Plasma Exchange

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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for plasma exchange when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Plasma exchange is considered medically necessary for the conditions listed below:

Autoimmune
- Severe multiple manifestations of mixed cryoglobulinemia (MC) such as cryoglobulinemic nephropathy, skin ulcers, sensory motor neuropathy, and widespread vasculitis in combination with immunosuppressive treatment;
- catastrophic antiphospholipid syndrome.

Hematologic
- ABO incompatible hematopoietic progenitor cell transplantation;
- hyperviscosity syndromes associated with multiple myeloma or Waldenstrom’s macroglobulinemia;
- idiopathic thrombocytopenic purpura in emergency situations;
- thrombotic thrombocytopenic purpura (TTP);
- atypical hemolytic-uremic syndrome;
- post-transfusion purpura;
- HELLP syndrome of pregnancy (a severe form of preeclampsia, characterized by hemolysis [H], elevated liver enzymes [EL], and low platelet [LP] counts);
- myeloma with acute renal failure.

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 (MS), with acute fulminant central nervous system (CNS) demyelination;
- myasthenia gravis in crisis or as part of preoperative preparation;
- paraproteinemia polyneuropathy; IgA, IgG;
- N-methyl D-aspartate receptor antibody encephalitis;
- Progressive multifocal leukoencephalopathy associated with natalizumab.

Renal
- Anti-glomerular basement membrane disease (Goodpasture syndrome);
- ANCA [antineutrophil cytoplasmic antibody]-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.

Transplantation
- ABO incompatible solid organ transplantation;
  o Kidney;
  o Heart (infants); and
- renal transplantation: antibody mediated rejection; HLA [human leukocyte antigen] desensitization;
- focal segmental glomerulosclerosis after renal transplant.

**When Policy Topic is not covered**
Plasma exchange 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;
- amyotropic lateral sclerosis;
- ANCA (antineutrophil cytoplasmic antibody) -associated rapidly progressive glomerulonephritis (Wegener’s granulomatosis or GPA without 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);
- idiopathic thrombocytopenic purpura; refractory or non-refractory;
- inclusion body myositis;
- Lambert-Eaton myasthenic syndrome;
- multiple sclerosis; chronic progressive or relapsing remitting;
mushroom poisoning;
- myasthenia gravis with anti-MuSK antibodies;
- neuromyelitis optica (NMO);
- overdose and poisoning (other than mushroom poisoning);
- paraneoplastic syndromes;
- paraproteinemia polyneuropathy; IgM
- pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
- pemphigus vulgaris;
- phytic acid storage disease (Refsum’s disease);
- POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes);
- psoriasis;
- red blood cell alloimmunization in pregnancy;
- rheumatoid arthritis;
- sepsis;
- scleroderma (systemic sclerosis);
- stiff person syndrome;
- Sydenham’s chorea (SC);
- systemic lupus erythematosus; manifestations other than nephritis; nephritis; and
- thyrotoxicosis and
- hyperviscosity syndromes with renal failure (other than associated with multiple myeloma or Waldenström macroglobulinemia).

Considerations
Patients receiving plasma exchange (PE) as a treatment of CIDP should meet the diagnostic criteria for CIDP, which are included in an Appendix to this policy.

The use of PE in patients with acute, life-threatening complications of chronic autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus (SLE), may need to be considered on an individual basis. An example of such a situation would be the development of a severe vasculitis, in which it is hoped that the use of PE can acutely lower the level of serum autoantibodies until an alternate long-term treatment strategy can be implemented. However, in these situations, the treatment goals and duration of treatment with PE need to be clearly established prior to its initiation; without such treatment goals, the use of an acute short-term course of PE may insidiously evolve to a chronic use of PE with uncertain benefit.

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. PE is a nonspecific therapy, because 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.
Data from published studies, clinical input, and/or guidelines from the American Society for Apheresis support the use of PE for selected autoimmune, hematologic, neurologic, renal, and transplantation conditions.

**Background**
The terms therapeutic apheresis, plasmapheresis, and plasma exchange are often used interchangeably but should properly be used to 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 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. Plasma exchange 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 2 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).

**Rationale**

This evidence review was created in 1995 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through July 21, 2017. The following is a summary of the key literature to date.

Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

**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.(2) 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 unknown to what extent plasma levels parallel clinical disease. For example, in many of the controlled trials discussed next, 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**

A 2016 systematic review by Kronbichler et al stated that the interpretation of studies evaluating PE for treating systemic lupus erythematosus is limited due to factors such as the available study designs, small numbers of patients, variability
in PE dosing and protocols. Reviewers did not identify any recent controlled trials evaluating the impact of PE on health outcomes in patients with systemic lupus.

Reporting on the results of a randomized controlled trial (RCT), Lewis et al (1992) concluded that PE had no benefit in patients with systemic lupus and glomerulonephritis compared with 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 et al (2002) reported on a prospective case series of 28 patients with proliferative lupus nephritis; 12 underwent synchronized plasmapheresis and pulse cyclophosphamide therapy, while the remaining 16 underwent cyclophosphamide alone. Although plasmapheresis was associated with a decreased time to remission of renal disease, at the end of the 4-year follow-up, there was no difference in outcome.

Multiple Sclerosis
There have been several RCTs of PE in patients with multiple sclerosis (MS) that have reported inconclusive results. Khatri et al (1985) studied 54 patients with chronic progressive MS randomized to sham or true PE. The degree of improvement in the PE group was greater than that in the control group. Weiner et al (1989) 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 1991 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 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. 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 et al (2000) 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 (73%) of the 73 patients received 3,4
diaminopyridine, with 79% reporting marked or moderate responses. In the same
year, a small RCT of 3,4 diaminopyridine also reported positive results, confirming
other anecdotal reports.(10) Anderson et al (1988) 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 2 patients (17%)
showed a minor improvement in neurologic symptoms.11

**Rheumatoid Arthritis**
In 1983, Dwosh et al 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.(12)

**Polymyositis and Dermatomyositis**
Miller et al (1992) conducted a randomized trial of PE in the treatment of 39
patients with polymyositis and dermatomyositis and found that PE was no more
effective than sham pheresis.(13)

**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 high doses of steroids can produce
significant adverse effects. Guillaume et al (1988) reported on a study of 40
patients with pemphigus randomized to prednisone alone or prednisone plus
plasmapheresis.(14) This study sought to determine whether plasmapheresis can
reduce the required dose of steroids, thus limiting its toxicity. Unfortunately,
disease control in the 2 groups was the same, and the authors concluded that
plasmapheresis in conjunction with low-dose steroids is not effective in treating
pemphigus.

