Name of Policy:  
Plasma Exchange (Plasmapheresis)

Policy #: 100  
Latest Review Date: June 2014
Category: Therapy  
Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
Plasma exchange (PE) is a procedure in which the plasma is isolated, then discarded and replaced with a substitution fluid such as albumin. Plasma exchange is a nonspecific therapy, since the entire plasma is discarded. PE has been used in a wide variety of acute and chronic conditions, as well as in the setting of solid organ transplantation.

The terms therapeutic apheresis, plasmapheresis, and plasma exchange (PE) are often used interchangeably, but when properly used denote different procedures. The American Society for Apheresis (ASFA) definitions for these procedures are as follows:

- **Apheresis**: A procedure in which blood of the patient or donor is passed through a medical device which separates out one or more components of blood and returns remainder with or without extracorporeal treatment or replacement of the separated component.
- **Plasmapheresis**: A procedure in which blood of a patient or the donor is passed through a medical device which separates out plasma from the other components of blood and the plasma is removed (i.e., less than 15% of total plasma volume) without the use of replacement solution.
- **Plasma exchange**: A therapeutic procedure in which blood of the patient is passed through a medical device which separates out plasma from other components of blood, the plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin and/ or plasma) or a combination of crystalloid/colloid solution.

This policy addresses only plasma exchange as a therapeutic apheresis procedure.

The rationale for PE is based on the fact that circulating substances, such as toxins or autoantibodies, can accumulate in the plasma. Also, it is hypothesized that removal of these factors can be therapeutic in certain situations. PE is essentially a symptomatic therapy, since it does not remove the source of the pathogenic factors. Therefore the success of PE will depend on whether the pathogenic substances are accessible through the circulation and whether their rate of production and transfer to the plasma component can be adequately addressed by PE. For example, PE can rapidly reduce levels of serum autoantibodies; however, through a feedback mechanism, this rapid reduction may lead to a rebound overproduction of the same antibodies. This rebound production of antibodies is thought to render the replicating pathogenic clone of lymphocytes more vulnerable to cytotoxic drugs; therefore, PE is sometimes used in conjunction with cyclophosphamide.

Applications of PE can be broadly subdivided into two general categories: 1) acute self-limited diseases, in which PE is used to acutely lower the circulating pathogenic substance; and 2) chronic diseases, in which there is ongoing production of pathogenic autoantibodies. Because PE does not address underlying pathology, and, due to the phenomenon of rebound antibody production, its use in chronic diseases has been more controversial than in acute self-limited diseases.

In addition, plasmapheresis has been used in the setting of solid organ transplantation. It has been used as a technique to desensitize high-risk patients prior to transplant and also as a treatment of antibody-mediated rejection reaction (AMR) occurring after transplant. Prior to
transplant, plasmapheresis has been most commonly used to desensitize patients receiving an ABO mismatched kidney, often in combination with a splenectomy. As a treatment of AMR, plasmapheresis is often used in combination with intravenous immunoglobulin (IVIg) or anti-CD-20 therapy (i.e., Rituxan).

**Policy:**

**Plasma exchange (plasmapheresis) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the following conditions:

**Autoimmune**
- Severe multiple manifestation of mixed cryoglobulinemia (MC) such as cryoglobulinemic nephropathy, skin ulcers, sensory motor neuropathy, and widespread vasculitis in combination with immunosuppressive treatment
- Catastrophic antiphospholipid syndrome (CAPS) *(effective 01/01/2013)*

**Hematologic**
- ABO incompatible hematopoietic progenitor cell transplantation
- Hyperviscosity syndromes associated with multiple myeloma or Waldenström’s macroglobulinemia
- Idiopathic thrombocytopenic purpura in emergency situations
- Thrombotic thrombocytopenic purpura (TTP)
- Atypical hemolytic-uremic syndrome
- Post transfusion purpura
- HELLP syndrome of pregnancy
- Myeloma with acute renal failure *(effective 01/01/2013)*

**Neurological**
- Acute inflammatory demyelinating polyneuropathy (Guillain-Barre’ syndrome; severity grade 1-2 within two weeks of onset; severity grade 3-5 within four weeks of onset; and children less than 10 years old with severe GBS)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multiple sclerosis with acute fulminant CNS demyelination
- Myasthenia gravis in crisis or as part of preoperative preparation
- Paraproteinemia polyneuropathy; IgA, IgG
- Neuromyelitis optica

**Renal**
- Anti-glomerular basement membrane disease (Goodpasture’s syndrome)
- ANCA-associated vasculitis [e.g., Wegener’s granulomatosis, also known as granulomatosis with polyangiitis (GPA)] with associated renal failure
- Dense deposit disease with factor H deficiency and/or elevated C3 Nephritic factor *(effective 01/01/2013)*
Transplantation
  • ABO incompatible solid organ transplantation;
    o kidney,
    o heart (infants)
  • Renal transplantation: antibody mediated rejection; HLA desensitization
  • Focal segmental glomerulosclerosis after renal transplant (effective 01/01/2013)

