Plasma Exchange (PE)

Policy # 00249
Original Effective Date: 03/19/2010
Current Effective Date: 04/19/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Immune Globulin Therapy is addressed separately in medical policy 00170.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider plasma exchange (PE) to be eligible for coverage 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 (ITP) in emergency situations;
- Thrombotic thrombocytopenic purpura (TTP);
- Atypical hemolytic-uremic syndrome (HUS);
- 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 and acute renal failure

Neurological
- Acute inflammatory demyelinating polyneuropathy (Guillain-Barre [GBS] syndrome); severity grade 1-2 within two weeks of onset; severity grade 3-5 within four weeks of onset; and children less than ten years old with severe GBS;
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP);
- Multiple sclerosis (MS); acute fulminant central nervous system (CNS) demyelination;
- Myasthenia gravis in crisis or as part of preoperative preparation;
- Paraproteinemia polyneuropathy; IgA, IgG.
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- Neuromyelitis optica (NMO) associated with severe symptoms in patients with contraindication or lack of response to glucocorticoids. *Note: Exchanges are carried out every other day for a total of seven exchanges.*

Renal
- Anti-glomerular basement membrane (GBM) disease (Goodpasture’s syndrome);
- ANCA [antineutrophil cytoplasmic antibody]-associated vasculitis [e.g., Wegener’s granulomatosis (also known as granulomatosis with polyangitis (GPA))] with associated renal failure;
- Dense deposit disease with factor H deficiency and/or elevated C3 Nephritic factor

Transplantation
- ABO incompatible solid organ transplantation;
  - Kidney;
  - Heart (infants);
- Renal transplantation: antibody mediated rejection; HLA desensitization;
- Focal segmental glomerulosclerosis after renal transplant.

When Services Are Considered Investigational
*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers plasma exchange (PE) to be *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 (GBS) in children less than ten years old with mild or moderate forms;
- Acute liver failure;
- Amyotrophic 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 (MC) 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;
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- Inclusion body myositis;
- Lambert-Eaton myasthenic syndrome;
- Multiple sclerosis; chronic progressive or relapsing remitting;
- Mushroom poisoning;
- Myasthenia gravis (MG) with anti-MuSK antibodies;
- 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 blood cell alloimmunization in pregnancy;
- Rheumatoid arthritis (RA);
- Sepsis;
- Scleroderma (systemic sclerosis);
- Sydenham chorea (SC);
- Systemic lupus erythematosus (including SLE [systemic lupus erythematosus] nephritis);
- Thyrotoxicosis;
- Hyperviscosity syndromes with renal failure (other than associated with multiple myeloma or Waldenstrom’s macroglobulinemia).

**Background/Overview**

Plasma exchange 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 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.
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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/collodid 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).

FDA or Other Governmental Regulatory Approval
The U.S. Food and Drug Administration (FDA) has a compliance program to ensure that source plasma, source leukocytes, and therapeutic exchange plasma for further manufacture into products for human use are safe, pure, potent, and appropriately labeled. The compliance program covers products intended for use both in injectable drug products (eg, immune globulin, albumin) and noninjectable products (eg, in vitro devices such as blood bank reagents).

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Centers for Medicare and Medicaid Services (CMS)
The CMS, Medicare Coverage Database, National Coverage Determination (NCD) for apheresis (therapeutic pheresis) 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 (Waldenstrom);
- 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 pruritis 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.”

Rationale/Source
This policy is updated regularly with searches of the MEDLINE database. The most recent literature review was performed through April 30, 2015. Following is a summary of the key literature to date.

Autoimmune Diseases
One potential type of evidence in support of the clinical effectiveness of 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 4-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 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 2 patients (17%) 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. Most of these studies were published in the late 1980s or early 1990s; 1 case series with 9 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 5 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 Haemolytic Uraemic 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/dipryidamole, 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 2 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.