**Stiff Man (or 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 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.(15-19) Most of
these studies were published in the late 1980s or early 1990s. A case series with 9
patients was published in 2014(18) and a case report of 2 patients was published
in 2016.(19)

**Cryoglobulinemia**
There are several types of cryoglobulinemia. Type I is associated with hematologic
disorders. Types II and III are considered mixed cryoglobulinemias. Mixed
cryoglobulinemia is a consequence of immune-complex mediated vasculitis and
may be associated with infectious and systemic disorders (eg, hepatitis C virus).
In 2010, Rockx and Clark published a review of studies evaluating PE for treating
cryoglobulinemia that included at least 5 patients.(20) They identified 11 studies (total N=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 and Hemolytic Uremic Syndrome

Once considered distinct syndromes, thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are now considered different manifestations of the same disease process (ie, thrombotic microangiopathy). In 2009, a systematic review evaluated the benefits and harms of different interventions for HUS and TTP (separately).(21) Interventions were compared with placebo or supportive therapy or a comparison of 2 or more interventions. Interventions examined included heparin, aspirin/dipyridamole, prostanooids, ticlopidine, vincristine, fresh frozen plasma (FFP) infusion, plasmapheresis with FFP, systemic corticosteroids, Shiga toxin-binding agents, or immunosuppressive agents. For TTP, 6 RCTs (N=331) 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 2 weeks (relative risk [RR], 1.48) and all-cause mortality (RR=1.91) in the PI group.

The authors concluded that PE with FFP 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, neurologic/extrarenal events, renal biopsy changes, proteinuria, or hypertension at the last follow-up visit. The incidence of bleeding was significantly greater in those receiving anticoagulation therapy compared with supportive therapy alone (risk difference, 0.35). 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 (2009) described data supporting use of PE in the atypical form of this disease, with results showing remission in up to 60% of patients.(22)

All studies in HUS have been conducted with patients with the diarrheal (typical) form of the disease. Because the available evidence for patients with typical HUS shows supportive therapy, including dialysis, to be the most effective treatment, evidence for 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

Idiopathic thrombocytopenic purpura is an acquired disease of 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.

**Posttransfusion Purpura**
Posttransfusion purpura is a rare disorder characterized by an acute severe thrombocytopenia occurring approximately 1 week after a blood transfusion in association with a high titer of antiplatelet alloantibodies. Because of its rapid effect, PE is considered the initial treatment of choice.

**HELLP Syndrome of Pregnancy**
The HELLP syndrome of pregnancy (characterized by hemolysis, elevated liver enzymes, and low platelet counts) is a severe form of preeclampsia. 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.

**Myeloma With Acute Renal Failure**
In 2015, Yu et al published a meta-analysis of RCTs on treatment of acute renal failure associated with multiple myeloma with chemotherapy alone vs chemotherapy and PE.(23) Four RCTs were identified and 3 of these had full text availability and were included in the data synthesis. None of the RCTs were double-blinded. The studies included a total of 63 patients receiving chemotherapy only and 84 patients receiving chemotherapy and PE. A variety of chemotherapy agents and PE protocols were used. In a pooled analysis, there was not a statistically significant difference in 6 month survival in the 2 groups (RR=0.92; 95% confidence interval [CI], 0.76 to 1.11; p=0.39). However, the dialysis dependent rate among survivors at 6 months was significantly lower in the chemotherapy plus PE group compared with the group receiving chemotherapy alone (RR=2.02; 95% CI, 1.03 to 3.96; p=0.04).

**NEUROLOGIC**

**Guillain-Barré Syndrome**
Guillain-Barré syndrome (GBS) is an acute demyelinating neuropathy whose severity is graded on a scale of 1 to 5. In 2017, The Cochrane Collaboration published an updated systematic review of the evidence concerning the efficacy of PE for treating GBS.(24) Reviewers included RCTs evaluating PE alone in children and/or adults with disease of any severity. Eight eligible trials were identified. The primary outcome measure of the review was the time to recover walking with aid. However, reviewers noted that the outcome “change in disability grade” was the primary end point of many of the trials and this was included as a secondary outcome of the Cochrane review. Not enough trials reported the primary outcome of interest. However, 3 trials reported the proportion of patients who recovered walking with assistance after 4 weeks; in a pooled analysis, a significantly greater proportion of patients recovered after PE than control (RR=1.60; 95% CI, 1.19 to 2.15; I²=34%). In a pooled analysis of 5 trials comparing improvement in walking by at least 1 grade after 4 weeks, a secondary outcome, PE was significantly more
effective than sham or supportive treatment (RR=1.64; 95% CI, 1.37 to 1.96; I²=0%). There were also significantly fewer patients on a ventilator at 4 weeks with PE vs control (RR=0.53; 95% CI, 0.39 to 0.74; I²=43%). None of the studies in this review included patients younger than 10 years old.

A 2011 RCT from Iran evaluated PE for treating young children with severe GBS.(25) 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 PE (n=21) or IVIg (n=20). Mean patient age was 96 months in the PE group and 106 months in the IVIg group. Mean (standard deviation [SD]) duration of ventilation, the primary outcome, was 11 (1.5) days in the PE group vs 13 (2.1) days in the IVIg group (p=0.037). Duration of stay in the intensive care unit, a secondary outcome, was 15.0 (2.6) days in the PE group and 16.5 (2.1) days in the IVIg group (p=0.94).

**Chronic Inflammatory Demyelinating Polyradiculoneuropathy**
A 2015 Cochrane review by Mehnidiratta and Hughes identified 2 randomized trials on PE for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).(26) 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 with sham treatment. The other study included 18 patients and used a crossover design to compare PE and sham treatment. A pooled analysis of data from the 2 trials found a statistically significantly greater improvement in impairment after 4 weeks with PE vs sham (mean difference in Neuropathy Impairment Score: 31 points, 95% CI, 16 to 45 points). The scale ranges from 0 (normative) to 280 (maximally affected). Data on other outcomes were not suitable for pooled analysis.

**Acute Fulminant Central Nervous System Demyelination**
The conclusion plasmapheresis may be considered medically necessary in patients with acute fulminant central nervous system demyelination is based on the results of a 1999 randomized, double-blinded trial, in which 22 patients with MS or other acute idiopathic inflammatory demyelinating diseases of the central nervous system were enrolled a minimum of 14 days after having failed to respond to at least 5 days of high-dose corticosteroids.(27) Patients were randomized to 7 real or sham PE procedures over a 14-day period. The primary outcome was a targeted neurologic deficit (ie, aphasia, cognitive dysfunction). Overall, moderate to marked improvement of the targeted outcome was obtained in 42% of the treatment group, compared with only 6% in the placebo group.