Plasma exchange (plasmapheresis) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational in all other conditions, including, but not limited, to the following:
  • ABO incompatible solid organ transplant; liver
  • Acute disseminated encephalomyelitis
  • Acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome) in children less than 10 years old with mild or moderate forms
  • Acute liver failure
  • Amyotrophic lateral sclerosis (ALS)
  • ANCA-associated vasculitis [e.g., Wegener’s granulomatosis, also known as granulomatosis with polyangiitis (GPA)] without associated renal failure
  • Aplastic anemia
  • Asthma
  • Autoimmune hemolytic anemia; warm autoimmune hemolytic anemia; cold agglutinin disease
  • Chronic fatigue syndrome
  • Coagulation factor inhibitors
  • Cryoglobulinemia; except for severe mixed cryoglobulinemia; as noted above
  • Dermatomyositis and polymyositis
  • Focal segmental glomerulosclerosis (other than after renal transplant)
  • Heart transplant rejection treatment
  • Hemolytic uremic syndrome (HUS); typical (diarrheal-related)
  • Hyperviscosity syndromes with renal failure (other than associated with multiple myeloma or Waldenström’s macroglobulinemia).
  • Idiopathic thrombocytopenic purpura; refractory or non-refractory
  • Inclusion body myositis
  • Lambert-Eaton myasthenic syndrome
  • Macular Degeneration (Age Related)
  • Multiple sclerosis with chronic progressive or relapsing remitting course
  • Mushroom poisoning
  • Myasthenia gravis with anti-MuSK antibodies
  • Obsessive compulsive disorder
  • Overdose and poisoning (other than mushroom poisoning)
  • Paraneoplastic syndromes
  • Paraproteinemia polyneuropathy; IgM
  • Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
  • Pemphigus vulgaris
• Phytanic acid storage disease (Refsum’s disease)
• POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes)
• Psoriasis
• Red cell alloimmunization in pregnancy
• Regional enteritis (Crohn’s disease)
• Rheumatoid arthritis
• Scleroderma (systemic sclerosis)
• Sepsis
• Stiff-man syndrome
• Sydenham’s chorea
• Systemic lupus erythematosus (including SLE nephritis)
• Thyrotoxicosis

Blue Cross and Blue Shield of Alabama will give individual case consideration for coverage of plasma exchange in patients with acute, life-threatening complications of chronic autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus. However, in these situations, treatment goal and duration of treatment with PE need to be clearly established prior to its initiation to ensure that short term treatment of the acute complication does not evolve to a chronic use of PE with uncertain benefit.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

**Key Points:**
**Autoimmune Diseases**
One potential type of evidence in support of the clinical effectiveness of plasma exchange (PE) in treating autoimmune diseases is the identification of a pathogenic component of plasma that is reliably eliminated by plasmapheresis. Although many laboratory abnormalities are associated with autoimmune connective tissue diseases, it is unclear which, if any, cause the clinical manifestations of the disease. Furthermore, it is not known to what extent plasma levels parallel clinical disease. For example, in many of the controlled trials discussed as follows, PE reliably reduced circulating autoantibodies and immune complexes, but without demonstrable clinical benefit. It may be that the patient had already suffered irreversible damage or that the pathogenesis of the disease was a local process unrelated to circulating factors. Over the past 10 years, randomized trials of PE have been conducted and, in general, have shown a lack of effectiveness as treatment of chronic autoimmune diseases. Clinical results of randomized trials of plasmapheresis for specific chronic autoimmune diseases are discussed here.
Systemic Lupus Erythematosus
Reporting on the results of a randomized controlled trial (RCT), Lewis and colleagues concluded that PE had no benefit in patients with systemic lupus and glomerulonephritis compared to a standard therapy regimen of prednisone and cyclophosphamide. Plasmapheresis has also been investigated as a technique to improve the effectiveness of cyclophosphamide therapy. For example, it is thought that the acute lowering of pathogenic autoantibodies with plasmapheresis may result in their rebound production. It is hoped that the pathogenic lymphocytes would be more sensitive to cyclophosphamide at this point. Danieli and colleagues reported on a prospective nonrandomized trial of 28 patients with proliferative lupus nephritis; 12 underwent synchronized plasmapheresis and pulse cyclophosphamide therapy, while the remaining 16 underwent cyclophosphamide alone. While plasmapheresis was associated with a decreased time to remission of renal disease, at the end of the four year follow-up, there was no difference in outcome.

Multiple Sclerosis (MS)
There have been several RCTs of PE in patients with MS that have reported inconclusive results. Khatri and colleagues studied 54 patients with chronic progressive MS randomized to receive sham or true PE. The degree of improvement in the PE group was greater than that in the control group. Weiner et al reported on a study that randomized patients with acute attacks of MS to receive either PE or sham treatments; there was no statistical difference in improvement between groups, although patients receiving PE did have a faster recovery rate from acute attacks. A Canadian trial randomized 168 patients with progressive MS to receive either PE or immunosuppressive therapy. There were no significant differences in the rates of treatment failures between groups.

