011; Szczeplorkowski, 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 antiphospholipids 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 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; National Institutes of Health [NIH], Jul 2012; 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, 2012; 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; 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], Dec 2011).

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, 2012; 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 on the etiology and aims to accomplish cessation of bleeding and suppression of inhibitor production. This may be accomplished by replacing the factor or bypassing it. Inhibitor suppression may be accomplished by the administration of high dose corticosteroids and IVIG. It has been proposed that PP may be useful in the removal of inhibitors, but its effectiveness has not been proven (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; 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 Health Institute, 2012).

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, 2011; 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, secondary progressive or chronic progressive forms of MS (NINDS, 2012; Szczepiorkowski, et al., 2010; Smith, et al., 2003).

AAN (2011) guidelines stated that PP should be considered for the adjunctive treatment of exacerbations in relapsing forms of MS (based on one study of 12 patients), but should not be offered for chronic progressive or secondary progressive MS.

In their 2008 guideline on current therapeutic recommendations for the treatment of MS, the Multiple Sclerosis Therapy Consensus Group stated 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 in hepatorenal syndrome, following the administration of gadolinium (Gd) containing contrast agents, or following liver transplantation. Treatment includes pharmacotherapy (e.g., steroids) and renal transplantation. PP has been proposed as a treatment modality because of the high failure rate of other therapies. However, there is insufficient evidence to support PP for this condition (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).

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).

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

In guidelines for the management of pemphigus vulgaris, the British Association of Dermatologists (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 (Kuwabara, 2012; Chan, 2009; 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], 2012).

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. 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, 2010).

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

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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 therapy with data showing that PP is as good as or better than other conventional therapies.

In conditions in which PP is used as an adjunctive therapy, the primary therapies for those conditions have demonstrated better outcomes (e.g., improvement in symptoms, remission, improved survival rates) and PP is only recommended if primary therapy isn't effective. Clinical trials have not proven PP to be as effective as or more effective than primary conventional therapies for the treatment of those conditions.

Due to the limited number of studies, small patient populations, short-term follow-ups and/or lack of comparisons to established conventional therapies, PP is not supported by the evidence in the published peer-reviewed scientific literature or by professional societies to be a beneficial treatment modality for various other conditions. Some studies reported mixed results or no improvement in outcomes (e.g., improvement in symptoms, remission, improved survival rates) following PP.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

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

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

ICD-9-CM Diagnosis Codes	Description
273.1	Monoclonal paraproteinemia
273.2	Other paraproteinemias

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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
582.1	Chronic glomerulonephritis with lesion of membranous glomerulonephritis
583.81 ^{††}	Nephritis and nephropathy, not specified as acute or chronic, in diseases classified elsewhere
996.81 ^{†††}	Complications of transplanted kidney
V42.0 ^{†††}	Organ or tissue replaced by transplant, Kidney

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

^{††}**Note:** Coverage is limited to underlying conditions indicated as covered in this Coverage Policy.

^{†††}**Note:** Coverage is limited to kidney transplantation with antibody mediated rejection (AMR)

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
203.00	Multiple myeloma, without mention of having achieved remission
203.02	Multiple myeloma, in relapse
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
287.41	Posttransfusion purpura
289.81	Primary hypercoagulable state
323.61	Infectious acute disseminated encephalomyelitis (ADEM)
323.81	Other causes of encephalitis and encephalomyelitis
340 ^{††}	Multiple sclerosis
341.0	Neuromyelitis optica
341.9	Demyelinating disease of central nervous system, unspecified
356.3	Refsum's disease
357.89	Other inflammatory and toxic neuropathy
358.30-358.39	Lambert-Eaton syndrome
446.4	Wegener's granulomatosis
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
584.5 ^{†††}	Acute kidney failure with lesion of tubular necrosis
656.10	Rhesus isoimmunization, unspecified as to episode of care or not applicable
656.11	Rhesus isoimmunization, delivered, with or without mention of antepartum condition
656.13	Rhesus isoimmunization, antepartum condition or complication
710.0	Systemic lupus erythematosus

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996.81 ^{††††}	Complications of transplanted kidney
988.1	Toxic effect of noxious substances eaten as food, mushrooms
V42.0 ^{††††}	Organ or tissue replaced by transplant, kidney
V42.1	Organ or tissue replaced by transplant, heart
V42.82	Peripheral stem cells replaced by organ or tissue replaced by transplant, other specified organ or tissue, peripheral stem cells

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

^{††}**Note:** Coverage is limited to acute attacks of multiple sclerosis

^{†††}**Note:** Coverage is limited to myeloma cast nephropathy

^{††††}**Note:** Coverage is limited to kidney transplantation with elevated human leukocyte antigens (HLA)

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

ICD-9-CM Diagnosis Codes	Description
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 type 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	Constitutional red blood cell aplasia
284.2	Myelophthisis
284.9	Aplastic anemia, unspecified
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
359.71	Inclusion body myositis
425.4	Other primary cardiomyopathies
570	Acute and subacute necrosis of liver
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
714.0-714.9	Rheumatoid arthritis
995.91	Sepsis
948.20-948.22	Burns classified according to the extent of body surface involved, 20-29 percent of body surface
948.30-948.33	Burns classified according to the extent of body surface involved, 30-39 percent of body surface
948.40-	Burns classified according to the extent of body surface involved, 40-49 percent

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948.44	of body surface
948.50-948.55	Burns classified according to the extent of body surface involved, 50-59 percent of body surface
948.60-948.66	Burns classified according to the extent of body surface involved, 60-69 percent of body surface
948.70-948.77	Burns classified according to the extent of body surface involved, 70-79 percent of body surface
948.80-948.88	Burns classified according to the extent of body surface involved, 80-89 percent of body surface
948.90-948.99	Burns classified according to the extent of body surface involved, 90 percent or more of body surface
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 noxious substance eaten as food, fish and shellfish
988.2	Toxic effect of noxious substances eaten as food, berries and other plants
988.8	Toxic effect of noxious substances eaten as food, other specified noxious substance eaten as food
988.9	Toxic effect of noxious substances eaten as food, unspecified noxious substance eaten as food
989.0-989.9	Toxic effect of other substances, chiefly nonmedicinal as to source
996.83	Complications of transplanted organ, heart
	All other codes

*Current Procedural Terminology (CPT®) © 2012 American Medical Association: Chicago, IL.

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