**Paraproteinemic Polyneuropathies**
A 1991 randomized, double-blinded trial compared PE with sham treatment in 39 patients with monoclonal gammopathy of undetermined significance-associated polyneuropathy.(28) After twice weekly PE for 3 weeks, the treatment group reported improvements in neurologic function in the IgG and IgA groups but not the IgM monoclonal gammopathy of undetermined significance groups. In addition, those from the sham group who later crossed over to the PE group also reported improvement.
**Myasthenia Gravis**
Several RCTs have been published. A 2011 trial from Germany, included patients with myasthenic crisis.(29) Patients were randomized to treatment with PE (n=10) or immunoadsorption (IA) (n=9). In both groups, 3 apheresis treatments were performed within 7 days; patients could have additional treatments if needed. A total of 16 (84%) of 19 of patients, 8 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 3 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 180 days after treatment, 1 patient in the PE group and 3 patients in the IA group experienced another myasthenic crisis; the number of events was too small for meaningful statistical analysis for this outcome. Although there were no statistically significant differences in outcomes in this study, the patient sample was very small and the study was likely underpowered.

A 2017 RCT by Alipour-Faz et al in Iran randomized 24 adults patients with myasthenia gravis to presurgical treatment with PE (n=12) or IVIG (n=12).(30) Treatments were given 10 to 30 days before thymectomy. All patients completed the study. Study outcomes were duration of hospitalization (days), length of postsurgical intensive care unit stay (hours), duration of intubation (hours), duration of surgery (hours), and dose of steroids (milligrams). Most outcomes were similar in the 2 groups. One outcome, length of intubation period, differed significantly between groups. The median length of intubation was 0 hours in the IVIG group and 13 hours in the PE group (p=0.01).

**Neuromyelitis Optica**
Neuromyelitis optica (NMO) is a rare inflammatory disorder of the central nervous system that predominantly affects the optic nerves and spinal cord. No RCTs evaluating PE for treatment of patients with NMO were identified. Several retrospective nonrandomized studies have evaluated PE as add-on therapy to intravenous (IV) corticosteroids.

In 2016, Abboud et al reviewed 83 admissions for acute relapse of NMO at a single center in the United States.(31) Relapses could involve the spinal cord, optic nerve, and/or the brain. Patients were initially treated with IV corticosteroids alone for 5 days, and if they did not respond, they were then treated with 5 to 7 sessions of PE in their second week of hospitalization. Eighteen relapses (16 patients) were treated with IV corticosteroid therapy alone, and 65 relapses (43 patients) were treated with IV corticosteroid plus PE. Patients were assessed using the Expanded Disability Status Score (EDSS), which has a possible range of 1 to 10, with higher numbers indicating more disability. The primary end point was a return to baseline EDSS (before admission) on discharge. The EDSS scores at baseline and discharge were calculated retrospectively based on available records and without blinding to treatment group.
In the relapses treated with IV corticosteroids only, the median baseline EDSS was 2.5, which increased to 4.5 at presentation and decreased to a median of 4 at discharge. In comparison, among the relapses that were also treated with PE, the median baseline EDSS was 5.75 which increased to 7.75 at presentation and decreased to a median of 6.5 at discharge. At discharge, 3 relapses (17%) in the IV corticosteroid-only group improved to baseline EDSS or lower at discharge compared with 31 relapses in the IV corticosteroid plus PE group (p=0.016). Follow-up data at approximately 1 year (range, 6-18 months) were available on 50 (77%) of 65 relapses. At this longer term follow-up point, 6 relapses in the intravenous methylprednisolone (IVMP) only group and 33 in the IVMP group improved to an EDSS equal or below their baseline EDSS (p=0.039).

The study did not directly compare the efficacy of IV corticosteroid treatment alone with IV corticosteroids plus PE because the treatments were applied sequentially. Moreover, the patient populations differed; patients who received PE add-on treatment were older and more disabled at baseline. The finding that a greater proportion of the more severely ill population had resolution of acute relapses suggests that combination IV corticosteroid and PE therapy may be more beneficial than IV corticosteroids alone. However, to draw definitive conclusions, findings would need to be confirmed in randomized trials. Another study limitation was a lack of patient-level analyses and lack of other outcome measures at 1 year measuring disease progression.

Two other studies were conducted at a facility in Martinique, and they compared outcomes in patients treated before and after PE was introduced as a treatment. A 2009 study by Bonnan et al focused on spinal attacks associated with NMO.(32) The study reported on 43 patients with NMO, 18 of whom received PE as add-on therapy for at least 1 spinal attack. The study period was 1982 to 2008 and PE was introduced at the facility in 1999. The patients experienced a total of 96 spinal attacks; PE was used in 29 attacks. The PE-treated and corticosteroid-only groups had similar EDSS scores before the spinal attacks, and there was greater reduction in EDSSs following treatment with PE. In the PE group, the mean acute EDSS (SD) was 7.9 (1.3) and the mean EDSS after therapy was 5.1 (2.4), a mean decrease of 2.8 points. In comparison, the mean acute EDSS in the corticosteroid-only group was 8.0 (1.4), and the mean EDSS after treatment was 6.8 (1.9), a mean decrease of 1.2 points. The analysis was done on a per attack basis rather than a per-patient basis.

The 2012 study by Merle et al evaluated the impact of PE as an add-on therapy on optic outcomes in (32) patients treated for acute optic neuritis between 1996 and 2010.33 In 2006, PE was added to the treatment protocol and 16 of the 32 patients also received 5 daily consecutive PEs in the intensive care unit. Study outcomes were obtained from an eye examination performed at least 6 months after optic neuritis treatment. At the final follow-up visit, visual acuity was significantly better in the PE group than the corticosteroid-only group (20/400 vs 20/50, respectively, p=0.04). Visual acuity gain was 20/200 in the corticosteroid group and 20/30 in the PE group (p=0.01). Outcomes could be impacted by confounding factors. For example, longer disease duration was associated with
poorer outcomes in univariate analysis and, at baseline, disease duration was significantly longer in the corticosteroid group than the PE group (mean, 10.8 and 5.8 years, respectively, p<0.001).

Limitations of the Bonnan et al and Merle et al studies include that patients may have overlapped between studies, and lack of randomization may have led to baseline between-group differences in factors that affected outcomes. In addition, both studies are subject to bias due to use of historical controls, i.e., patients in the latter time period received PE and care could also have improved over time in other ways that led to improved outcomes.

A retrospective review of registry data was published by Kleiter et al in 2016. The investigators identified 185 patients NMO added to the registry since 2008; together, they experienced 871 acute attacks. Various first-line treatment of NMO attacks were used, most commonly high-dose intravenous steroids (70.3% of treatment courses). PE was the first-line treatment in 27 (15%) of 185 patients. The investigators did not report on the efficacy of PE as second-line or add-on treatment.