Lambert-Eaton Myasthenic Syndrome (LEMS) and Other Paraneoplastic Syndromes
Paraneoplastic neuromuscular syndromes are characterized by the production of tumor antibodies that cross-react with the patient’s nervous system tissues. The Lambert-Eaton myasthenic syndrome (LEMS) characterized by proximal muscle weakness of the lower extremities and associated most frequently with small cell lung cancer, is the most common paraneoplastic syndrome. The presumed autoimmune nature of LEMS and other paraneoplastic syndromes led to the use of a variety of immunomodulatory therapies, including PE. However, there are minimal data in the published literature and no controlled trials. The largest case series focusing on LEMS was reported by Tim and colleagues and included 73 patients with LEMS, 31 of whom were found to have lung cancer. Although detailed treatment strategies are not provided, 19 underwent plasmapheresis, with 27% reporting a moderate to marked response. However, the improvement after plasmapheresis, even when marked was only transient. Patients also received other therapies, for example, various chemotherapy regimens for the underlying lung cancer. In addition, 53 of the 73 patients received 3.4 diaminopyridine, with 79% reporting marked or moderate responses. A small RCT of 3.4 diaminopyridine has also reported positive results, confirming other anecdotal reports. Anderson and colleagues reported on a case series of 12 patients with paraneoplastic cerebellar degeneration. Although plasmapheresis was associated with an acute drop in the autoantibody titer, only two patients showed a minor improvement in neurologic symptoms.
Rheumatoid Arthritis
In 1983, Dwosh and colleagues reported on 26 patients with chronic rheumatoid arthritis randomized in a crossover design to either true or sham PE. The authors concluded that PE did not have any clinical benefit despite impressive laboratory changes.

Polymyositis/Dermatomyositis
Miller and colleagues conducted a randomized trial of PE in the treatment of 39 patients with polymyositis and dermatomyositis and found that it was no more effective than sham pheresis.

Pemphigus
Pemphigus is an autoimmune blistering skin disease that is characterized by serum antibodies that bind to squamous epithelia. Steroids or other immunosuppressants are the most common forms of treatment, but the high doses of steroids can produce significant side effects. Guillaume and colleagues reported on a study of 40 patients with pemphigus randomized to receive prednisone alone or prednisone plus plasmapheresis. The goal of the study was to determine whether plasmapheresis could reduce the required dose of steroids, thus limiting its toxicity. Unfortunately, disease control in the two groups was the same, and the authors concluded that plasmapheresis in conjunction with low-dose steroids is not effective in treating pemphigus.

Stiff Man (aka Stiff Person) Syndrome
Stiff man syndrome is an autoimmune disorder characterized by involuntary stiffness of axial muscles and intermittent painful muscle spasm. Stiff man syndrome may be idiopathic in nature or seen in association with thymoma, Hodgkin's disease, and small cell lung; colon; or breast cancer. The mainstay of treatment of stiff man syndrome is diazepam. The published literature regarding plasmapheresis consists of small case series and anecdotal reports. Most of these studies were published in the late 1980s or early 1990s; one case series with nine patients was published in 2014.

Cryoglobulinemia
There are several types of cryoglobulinemia. Type I is associated with hematologic disorders. Types II and III are considered mixed cryoglobulins. Mixed cryoglobulin syndrome is a consequence of immune-complex mediated vasculitis and may be associated with infectious and systemic disorders (e.g., hepatitis C virus). In 2010, Rockx and Clark published a review of studies evaluating PE for treating cryoglobulinemia that included at least five patients. They identified 11 studies with a total of 156 patients. The authors concluded, “The quality and variability of the evidence precludes a meta-analysis or even a systematic analysis. However, these studies weakly support the use of plasma exchange largely on a mechanistic basis.”

Hematologic
Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS)
Once considered distinct syndromes, TTP and HUS are now considered different manifestations of the same disease process, i.e., thrombotic microangiopathy. In 2009, a systematic review evaluated the benefits and harms of different interventions for HUS and TTP (separately). Interventions compared with placebo or supportive therapy or a comparison of two or more interventions. Interventions examined included heparin, aspirin/dipyridamole, prostanoids,
ticlopidine, vincristine, fresh frozen plasma (FFP) infusion, plasmapheresis with fresh frozen plasma, systemic corticosteroids, Shiga toxin-binding agents, or immunosuppressive agents. For TTP, 6 RCTs (n=331 participants) were identified evaluating PE with FFP as the control. Interventions tested included antiplatelet therapy plus PE with FFP, FFP transfusion, and PE with cryosupernatant plasma. Two studies compared plasma infusion (PI) to PE with FFP and showed a significant increase in failure of remission at two weeks (risk ratio [RR]: 1.48) and all-cause mortality (RR: 1.91) in the PI group. The authors concluded that PE with fresh frozen plasma is the most effective treatment available for TTP. Seven RCTs included children with HUS. None of the assessed interventions was superior to supportive therapy alone for all-cause mortality, neurological/extrarenal events, renal biopsy changes, proteinuria, or hypertension at the last follow-up visit. Bleeding was significantly higher in those receiving anticoagulation therapy compared to supportive therapy alone (RR: 25.89). For patients with HUS, supportive therapy including dialysis was the most effective treatment. All studies in HUS have been conducted in the diarrheal form of the disease. There were no RCTs evaluating the effectiveness of any interventions on patients with atypical HUS who have a more chronic and relapsing course. A recent review article by Noris and Remuzzi describes the data supporting use of PE in the atypical form of this disease, with results showing remission in up to 60% of patients. Because the available evidence for patients with typical HUS shows supportive therapy, including dialysis, to be the most effective treatment, all studies in HUS have been conducted with patients with the diarrheal (typical) form of the disease; the use of PE for the treatment of typical HUS is inadequate to draw clinical conclusions. PE for HUS was considered medically necessary in previous updates. PE remains medically necessary for atypical HUS.

**Idiopathic Thrombocytopenic Purpura (ITP)**

ITP is an acquired disease of either adults or children characterized by the development of autoantibodies to platelets. Management of acute bleeding due to thrombocytopenia typically involves immediate platelet transfusion, occasionally in conjunction with a single infusion of intravenous immunoglobulin (IVIg). PE has been occasionally used in emergency situations.

**Post-transfusion Purpura**

Post-transfusion purpura is a rare disorder characterized by an acute severe thrombocytopenia occurring about 1 week after a blood transfusion in association with a high titer of anti-platelet alloantibodies. Due to its rapid effect, PE is considered the initial treatment of choice.

**HELLP Syndrome of Pregnancy**

The HELLP syndrome of pregnancy (characterized by hemolysis [H], elevated liver enzymes [EL], and low platelet [LP] counts) is a severe form of preeclampsia, characterized by hemolysis, elevated liver enzymes, and low platelet counts. The principal form of treatment is delivery of the fetus. However, for patients with severe thrombocytopenia, PE may be indicated if the fetus cannot safely be delivered, or if the maternal thrombocytopenia persists into the postnatal period.

**Neurological**

**Guillain-Barré Syndrome (GBS)**

Guillain-Barré syndrome is an acute demyelinating neuropathy whose severity is graded on a scale of 1 to 5 (the disability scale is summarized in the Appendix to this policy). In 2012, The
Cochrane Collaboration published an updated systematic review of the evidence concerning the efficacy of PE for treating GBS. Six eligible trials (n=649) were identified comparing PE versus supportive treatment alone. No additional trials were published since the 2002 review. The primary outcome measures of the review included time to recover walking with aid and time to onset of motor recovery in mildly affected patients. A pooled analysis of data from three trials found that PE significantly increased the proportion of patients who recovered the ability to walk with assistance after four weeks (RR: 1.60, 95% confidence interval [CI]: 1.19 to 2.15). Data on time to onset of motor recovery were not pooled. Pooled analyses found that PE led to significant improvement in secondary outcomes including reduced time to recover walking without aid, increased likelihood of full muscle strength recovery and reduced likelihood of severe motor sequelae. However, there was a significantly higher risk of relapse in the group that received PE compared to supportive treatment alone (RR: 2.89, 95% CI: 1.05 to 7.93, 6 trials).

A 2007 systematic review evaluated the available randomized trials of immunotherapy to treat GBS. In four trials with severely affected adult participants (n=585), those treated with plasma exchange (PE) improved significantly more on the disability scale four weeks after randomization than those who were not (weighted mean difference [WMD]: -0.89; range: -1.14 to -0.63). In five trials (n=582), the improvement on the disability grade scale with IVIg was very similar to that with PE, WMD: -0.02 (range: -0.25 to 0.20). There was also no significant difference between IVIg and PE for any of the other outcome measures. There was one trial that included patients (n=91) with the mild form of GBS who were able to walk unaided at enrollment. Patients were randomized to receive either two sessions of PE in three days or supportive care. The number of patients with one or more grades of improvement at one month was significantly greater, 26/45 in the treated compared to the control group, 13/45. Fewer patients in the PE-treated group had clinical deterioration (4%) as compared to the control group (39%) or required ventilation; PE group (2% ) versus the control group (13%). In one trial (n=148), following PE with IVIg, did not produce significant extra benefit. Limited evidence from three open trials in children suggested that IVIg hastens recovery compared with supportive care alone. None of the treatments significantly reduced mortality. The authors concluded that “since approximately 20% of patients die or have persistent disability despite immunotherapy, more research is needed to identify better treatment regimens and new therapeutic strategies.”

In 2003, a report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN), Practice parameter: immunotherapy for Guillain-Barré syndrome, was published. The following are the key findings: 1) treatment with PE or IVIg hastens recovery from Guillain-Barré syndrome; 2) combining the two treatments is not beneficial; and 3) steroid treatment given alone is not beneficial. The AAN’s recommendations are: 1) PE is recommended for nonambulant adult patients with GBS who seek treatment within four weeks of the onset of neuropathic symptoms (PE should also be considered for ambulant patients examined within two weeks of the onset of neuropathic symptoms); 2) IVIg is recommended for nonambulant adult patients with GBS within two or possibly four weeks of the onset of neuropathic symptoms (the effects of PE and IVIg are equivalent); 3) corticosteroids are not recommended for the management of GBS; 4) sequential treatment with PE followed by IVIg,
or immunoabsorption followed by IVIg is not recommended for patients with GBS; and 5) PE and IVIg are treatment options for children with severe GBS.

A 2011 RCT from Iran addresses PE for treating young children with severe GBS. The study included 41 children with GBS who required mechanical ventilation and had muscle weakness for no more than 14 days. Patients were randomized to receive PE (n=21) or intravenous immunoglobulin (IVIg) (n=20). Mean age of the patients was 96 months in the PE group and 106 months in the IVIg group. Duration of ventilation, the primary outcome, was a mean of 11 days (standard deviation [SD]=1.5) in the PE group and 13 days (SD=2.1) in the IVIg group, p=0.037. Duration of stay in the intensive care unit, a secondary outcome, was 15.0 days (SD=2.6 days) in the PE group and 16.5 days (SD=2.1 days) in the IVIg group; p=0.94.

In conclusion, the available evidence is sufficient regarding PE for the treatment of patients with all severity grades of GBS. This therapy has a beneficial impact on net health outcome for all severity grades. The published studies are insufficient regarding PE for treatment of GBS in the pediatric population. However, based on limited published data, as well as extrapolated data from studies in adults and clinical input, PE may be considered as a treatment option for children younger than 10 years-old with severe GBS.

**Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)**

A 2012 Cochrane review by Mehnidiratta and Hughes identified two randomized trials on PE for CIDP. Both trials were considered to be of high quality, but both had small sample sizes. One trial with 29 patients used a parallel design and compared PE to sham treatment. The other study included 15 patients and used a cross-over design to compare PE and sham treatment. A pooled analysis of data from the two trials found a statistically significantly greater improvement in impairment after four weeks with PE versus sham (mean difference 31 points on the Neuropathy Impairment Score, 95% CI: 16 to 45 points). The scale ranges from 0 (normal) to 280 (maximally affected). Data on other outcomes were not suitable for pooled analysis.

**Acute Fulminant Central Nervous System (CNS) Demyelination**

The policy statement, which suggests that plasmapheresis may be considered medically necessary in patients with acute fulminant CNS demyelination, is based on the results of a randomized, double-blinded trial, in which 22 patients with MS or other acute idiopathic inflammatory demyelinating diseases of the CNS were enrolled a minimum of 14 days after having failed to respond to at least five days of high-dose corticosteroids. Patients were randomized to receive either seven real or sham PE procedures over a 14-day period. The primary outcome was a targeted neurologic deficit (i.e., aphasia, cognitive dysfunction, etc.). Overall, moderate to marked improvement of the targeted outcome was obtained in 42% of the treatment group, compared to only 6% in the placebo group.

**Paraproteinemic Polyneuropathies**

A randomized, double-blinded trial compared PE to sham treatment in 39 patients with monoclonal gammopathy of undetermined significance (MGUS)-associated polyneuropathy. After twice weekly PE for three weeks, the treatment group reported improvements in neurologic function in the IgG and IgA groups but not the IgM MGUS groups. In addition,
those from the sham group who were later crossed over to the PE group also reported improvement.

**Myasthenia Gravis**
Several RCTs have been published. One of these, a 2011 trial from Germany, included patients with myasthenic crisis. Patients were randomized to treatment with PE (n=10) or immunoadsorption (IA) (n=9). In both groups, three apheresis treatments were performed within seven days; patients could have additional treatments if needed. A total of 16 of 19 (84%) of patients, eight in each group, completed the study and were included in the efficacy analysis. The mean number of treatments was 3.5 in the PE group and 3.4 in the IA group (p>0.05). The primary outcome was change in the modified clinical score (maximum of three points) on day 14 after the last treatment. The baseline modified clinical score was 2.6 in the PE group and 2.5 in the IA group. At day 14, score improvement was 1.6 points in the PE group and 1.4 points in the IA group (p>0.05). Within the 180 days after treatment, one patient in the PE group and three patients in the IA group experienced another myasthenic crisis; the number of events was too small for meaningful statistical analysis for this outcome. There were no statistically significant differences in outcomes in this study, but the sample was very small and the study was probably underpowered.

Two trials included patients with myasthenia gravis in the absence of myasthenic crisis. A randomized trial from China was published in 2009. Liu et al assigned 40 patients with late-onset myasthenia gravis to treatment with double-filtration plasmapheresis (n=15), IA (n=10), or intravenous immune globulin (n=15). Treatment was clinically effective, defined as at least a 50% improvement in the relative symptom score, in 12 of 15 (80%) of the plasmapheresis group, 7 of 10 (70%) in the IA group, and 6 of 15 (40%) of the immune globulin group. The clinical efficacy rate was significantly higher in both the plasmapheresis and immunoadsorption groups compared with the immune globulin group (p<0.05). Findings were similar for other outcomes; the study was limited by the small sample size. A 2011 trial by Barth et al in Canada randomized patients with myasthenia gravis to treatment with PE (n=43) or IVIg (n=41). Patients had moderate to severe myasthenia gravis, as defined by a score of at least 10.5 on the Quantitative Myasthenia Gravis Score (QMGS) for disease severity, and worsening weakness requiring a change in treatment. Patients were not experiencing myasthenic crisis. At day 14, there was not a statistically significant difference between groups in the change on the QMGS, the primary efficacy outcome. Mean QMGSs at day 14 were 4.7 in the PE group and 3.2 in the IVIg group (p=0.13). Moreover, at day 14, 69% were considered improved on PE versus 65% in IVIg; the difference between groups was not statistically significant (p=0.74). Safety outcomes were published in 2013. Forty-two patients received a total of 203 PE procedures; 40 completed the full course of five procedures. Complications occurred in 19 of 42 patients (45%). Two of the complications were serious. One patient had hypertension, heart failure, and pneumonia; all of these were unrelated to the procedures. The other patient had a myocardial infarction, which could have been exacerbated by PE.

The results from the few trials evaluating treatment of myasthenia gravis suggest that PE is reasonably safe in patients with moderate to severe myasthenia crisis. There is some evidence on the comparative efficacy of PE versus IVIg, but the trials are small and report mixed results, and therefore definitive conclusions cannot be made.
Renal
Rapidly Progressive Glomerulonephritis (RPGN)
RPGN is a general term describing the rapid loss of renal function in conjunction with the finding of glomerular crescents on renal biopsy specimens. There are multiple etiologies of RPGN including vasculitis, the deposition of anti-glomerular basement membrane (GBM) antibodies as seen in Goodpasture’s syndrome, or the deposition of immune complexes as seen in various infectious diseases or connective tissue diseases. PE has long been considered a treatment alternative in immune-mediated RPGN. However, there have been few controlled clinical trials published, and their interpretation is difficult due to the small number of patients, choice of intermediate outcomes (i.e., the reduction in antibody levels as opposed to more direct patient outcomes), and heterogeneity in patient groups. Aside from cases of Goodpasture’s disease, the rationale for PE in idiopathic RPGN is not as strong, due to the lack of an identifiable immune component. Studies of PE in this population have not demonstrated a significant improvement in outcome compared to the use of pulse steroid therapy.