The available nonrandomized retrospective studies have methodologic limitations (e.g., lack of randomization, use of historical control groups), and findings need to be confirmed in well-designed and conducted randomized trials. Limitations of the available studies include lack of randomization, use of historic

**N-methyl D-aspartate Receptor Antibody Encephalitis**
A 2017 review by the American Society for Apheresis (ASFA) stated that, if left untreated, this condition leads to decline in the autonomic function and, ultimately, to death. They state that approximately 50% of patients respond to one of several first-line immunotherapies, which includes plasma exchange. There is little published evidence. A retrospective evaluation of 14 patients with anti-N-methyl-D-aspartate receptor antibody encephalitis found improvement in the modified Rankin score in 7 of 10 patients treated with plasma exchange compared with 3 of 10 patients treated with corticosteroids.

**Progressive multifocal leukoencephalopathy associated with natalizumab**
As stated in the 2017 ASFA review, stated above, progressive multifocal leukoencephalopathy (PML) is a potentially fatal side effect of natalizumab, a treatment option for relapsing multiple sclerosis. If PML is suspected, natalizumab should be stopped immediately. In addition, plasma exchange, which was shown in a small study of 12 patients to reduce serum natalizumab concentration by 92% in a week, can be used to quickly clear natalizumab from the bloodstream and reduce the consequences of PML.

**RENAL**

**Rapidly Progressive Glomerulonephritis**
Rapidly progressive glomerulonephritis (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 antiglomerular basement membrane antibodies, as seen in Goodpasture 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 (ie, the reduction in antibody levels as opposed to more direct patient outcomes), and heterogeneity in patient groups. (38) Aside from cases of Goodpasture disease, the rationale for PE in idiopathic RPGN is not strong, because of the lack of an identifiable immune component. Studies of PE in this population have not demonstrated a significant improvement in outcome compared with the use of pulse steroid therapy. (39)

**Antineutrophil Cytoplasmic Antibody–Associated Vasculitis**

In 2011, Walsh et al published a meta-analysis of studies on PE in adults with the diagnosis of either idiopathic renal vasculitis or rapidly progressive glomerulonephritis. (40) A total of 9 trials including 387 patients were identified. Clinical populations in the studies were somewhat ill-defined, but most patients appeared to have antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis. In pooled analysis, the risk of end-stage renal disease was significantly lower in patients treated with adjunctive PE compared with standard care alone (RR=0.64; 95% CI, 0.47 to 0.88). The risk of death did not differ statistically between the 2 groups (RR=1.01; 95% CI, 0.71 to 1.40).

In 2007, Jayne et al published a relatively large RCT, included in the previously mentioned meta-analysis. (41) 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 the addition of intravenous methylprednisolone. Patients (N=137) with a new diagnosis of ANCA-associated systemic vasculitis confirmed by renal biopsy and serum creatinine greater than 5.8 mg/dL were randomized to 7 PEs (n=70) or 3000 mg of IVMP (n=67). Both groups received oral cyclophosphamide and oral prednisolone. The primary end point was dialysis independence at 3 months. Secondary end points included renal and patient survival at 1 year and severe adverse event rates. At 3 months, 33 (49%) of 67 were alive and independent of dialysis after IVMP, compared with 48 (69%) of 70 after PE. Compared with IVMP, PE was associated with a reduction in risk for progression to end-stage renal disease (24% at 12 months). At 1 year, patient survival was 51 (76%) of 67 in the IVMP group and 51 (73%) of 70 in the PE group, and severe adverse events occurred in 48% of the IVMP group and in 50% of the PE group. Compared with IVMP, PE increased the rate of renal recovery in patients with ANCA-associated systemic vasculitis who presented with renal failure. Patient survival and severe adverse event rates were similar in both groups. Long-term outcomes of patients in this trial were published in 2013. (42) 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 IVMP group (p=0.75). Similarly, the difference between groups in the proportion of patients with end-stage renal disease (33% in the PE group vs 49% in the IVMP group, p=0.08) was not
statistically significant. According to results of this trial, PE appears to have a short-term benefit on preserving renal function in this population, but long-term efficacy remains uncertain.

**TRANSPANTATION**

**Solid Organ Transplant**
Before 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 (ie, 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; 2 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-CD20 (ie, rituximab). Plasmapheresis is more commonly used in patients receiving a living kidney transplant from an ABO mismatched donor.(43) A variety of protocols have also been developed for the treatment of AMR, often in combination with other therapies, such as IVIg or anti-CD20.(44-47) Most 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.

**MISCELLANEOUS POTENTIAL APPLICATIONS OF PE**

**Acute Liver Failure**
One controlled study was identified, an unblinded RCT published in 2016 by Larsen that evaluated high-volume PE in patients with acute liver failure (ALF).(48) Patients with a diagnosis of ALF and at least grade 2 encephalopathy were randomized to standard care only (n=90) or standard care plus high-volume PE (n=92). Entry into the study occurred within 24 hours of grade 2 encephalopathy onset. The high-volume PE procedure consisted of exchanging 15% of ideal body weight (8 to 12 liters per day per procedure). Patients’ plasma was removed at the rate of 1 to 2 liters per hour and was replaced with an equivalent amount of fresh-frozen plasma. Patients underwent PE on 3 consecutive days. The primary endpoint was transplant-free survival at the time of hospital discharge. Mean length of hospital stay was 21.9 days in the PE group and 41.8 days in the standard care group. The number of patients surviving to hospital discharge was 54 (58.7%) in the PE group and 43 (47.8%) in the group receiving standard care only; the difference between groups was statistically significant. Survival of patients who had a liver transplant (24, 26% in the PE group and 32, 36% in the standard care group) was not significantly impacted by the addition of PE. However, the rate of survival to hospital discharge was significantly higher with PE in the subset of patients who were not listed for transplantation due to
contraindications such as medical comorbidities (28, 30% in the PE group and 36, 40% in the standard care group, p=0.03). Limitations of the study include that it was not blinded and that the survival outcome was measured only at hospital discharge, a period of several weeks and longer-term outcomes were not reported. In addition, the PE protocol and transplantation criteria in Denmark, where the study was conducted, may differ from the U.S.

**Asthma**
There has been some research interest in the use of plasmapheresis in patients with severe, steroid-dependent asthma. However, 1 small crossover trial with 4 patients, published in 2001, did not suggest treatment effectiveness.(49) No subsequent controlled studies have been published.