Antineutrophil Cytoplasmic Antibody (ANCA)-associated Vasculitis
In 2011, Walsh and colleagues published a meta-analysis of studies on plasma exchange in adults with the diagnosis of either idiopathic renal vasculitis or rapidly progressive glomerulonephritis. A total of nine trials including 387 patients were identified. The clinical populations in the studies were somewhat ill-defined, but most patients appeared to have ANCA-associated vasculitis. In a pooled analysis of study findings, there was a significantly lower risk of end-stage renal disease in patients treated with adjunctive PE compared to standard care alone (RR 0.64, 95% CI: 0.47 to 0.88). The risk of death did not differ significantly in the two groups (RR: 1.01, 95% CI: 0.71-1.40).

A relatively large RCT, included in the previously mentioned meta-analysis, was published in 2007 by Jayne et al. This was a multicenter trial conducted on behalf of the European Vasculitis Study Group. The study investigated whether the addition of PE was more effective than intravenous methylprednisolone. Patients (n=137) with a new diagnosis of ANCA-associated systemic vasculitis confirmed by renal biopsy and serum creatinine greater than 500 µmol/L (5.8 mg/dL) were randomly assigned to receive 7 PEs (n=70) or 3000 mg of intravenous methylprednisolone (n=67). Both groups received oral cyclophosphamide and oral prednisolone. The primary end point was dialysis independence at three months. Secondary end points included renal and patient survival at one year and severe adverse event rates. At three months, 33 (49%) of 67 were alive and independent of dialysis after intravenous methylprednisolone, compared with 48 (69%) of 70 after PE. Compared with intravenous methylprednisolone, PE was associated with a reduction in risk for progression to end-stage renal disease of 24% at 12 months. At one year, the patient survival rate was 51 (76%) of 67 in the intravenous methylprednisolone group; 51 (73%) of 70 in the PE group; severe adverse event rates, 32 of 67 (48%) in the intravenous methylprednisolone group; 35 of (50%) 70 in the PE group. PE increased the rate of renal recovery in ANCA-associated systemic vasculitis that presented with renal failure when compared with intravenous methylprednisolone. Patient survival and severe adverse event rates were similar in both groups. Long-term outcomes of patients from the Jayne et al trial were published in 2013. Median follow-up was 3.95 years. A total of 70 of 136 patients had died, 35 (51%) in the PE group and 35 (51%) in the IV.
methylprednisolone group; the difference between groups was not statistically significant (p=0.75). Similarly, there was not a statistically significant difference between groups in the proportion of patients with end-stage renal disease (33% in the PE group vs 49% in the IV methylprednisolone group, p=0.08). According to findings of this trial, PE appears to have a short-term benefit on preserving renal function in this population, but long-term efficacy remains uncertain.

Transplantation
Solid Organ Transplant
Prior to 2006, plasmapheresis in the setting of solid organ transplant was not addressed by this policy. However, plasmapheresis has been extensively used in this setting, both as pretransplant prophylaxis (i.e., desensitization) for highly sensitized patients at high risk of antibody-mediated rejection (AMR), and as a treatment of AMR after transplant. Desensitization protocols vary among transplant centers; two commonly used protocols are referred to as the Cedars-Sinai protocol and the Johns Hopkins protocol. The Cedars-Sinai protocol consists of high-dose IVIg (2 g/kg) and is offered to patients awaiting either a deceased or live donor. The Johns Hopkins protocol consists of low-dose IVIg (100 mg/kg) in combination with plasmapheresis with or without treatment with anti-CD-20 (i.e., Rituxan). Plasmapheresis is more commonly used in patients receiving a living kidney transplant from an ABO mismatched donor. A variety of protocols have also been developed for the treatment of AMR, often in combination with other therapies, such as IVIg or anti-CD-20. The majority of studies of plasmapheresis in the transplant setting are retrospective case series from single institutions. Therefore, it is not possible to compare immunomodulatory regimens to determine their relative efficacy. Nevertheless, in part based on the large volume of literature published on this subject, it appears that plasmapheresis is a component of the standard of care for the management of AMR.

Other conditions or applications
Asthma
There has been some research interest in the use of plasmapheresis in patients with severe, steroid-dependent asthma. However, preliminary results do not suggest treatment effectiveness.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) and Sydenham’s chorea (SC)
PANDAS is defined as rapid, episodic onset of obsessive-compulsive disorder (OCD) and/or tic disorder symptoms after a Group A β-hemolytic streptococcal infection (GABHS). SC is the neurologic manifestation of acute rheumatic fever. The choreatic symptoms of Sydenham’s chorea are characterized by involuntary rapid and jerky movements that affect the extremities, trunk, and face. SC is generally a self-limited disorder with symptoms resolving in weeks to months. Perlmutter and colleagues conducted an RCT to evaluate the effectiveness of PE and IVIg in reducing the severity of neuropsychiatric symptoms in children diagnosed in the PANDAS subgroup. Children (n=30) with clear evidence of a strep infection as the trigger of their OCD and tics were randomized to receive PE (n=10; 5 to 6 procedures over two weeks), IVIg (n=9; 2 gm/kg over two days) or placebo (n=10; mimic IVIg). All were severely ill at the time of treatment. At one month, both active treatment groups demonstrated symptom improvement, but those in the placebo group were unchanged. The treatment effect was still
Garvey and colleagues conducted an RCT designed to determine if IVIg or PE would be superior to prednisone in decreasing the severity of chorea. Children with Sydenham’s chorea (n=18) were randomized to treatment with PE (n= 8; 5 to 6 procedures over 1 to 2 weeks), IVIg (n=4; 2 gm/kg over two days), or prednisone (n=6; 1 mg/kg/day for 10 days followed by taper over next 10 days). The primary outcome was chorea severity at one month. The secondary outcome variable was chorea severity at one year following treatment. There was no significant difference between the baseline chorea severity scores by the treatment group. Chorea severity was assessed at baseline and at 1, 2, 3, 6, and 12 months following treatment. The chorea rating scale scores range from 0 (no chorea) to 18 (severe or paralytic chorea). A score of nine or higher was required for study entry. Baseline medications to control choreatic symptoms were discontinued one week prior to baseline assessment and each follow-up evaluation. Mean chorea severity for the entire group was lower at the one-month follow-up evaluation (overall 48% improvement). The between-group differences were not statistically significant. Larger studies are needed to confirm these clinical observations.

Summary
In conclusion, due to data from published studies and/or clinical support, plasma exchange is considered medically necessary for selected conditions. For conditions in which there is a lack of efficacy data and clinical support, plasma exchange is considered investigational.

Practice Guidelines and Position Statements
The 2014 National Comprehensive Cancer Network guideline on multiple myeloma stated that plasmapheresis is an adjunctive treatment for patients being treated for multiple myeloma who cannot be treated with stem-cell transplant. Primary treatments include chemotherapy, targeted therapy, and steroids given alone or in combination.

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

- Established effective
  - Acute inflammatory demyelinating polyneuropathy / Guillain-Barre syndrome
  - Chronic inflammatory demyelinating polyneuropathy, short-term treatment
- Probably effective
  - Relapses in multiple sclerosis
- Possibly effective
  - Fulminant demyelinating CNS disease
- Established ineffective
  - Chronic or secondary progressive multiple sclerosis
- Insufficient evidence
  - Myasthenia gravis
Sydenham’s chorea
Acute obsessive-compulsive disorder and tics in PANDAS

In 2013, the American Society for Apheresis (ASFA) released updated guidelines on the use of therapeutic apheresis. Previously, the guidelines had been updated in 2010 and treatment categories were introduced in a 2007 guideline. The following is a description of the ASFA categories and categories:

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Category I includes diseases for which TA (therapeutic apheresis) is accepted as first-line treatment, either as a primary standalone treatment or in conjunction with other treatments. Note that this designation need not imply that TA is mandatory in all cases.</td>
</tr>
<tr>
<td>II</td>
<td>Category II denotes diseases for which TA is accepted as second-line treatment, either as a standalone treatment or in conjunction with other treatments.</td>
</tr>
<tr>
<td>III</td>
<td>Category III diseases are those for which the optimum role of TE is not established and treatment decisions on an individual basis are recommended.</td>
</tr>
<tr>
<td>IV</td>
<td>Category IV indicates disorders for which published evidence suggests or demonstrates that TE is ineffective or harmful.</td>
</tr>
</tbody>
</table>

Below are the indications for therapeutic plasma exchange followed by the ASFA category recommendations for 2007, 2010 and 2013.