**Sepsis**
In 2014, Rimmer et al published a systematic review and meta-analysis of literature on PE for treatment of sepsis and septic shock.(50) Reviewers identified 4 RCTs comparing PE with usual care; the trials included a total of 194 patients. All of the trials were rated as unclear or high risk of bias. In a pooled analysis of data from the 4 trials, PE was not significantly associated with a reduction in mortality risk (RR=0.83; 95% CI, 0.45 to 1.52). Data were insufficient for pooled analyses of other outcomes. The evidence identified in this systematic review is insufficient for drawing conclusions about the impact of PE for treating sepsis on the net health outcome.

**Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections and Sydenham Chorea**
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is defined as rapid, episodic onset of obsessive-compulsive disorder (OCD) and/or tic disorder symptoms after a group A beta-hemolytic streptococcal infection (GABHS). Sydenham chorea (SC) is the neurologic manifestation of acute rheumatic fever. The choreatic symptoms of SC 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 et al (1999) 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.(51) Children (N=30) with clear evidence of a strep infection as the trigger of their OCD and tics were randomized to PE (n=10; 5-6 procedures over 2 weeks), IVIg (n=10; 2 g/kg over 2 days,) or placebo (n=10; mimic IVIg). All were severely ill at the time of treatment. At 1 month, both active treatment groups demonstrated symptom improvement, but those in the placebo group were unchanged. The treatment effect was still apparent after 1 year. However, 50% of children were on the same or higher doses of their baseline medications; thus it is not entirely clear that IVIg or PE had a beneficial effect. This study needs to be replicated with a larger number of patients. The authors noted that children in the placebo group (IVIg control group) subsequently received PE in an open trial and had only minor improvements.
Garvey et al (2005) conducted an RCT designed to determine whether IVIg or PE was superior to prednisone in decreasing the severity of chorea. (52) Children with SC (N=18) were randomized to treatment with PE (n= 8; 5-6 procedures over 1-2 weeks), IVIg (n=4; 2 g/kg over 2 days), or prednisone (n=6; 1 mg/kg/d for 10 days followed by taper over next 10 days). The primary outcome was chorea severity at 1 month. The secondary outcome variable was chorea severity at 1 year after treatment. There was no significant difference between the baseline chorea severity scores by treatment group. Chorea severity was assessed at baseline and at 1, 2, 3, 6, and 12 months after treatment. The Chorea Rating Scale scores range from 0 (no chorea) to 18 (severe or paralytic chorea). A score of 9 or higher was required for study entry. Baseline medications to control choreatic symptoms were discontinued 1 week before baseline assessment and each follow-up evaluation. Mean chorea severity for the entire group was lower at the 1-month follow-up evaluation (overall 48% improvement). Between-group differences were not statistically significant. Larger studies are needed to confirm these clinical observations.

Other Conditions
Outcome data are inadequate to validate the use of PE in other conditions listed in the Policy as investigational and not otherwise discussed in the Rationale section.

SUMMARY OF EVIDENCE
Due to data from published studies and/or clinical support, PE is considered medically necessary for selected conditions. For conditions in which there is a lack of efficacy data and clinical support, PE is considered investigational.

SUPPLEMENTAL INFORMATION

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received through 2 physician specialty societies and 3 academic medical centers while this policy was under review in 2012. There was consensus or near-consensus that PE for dense deposit disease with factor H deficiency and/or elevated C3 nephritis factor, catastrophic antiphospholipid syndrome, focal segmental glomerulosclerosis after renal transplant, and myeloma with acute renal failure may be considered medically necessary. Clinical input was mixed on the medical necessity of hyperviscosity syndromes with renal failure (other than associated with multiple myeloma or Waldenström macroglobulinemia). In addition, there was no consensus about an optimal creatinine threshold for instituting plasma exchange in patients with renal failure associated with ANCA-associated vasculitis or other diagnoses.
PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network
In the current National Comprehensive Cancer Network guidelines on multiple myeloma (v.3.2017), use of plasmapheresis to improve renal function is a category 2B recommendation. Plasmapheresis should also be used as adjunctive therapy for hyperviscosity.(53)

American Academy of Neurology
In 2011, the American Academy of Neurology issued an evidence-based guideline on plasmapheresis in the treatment of neurologic disorders.(54) The primary conclusions based on their evidence review are provided in Table 1.

Table 1. Guidelines on Use Plasmapheresis to Treat Neurologic Disorders

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammatory demyelinating polyneuropathy/Guillain-Barré syndrome</td>
<td>Established effective</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy, short-term treatment</td>
<td>Established effective</td>
</tr>
<tr>
<td>Relapses in multiple sclerosis</td>
<td>Probably effective</td>
</tr>
<tr>
<td>Fulminant demyelinating central nervous system disease</td>
<td>Possibly effective</td>
</tr>
<tr>
<td>Chronic or secondary progressive multiple sclerosis</td>
<td>Established ineffective</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>Sydenham’s chorea</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>Acute obsessive-compulsive disorder and tics in PANDAS</td>
<td>Insufficient evidence</td>
</tr>
</tbody>
</table>

PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

Established effective
- Acute inflammatory demyelinating polyneuropathy/Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyneuropathy, short-term treatment

Probably effective
- Relapses in multiple sclerosis

Possibly effective
- Fulminant demyelinating central nervous system 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 2003, AAN published a practice parameter on Guillain-Barré syndrome (GBS).(55) The following are the key findings: (1) treatment with plasma exchange (PE) or intravenous immunoglobulin hastens recovery from GBS; (2)
combining the 2 treatments is not beneficial; and (3) steroid treatment given alone is not beneficial. AAN’s recommendations are:

- PE is recommended for adults with GBS who are nonambulant and who seek treatment within 4 weeks of the onset of neuropathic symptoms;
- PE should be considered for ambulant patients examined within 2 weeks of the onset of neuropathic symptoms);
- PE is a treatment option for children with severe GBS;

**American Society for Apherisis**
In 2016, the American Society for Apherisis updated its guidelines on use of therapeutic apheresis (Seventh Special Issue).(56) Previously, the guidelines had been updated in 2013 (Sixth Special Issue).(57) The following is a description of the Society categories (see Table 2), 2013 recommendations (see Table 3), and new indications added in 2016 (see Table 4).

**Table 2. American Society for Apheresis Categories**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>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>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>Diseases for which the optimum role of TA is not established and treatment decisions on an individual basis are recommended.</td>
</tr>
<tr>
<td>IV</td>
<td>Disorders for which published evidence suggests or demonstrates that TA is ineffective or harmful.</td>
</tr>
</tbody>
</table>

**Table 3. American Society for Apheresis 2013 Key Recommendations**

<table>
<thead>
<tr>
<th>Disease Group/Name/Condition</th>
<th>2013 Category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmune</strong></td>
<td></td>
</tr>
<tr>
<td>Catastrophic antiphospholipid syndrome</td>
<td>II</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>I</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>III</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td>Manifestations other than nephritis</td>
<td>NC</td>
</tr>
<tr>
<td>Severe</td>
<td>II</td>
</tr>
<tr>
<td>Nephritis</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
</tr>
<tr>
<td>ABO-incompatible hematopoietic progenitor cell transplantation</td>
<td>II</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>III</td>
</tr>
<tr>
<td>Pure red blood cell aplasia</td>
<td>II</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia:</td>
<td></td>
</tr>
<tr>
<td>Warm autoimmune hemolytic anemia</td>
<td>III</td>
</tr>
<tr>
<td>Cold agglutinin disease</td>
<td>II</td>
</tr>
<tr>
<td>Coagulation factor inhibitors</td>
<td>IV</td>
</tr>
<tr>
<td>Hyperviscosity in monoclonal gammopathies</td>
<td>I</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura</td>
<td>NC</td>
</tr>
<tr>
<td>Refractory immunoadsorption</td>
<td>NC</td>
</tr>
<tr>
<td>Refractory or nonrefractory</td>
<td>NC</td>
</tr>
<tr>
<td>Myeloma and acute renal failure (in 2010 and 2013 myeloma cast nephropathy)</td>
<td>III</td>
</tr>
<tr>
<td>Posttransfusion purpura</td>
<td></td>
</tr>
<tr>
<td>Red blood cell alloimmunization in pregnancy</td>
<td>II</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Level</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>I</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>III</td>
</tr>
<tr>
<td>Sepsis</td>
<td>III</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>III</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td></td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>II</td>
</tr>
<tr>
<td>AIDP (Guillain-Barré syndrome)</td>
<td>I</td>
</tr>
<tr>
<td>AIDP, post IVIg</td>
<td>III</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyradiculoneuropathy</td>
<td>I</td>
</tr>
<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>II</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>II</td>
</tr>
<tr>
<td>Acute CNS inflammatory demyelinating disease</td>
<td>II</td>
</tr>
<tr>
<td>Devic syndrome</td>
<td>NC</td>
</tr>
<tr>
<td>Chronic progressive</td>
<td>III</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td></td>
</tr>
<tr>
<td>In 2013, moderate-severe</td>
<td>I</td>
</tr>
<tr>
<td>In 2013, pre-thymectomy</td>
<td>I</td>
</tr>
<tr>
<td>Paraneoplastic neurologic syndromes</td>
<td>III</td>
</tr>
<tr>
<td>Paraproteinemic polyneuropathies</td>
<td>I</td>
</tr>
<tr>
<td>IgG/IgA</td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td>I</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>III</td>
</tr>
<tr>
<td>Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; SC</td>
<td></td>
</tr>
<tr>
<td>PANDAS (2007, severe)</td>
<td>I</td>
</tr>
<tr>
<td>SC (2007, severe)</td>
<td>I</td>
</tr>
<tr>
<td>Rasmussen’s encephalitis</td>
<td>III</td>
</tr>
<tr>
<td>Stiff-person syndrome</td>
<td>III</td>
</tr>
<tr>
<td>Neuromyelitis optica spectrum disorders</td>
<td>II</td>
</tr>
<tr>
<td>Acute</td>
<td>II</td>
</tr>
<tr>
<td>Maintenance</td>
<td>III</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
</tr>
<tr>
<td>ANCA-associated rapidly progressive glomerulonephritis (Wegener granulomatisis)</td>
<td>I</td>
</tr>
<tr>
<td>Dialysis dependence</td>
<td>I</td>
</tr>
<tr>
<td>Dialysis independence</td>
<td>III</td>
</tr>
<tr>
<td>Antiglomerular basement membrane disease (Goodpasture syndrome)</td>
<td></td>
</tr>
<tr>
<td>DAH</td>
<td>I</td>
</tr>
<tr>
<td>Dialysis dependence and no DAH</td>
<td>III</td>
</tr>
<tr>
<td>Dialysis independence</td>
<td>I</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>NC</td>
</tr>
<tr>
<td>Secondary</td>
<td>NC</td>
</tr>
<tr>
<td>Recurrent</td>
<td>I</td>
</tr>
<tr>
<td>HUS; thrombotic microangiopathy; transplant-associated microangiopathy</td>
<td></td>
</tr>
<tr>
<td>Idiopathic HUS</td>
<td>NC</td>
</tr>
<tr>
<td>Transplant-associated microangiopathy</td>
<td>NC</td>
</tr>
<tr>
<td>Diarrhea-associated pediatric</td>
<td>NC</td>
</tr>
<tr>
<td>Atypical HUS due to complement factor H</td>
<td>I</td>
</tr>
<tr>
<td>Diarrhea associated HUS or typical H</td>
<td></td>
</tr>
<tr>
<td>In 2013, Shiga toxin-associated</td>
<td>IV</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em> associated</td>
<td>III</td>
</tr>
<tr>
<td>Renal transplantation: antibody mediated rejection; HLA desensitization</td>
<td></td>
</tr>
<tr>
<td>Antibody mediated rejection</td>
<td>I</td>
</tr>
<tr>
<td>HLA desensitization</td>
<td>II</td>
</tr>
<tr>
<td>Desensitization, living donor, positive cross-match due to donor-specific HLA</td>
<td>I</td>
</tr>
</tbody>
</table>
antibody
High PRA: cadaveric donor

**Rheumatic**
Scleroderma (progressive systemic sclerosis)

**Transplantation**
ABO-incompatible solid organ transplantation

**Kidney**
In 2013, desensitization, living-donor
Humeral rejection
Heart (infants)
Liver (2010 perioperative)
In 2013, desensitization living-donor
Desensitization, deceased-donor
Humeral rejection

**Heart transplant rejection**
Treatment

ABO: A, B, and O blood types; AIDP: acute inflammatory demyelinating polyneuropathy; ANCA: antineutrophil cytoplasmic antibody; CNS: central nervous system; DAH: diffuse alveolar hemorrhage; HUS: hemolytic uremic syndrome; Ig: immunoglobulin; IVIg: intravenous immunoglobulin; NC: not categorized; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; PRA: Panel Reactive Antibody; SC: Sydenham chorea.