Indication Categories for Therapeutic Apheresis- Plasma Exchange

<table>
<thead>
<tr>
<th>Disease group/Name/Condition</th>
<th>2007</th>
<th>2010</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catastrophic antiphospholipid syndrome</td>
<td>III</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>III</td>
<td>IV</td>
<td>III</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manifestations other than nephritis</td>
<td>III</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Severe NC</td>
<td>NC</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Nephritis</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>Hematologic:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABO incompatible hematopoietic progenitor cell transplantation</td>
<td>II</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Pure red blood cell aplasia</td>
<td>III</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Warm autoimmune hemolytic anemia</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Cold agglutinin disease</td>
<td>III</td>
<td>II</td>
<td>II</td>
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<tr>
<td>Coagulation factor inhibitors</td>
<td>III</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>Hyperviscosity in monoclonal gammopathies</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenia purpura</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory immunoadsorption</td>
<td>II</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Refractory or non-refractory</td>
<td>IV</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Myeloma and acute renal failure</td>
<td>III</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Post-transfusion purpura</td>
<td>III</td>
<td>III</td>
<td>III</td>
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<tr>
<td>Red blood cell alloimmunization in pregnancy</td>
<td>II</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Condition</td>
<td>Level 1</td>
<td>Level 2</td>
<td>Level 3</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Thrombotic thrombocytopenia purpura</strong></td>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Sepsis (in 2010, sepsis with multiorgan failure)</td>
<td>III</td>
<td>III</td>
<td>III</td>
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<tr>
<td>Thyrotoxicosis (in 2010, thyroid storm)</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td><strong>Neurological:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>III</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome)</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td>Chronic inflammatory demyelinating polyradiculoneuropathy</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>II</td>
<td>II</td>
<td>II</td>
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<tr>
<td>Multiple sclerosis</td>
<td>II</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Acute CNS inflammatory demyelinating disease</td>
<td>II</td>
<td>II</td>
<td>II</td>
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<tr>
<td>Devic’s syndrome</td>
<td>III</td>
<td>NC</td>
<td>NC</td>
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<tr>
<td>Chronic progressive</td>
<td>III</td>
<td>III</td>
<td>III</td>
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<tr>
<td>Myasthenia gravis</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td>Paraneoplastic neurologic syndromes</td>
<td>III</td>
<td>III</td>
<td>III</td>
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<tr>
<td>Paraproteinemic polyneuropathies</td>
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<tr>
<td>IgG/IgA</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td>IgM</td>
<td>II</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Sydenham’s chorea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe PANDAS (2010 exacerbations)</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td>Severe SC</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td>Rasmussen’s encephalitis</td>
<td>II</td>
<td>NC</td>
<td>III</td>
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<tr>
<td>Stiff-person syndrome</td>
<td>III</td>
<td>IV</td>
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<tr>
<td><strong>Renal:</strong></td>
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<tr>
<td>ANCA-associated rapidly progressive glomerulonephritis (Wegener’s granulomatosis)</td>
<td>II</td>
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<tr>
<td>Dialysis dependence</td>
<td>NC</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Dialysis independence</td>
<td>NC</td>
<td>III</td>
<td>III</td>
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<tr>
<td>Anti-glomerular basement membrane disease (Goodpasture’s syndrome)</td>
<td>I</td>
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<td></td>
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<tr>
<td>Diffuse alveolar hemorrhage (DAH)</td>
<td>NC</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Dialysis dependence and no DAH</td>
<td>NC</td>
<td>IV</td>
<td>III</td>
</tr>
<tr>
<td>Dialysis independence</td>
<td>NC</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>III</td>
<td>NC</td>
<td>NC</td>
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<tr>
<td>Secondary</td>
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<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Recurrent</td>
<td>NC</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome (HUS);thrombotic microangiopathy; transplant associated microangiopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic HUS</td>
<td>III</td>
<td>III</td>
<td>NC</td>
</tr>
<tr>
<td>Transplant-associated microangiopathy</td>
<td>III</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Diarrhea associated pediatric</td>
<td>IV</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Atypical HUS due to complement factor gene mutations</td>
<td>NC</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Atypical HUS due to autoantibody to factor H</td>
<td>NC</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Diarrhea associate HUS or typical H</td>
<td>NC</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>Rapidly progressive glomerulonephritis</td>
<td>III</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Renal transplantation: antibody mediated rejection; HLA desensitization</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Antibody mediated rejection | II | I | III
LA desensitization | II | NC | I
Desensitization, living donor, positive crossmatch due to donor specific HLA antibody | NC | II | III
High PRA; cadaveric donor | NC | III | III

Rheumatic:
Scleroderma (progressive systemic sclerosis) | III | III | III

Transplantation:
ABO incompatible solid organ transplantation
Kidney | II | II | I/II
Heart (infants) | II | II | NC
Liver (2010 perioperative) | III | III | I/II/III
Heart transplantation rejection
Treatment | III | NC | NC

Abbreviations: NC—not categorized

Key Words:
Plasma exchange, plasmapheresis, apheresis, therapeutic apheresis, therapeutic plasma exchange, Rheo, Rheopheresis, focal glomerulosclerosis, FGS, focal segmental glomerulosclerosis, FSGS, Neuromyelitis optica, NMO, Devic syndrome

Approved by Governing Bodies:
Plasmapheresis is a procedure and therefore not subject to FDA approval.

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational and will be reviewed for medical necessity.

Coding:
CPT code: 36514 Therapeutic apheresis; for plasma pheresis

References:
79. White, NB. Successful rescue therapy with plasmapheresis and intravenous immunoglobulin for acute humoral renal transplant rejection. Transplantation 2004; 78(5); 772-4.

Policy History:
TEC Assessment, November 1998
Medical Policy Group, March 2003 (2)
Medical Policy Administration Committee, March 2003
Available for comment April 1-May 16, 2003
Medical Policy Group, March 2005 (1)
Medical Policy Administration Committee, July 2005 (2)
Available for comment July 28-September 10, 2005
Medical Policy Group, January 2006 (2)
Medical Policy Administration Committee, February 2006
Available for comment March 4-April 17, 2006
Medical Policy Group, September 2006 (4)
Medical Policy Administration Committee, September 2006
Available for comment September 22-November 5, 2006
Medical Policy Group, September 2008 (1)
Medical Policy Administration Committee, October 2008
Available for comment October 4-November 17, 2008
Medical Policy Group, June 2009 (1)
Medical Policy Administration Committee, July 2009
Available for comment July 2-August 15, 2009
Medical Policy Group, September 2009 (2)
Medical Policy Administration Committee, October 2009
Available for comment October 3-November 17, 2009
Medical Policy Group, February 2010 (1): Updated policy for covered and non-covered conditions, reference list
Medical Policy Administration Committee, April 2010
Available for comment April 7-May 21, 2010
Medical Policy Group, January 2012 (3): Updated Key Points and References
Medical Policy Panel, May 2013
Medical Policy Group, May 2013 (1): Update to Policy with added coverage for CAPS, myeloma with renal failure, dense deposit disease with factor H and/or C3 Nephritic factor and focal segmental glomerulosclerosis after renal transplant. Serum creatinine threshold removed from ANCA-associated vasculitis criteria; updated Key Points and References Available for comment May 22 through July 5, 2013

Medical Policy Panel, May 2014

Medical Policy Group, June 2014 (1): Update to Key Points and References; no change to policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.