**Table 4. American Society for Apheresis New Indications Added in 2016**

<table>
<thead>
<tr>
<th>Disease Group/Name/Condition</th>
<th>2016 Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic (neuro-) dermatitis (atopic eczema), recalcitrant</td>
<td>III</td>
</tr>
<tr>
<td>Cardiac neonatal lupus</td>
<td>III</td>
</tr>
<tr>
<td>Complex regional pain syndrome</td>
<td>III</td>
</tr>
<tr>
<td>Erythropoietic porphyria, liver disease</td>
<td>III</td>
</tr>
<tr>
<td>Hashimoto’s encephalopathy: steroid-responsive encephalopathy associated with autoimmune thyroiditis</td>
<td>II</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td></td>
</tr>
<tr>
<td>Postpartum</td>
<td>III</td>
</tr>
<tr>
<td>Antepartum</td>
<td>IV</td>
</tr>
<tr>
<td>Hematopoietic cell transplantation, Human leukocyte antigen desensitization</td>
<td>III</td>
</tr>
<tr>
<td>Hemophagocytic lymphohistiocytosis; hemophagocytic syndrome; macrophage activating syndrome</td>
<td>III</td>
</tr>
<tr>
<td>N-methyl D-aspartate receptor antibody encephalitis</td>
<td>I</td>
</tr>
<tr>
<td>Prevention of RhD alloimmunization after red blood cell exposure</td>
<td>III</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy associated with natalizumab</td>
<td>I</td>
</tr>
<tr>
<td>Pruritus due to hepatobiliary diseases</td>
<td>III</td>
</tr>
<tr>
<td>Thrombotic microangiopathy, coagulation mediated</td>
<td>III</td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
</tr>
<tr>
<td>HBV-PAN</td>
<td>II</td>
</tr>
<tr>
<td>Idiopathic PAN</td>
<td>IV</td>
</tr>
<tr>
<td>EGPA</td>
<td>III</td>
</tr>
<tr>
<td>Behçet disease</td>
<td>III</td>
</tr>
</tbody>
</table>

EGPA5: eosinophilic granulomatosis with polyangiitis; PAN: polyarteritis nodosa.

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**

Not applicable.
**MEDICARE NATIONAL COVERAGE**

The Centers for Medicare and Medicaid Services, Medicare Coverage Database, National Coverage Determination for apheresis (therapeutic pheresis), (58) last revised in 1992, states:

“For purposes of Medicare coverage, apheresis is defined as an autologous procedure, i.e., blood is taken from the patient, processed, and returned to the patient as part of a continuous procedure (as distinguished from the procedure in which a patient donates blood preoperatively and is transfused with the donated blood at a later date). Apheresis is covered for the following indications: Plasma exchange for acquired myasthenia gravis; Leukapheresis in the treatment of leukemia; Plasmapheresis in the treatment of primary macroglobulinemia (Waldenström); Treatment of hyperglobulinemias, including (but not limited to) multiple myelomas, cryoglobulinemia and hyperviscosity syndromes; Plasmapheresis or plasma exchange as a last resort treatment of thrombotic thrombocytopenic purpura (TTP); Plasmapheresis or plasma exchange in the last resort treatment of life threatening rheumatoid vasculitis; Plasma perfusion of charcoal filters for treatment of pruritus of cholestatic liver disease; Plasma exchange in the treatment of Goodpasture's Syndrome; Plasma exchange in the treatment of glomerulonephritis associated with antiglomerular basement membrane antibodies and advancing renal failure or pulmonary hemorrhage; Treatment of chronic relapsing polyneuropathy for patients with severe or life threatening symptoms who have failed to respond to conventional therapy; Treatment of life threatening scleroderma and polymyositis when the patient is unresponsive to conventional therapy; Treatment of Guillain-Barre Syndrome; and Treatment of last resort for life threatening systemic lupus erythematosus (SLE) when conventional therapy has failed to prevent clinical deterioration.”

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**

Some currently unpublished trials that might influence this review are listed in Table 5.

**Table 5. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT01442233</td>
<td>Plasma Exchanges in Multiple Sclerosis (MS) Relapses (PLASMASEP)</td>
<td>80</td>
<td>Dec 2017</td>
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<tr>
<td>NCT02622854</td>
<td>Plasma Exchange vs Conservative Management in Non-severe Acute Hypertriglyceridemic Pancreatitis</td>
<td>20</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT02647255</td>
<td>Trial of Plasma Exchange for Severe Crescentic IgA Nephropathy (RESCUE)</td>
<td>150</td>
<td>Dec 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
References


**Billing Coding/Physician Documentation Information**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>36514</td>
<td>Therapeutic apheresis; for plasma pheresis</td>
</tr>
<tr>
<td>36516</td>
<td>Therapeutic apheresis; with extracorporeal selective adsorption or selective filtration and plasma reinfusion</td>
</tr>
<tr>
<td>S2120</td>
<td>Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation</td>
</tr>
</tbody>
</table>
### ICD-10 Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C88.0</td>
<td>Waldenstrom macroglobulinemia (includes macroglobulinemia)</td>
</tr>
<tr>
<td>D58.0-</td>
<td>Other hereditary hemolytic anemias code range</td>
</tr>
<tr>
<td>D58.9</td>
<td></td>
</tr>
<tr>
<td>D59.3</td>
<td>Hemolytic-uremic syndrome</td>
</tr>
<tr>
<td>D69.3</td>
<td>Immune thrombocytopenic purpura (includes idiopathic thrombocytopenic purpura)</td>
</tr>
<tr>
<td>D69.49</td>
<td>Other primary thrombocytopenia</td>
</tr>
<tr>
<td>D69.5</td>
<td>Thrombocytopenia, unspecified</td>
</tr>
<tr>
<td>D75.1</td>
<td>Secondary polycythemia</td>
</tr>
<tr>
<td>D89.2</td>
<td>Hypergammaglobulinemia, unspecified</td>
</tr>
<tr>
<td>G35</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>G36.0</td>
<td>Neuromyelitis optica [Devic]</td>
</tr>
<tr>
<td>G60.9</td>
<td>Hereditary and idiopathic neuropathy, unspecified</td>
</tr>
<tr>
<td>G61.0</td>
<td>Guillain-Barre syndrome (includes acute infective polyneuritis)</td>
</tr>
<tr>
<td>G61.81</td>
<td>Chronic inflammatory demyelinating polyneuritis</td>
</tr>
<tr>
<td>G70.00-</td>
<td>Myasthenia gravis, code range</td>
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<tr>
<td>G70.01</td>
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</tr>
<tr>
<td>M31.0</td>
<td>Hypersensitivity angitis (includes Goodpasture’s syndrome)</td>
</tr>
<tr>
<td>M31.1</td>
<td>Thrombotic microangiopathy (includes thrombotic thrombocytopenic purpura)</td>
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<tr>
<td>M31.30-</td>
<td>Wegener’s granulomatosis code range</td>
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<td>M31.31</td>
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<tr>
<td>O14.20-</td>
<td>HELLP syndrome code range</td>
</tr>
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<td>O14.23</td>
<td></td>
</tr>
</tbody>
</table>

In 2003, CPT introduced a variety of CPT codes that describe different types of apheresis procedures. CPT codes 36514 specifically describe “therapeutic apheresis, for plasmapheresis.”

### Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/1/88</td>
<td>New policy titled <em>Therapeutic Apheresis</em> added to the Surgery section.</td>
</tr>
<tr>
<td>9/1/00</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/1/01</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/1/02</td>
<td>Title of policy changed to <em>Plasma Exchange / Plasmapheresis</em>. Policy statement revised to include Hemolytic uremic syndrome (HUS); IgA or IgG paraproteinemia polyneuropathy; HELLP syndrome of pregnancy and post-transfusion purpura as medically necessary.</td>
</tr>
<tr>
<td>9/1/03</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/1/04</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/1/05</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/1/06</td>
<td>Policy statement revised with addition of policy statements and discussion of plasmapheresis in the setting of solid organ transplantation, considered medically necessary. References 21-30 added.</td>
</tr>
</tbody>
</table>
No policy statement changes.

No policy statement changes.

No policy statement changes.

The policy statement has been modified to include: Guillain-Barré syndrome severity grades 1-2 as medically necessary; use in the pediatric population is investigational for mild and moderate forms of GBS and medically necessary for the severe form of GBS; the policy statement has been modified to include severe manifestations of mixed cryoglobulinemia (MC) as medically necessary when used in combination with immunosuppressive therapy; typical hemolytic uremic syndrome is investigational (considered medically necessary in previous updates) and investigational for treatment of PANDAS, Sydenham chorea, Refsum's disease, cryoglobulinemia (except severe MC), myasthenia gravis with anti-MuSk antibodies; additional conditions were added as investigational based on American Society for Apheresis (ASFA) review. Title changed from “Plasma Exchange (Plasmapheresis) to “Plasma Exchange.”

No policy statement changes.

Added “post-transfusion purpura” back into the medically necessary policy statement as it was mistakenly dropped in the last reorganization of the statements. The Guillain-Barré syndrome disability scale was added to the appendix.

Myeloma with acute renal failure and catastrophic antiphospholipid syndrome were changed to medically necessary. Dense deposit disease with Factor H deficiency and/or elevated C3 nephritis factor and focal segmental glomerulosclerosis after renal transplant were added as medically necessary. The investigational statement on focal segmental glomerulosclerosis was modified to indicate that it applied to situations other than after renal transplant. Hyperviscosity syndromes with renal failure (other than associated with multiple myeloma or Waldenstrom’s macroglobulinemia) added as investigational. In addition, the serum creatinine threshold was removed from the policy statement on ANCA-associated vasculitis.

No policy statement changes.

Minor changes to bullet points on multiple sclerosis for clarity only. No policy statement changes.

Neuromyelitis optica (NMO) added as investigational. CAPS abbreviation removed from medically necessary policy statement. Added additional details for clarity in investigational statement: ANCA (antineutrophil cytoplasmic antibody) -associated rapidly progressive glomerulonephritis (Wegener’s granulomatosis or GPA without renal failure).

No policy statement changes.

No policy statement changes.

N-methyl D-aspartate receptor antibody encephalitis and progressive multifocal leukoencephalopathy associated with natalizumab added to medically necessary statement.
Appendix
Diagnostic Criteria for Diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
The following criteria are adapted from the Task Force Report of the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. (Neurology 1991; 41:617-18) The report included mandatory, supportive, and exclusionary diagnostic criteria. Only the mandatory criteria are excerpted here. The criteria are based on a combination of clinical observations, physiologic studies, pathologic features (i.e., nerve biopsy), and studies of the cerebrospinal fluid (CSF).

I. Clinical
Mandatory
1. Progressive or relapsing motor and sensory, rarely only motor or sensory, dysfunction of more than 1 limb or a peripheral nerve nature, developing over at least 2 months.
2. Hypo- or areflexia. This will usually involve all 4 limbs.

II. Physiologic Studies
Mandatory
Nerve conduction studies including studies of proximal nerve segments in which the predominant process is demyelination.

Must have 3 of 4:
1. Reduction in conduction velocity (CV) in 2 or more motor nerves:
   a. <80% of lower limit of normal (LLN) is amplitude >80% of LLN
   b. <70% of LLN is amplitude <80% of LLN

2. Partial conduction block or abnormal temporal dispersion in 1 or more motor nerves: either peroneal nerve between ankle and below fibular head, median nerve between wrist and elbow, or ulnar nerve between wrist and below elbow.

   Criteria suggestive of partial conduction block: <15% change in duration between proximal and distal sites and >20% drop in negative peak (p) area or peak to peak (p-p) amplitude between proximal and distal sites.

   Criteria for abnormal temporal dispersion and possible conduction block: >15% change in duration between proximal and distal sites and >20% drop in p area or p-p amplitude between proximal and distal sites. These criteria are only suggestive of partial conduction block as they are derived from studies of normal individuals. Additional studies, such as stimulation across short segments or recording of individual motor unit potentials, are required for confirmation.

3. Prolonged distal latencies in 2 or more nerves:
a. >125% of upper limit of normal (LEN) is amplitude >80% of LLN
b. >150% of LEN if amplitude <80% of LLN.

4. Absent F waves or prolonged minimum
   a. >120% of ULN if amplitude >80% of LLN
   b. >150% of ULN if amplitude <80% of LLN.

III. Pathologic Features

Mandatory
Nerve biopsy showing unequivocal evidence of demyelination and remyelination.

Demyelination by either electron microscopy (>5 fibers) or teased fiber studies >12% of 50 fibers, minimum of 4 internodes each, demonstrating demyelination/remyelination.

IV. CSF Studies

Mandatory
1. Cell count <10/mm-3 if HIV-seronegative or <50/mm-3 is HIV seropositive
2. Negative VDRL

Guillain-Barré Syndrome Disability Scale

The following is the disability scale as first described by Hughes et al. in Lancet 1978; 2(8093):750-3

0. Healthy
1. Minor symptoms or signs of neuropathy but capable of manual work
2. Able to walk without support of a stick but incapable of manual work
3. Able to walk with a stick, appliance or support
4. Confined to bed or chair bound
5. Requiring assisted ventilation
6. Dead

The scale has been modified since 1978 and appears below as it did in the Hughes et al. 2007 systematic review published in Brain 2007; 130(9):2245-57.

0. Healthy
1. Minor symptoms or signs of neuropathy but capable of manual work/capable of running
2. Able to walk without support of a stick (5 m across an open space) but incapable of manual work/running
3. Able to walk with a stick, appliance or support (5 m across an open space)
4. Confined to bed or chair bound
5. Requiring assisted ventilation (for any part of the day or night)
6. Death

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