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 (ITP)**

Idiopathic thrombocytopenic purpura 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 IVlg. 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 1–5. 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 3 trials found that PE significantly increased the proportion of patients who recovered the ability to walk with assistance after 4 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 4 trials with severely affected adult participants (n=585), those treated with PE improved significantly more on the disability scale 4 weeks after randomization than those who were not (weighted mean difference [WMD]: -0.89; range: -1.14 to -0.63). In 5 trials (n=582), the improvement on the disability grade scale with IVlg was very similar to that with PE, WMD: -0.02 (range: -0.25 to 0.20). There was also no significant difference between IVlg and PE for any of the other outcome measures. There was 1 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 2 sessions of PE in 3 days or supportive care. The number of patients with one or more grades of improvement at 1 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 1 trial (n=148), following PE with IVlg, did not produce significant extra benefit. Limited evidence from 3 open trials in children suggested that IVlg 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 IVlg hastens recovery from Guillain-Barré syndrome; 2) combining the 2 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 4 weeks of the onset of neuropathic symptoms (PE should also be considered for ambulant patients examined within 2 weeks of the onset of neuropathic symptoms); 2) IVlg is recommended for nonambulant adult patients with GBS within 2 or possibly 4 weeks of the onset of neuropathic symptoms (the effects of PE and IVlg are equivalent); 3) corticosteroids are not recommended for the management of GBS; 4) sequential treatment with PE followed by IVlg, or immunoabsorption followed by IVlg is not recommended for patients with GBS; and 5) PE and IVlg 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 IVlg (n=20). Mean age of the patients was 96 months in the PE group and 106 months in the IVlg 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 IVlg 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 IVlg 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,
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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 2 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 2 trials found a statistically significantly greater improvement in impairment after 4 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 5 days of high-dose corticosteroids. Patients were randomized to receive either 7 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 3 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, 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 versus 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.
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Two trials included patients with myasthenia gravis in the absence of myasthenic crisis. Liu et al (2009) in China randomized 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 (80%) of 15 of the plasmapheresis group, 7 (70%) of 10 in the IA group, and 6 (40%) of 15 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 no statistically significant difference between groups in the change on the QMGS, the primary efficacy outcome. Mean QMGS at day 14 was 4.7 in the PE group versus 3.2 in the IVIg group (p=0.13). Moreover, at day 14, 69% were considered improved on PE versus 65% on IVIg; the difference between groups was not statistically significant (p=0.74). Safety outcomes were published in 2013.31 Forty-two patients received a total of 203 PE procedures; 40 completed the full course of 5 procedures. Complications occurred in 19 (45%) of 42 patients. Two 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.

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 reported mixed results, and therefore definitive conclusions cannot be made.

Neuromyelitis Optica

Neuromyelitis optica is a rare inflammatory disorder of the CNS 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 2015, Abboud et al reviewed 83 admissions for acute relapse of NMO at a single center in the United States. 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
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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 of 65 relapses (77%). 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. 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. 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, ie, patients
in the latter time period received PE and care could also have improved over time in other ways that led to improved outcomes.

The U.S. National Institute of Neurological Disorders and Stroke (NINDS) has an informational webpage on neuromyelitis optica which states that several treatments are available off-label to reduce symptoms and prevent relapses. These include mycophenolate mofetil, rituximab, and azathioprine. The informational page also states that individuals with frequent relapses have used low-dose steroids for longer periods. PE is mentioned as a potential alternative treatment in patients who are unresponsive to corticosteroid treatment, but is not specifically recommended. The NINDS website does not cite any evidence in support of any of the treatments for neuromyelitis optica.

In summary, the available nonrandomized retrospective studies have methodologic limitations, and findings need to be confirmed in well-designed and conducted randomized trials.

Renal
Rapidly Progressive Glomerulonephritis (RPGN)
Rapidly progressive glomerulonephritis 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. Plasma exchange 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 9 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 2 groups (RR:1.01, 95% CI: 0.71-1.40).

In 2007, Jayne et al published a relatively large RCT, included in the previously mentioned meta-analysis. 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 randomly assigned to receive 7 PEs (n=70) or 3000 mg of IVMP (n=67). Both groups received oral cyclophosphamide and oral

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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 versus 51 (73%) of 70 in the PE group, and severe adverse events occurred in 48% of the IVMP group versus 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. 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.

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 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., rituximab). 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, e.g. 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.

Sepsis
In 2014, Rimmer et al published a systematic review and meta-analysis of literature on PE for treatment of sepsis and septic shock. The authors 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 (PANDAS) and Sydenham chorea (SC)**

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections 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). Sydenham chorea 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. Sydenham chorea 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 2 weeks), IVIg (n=9; 2 gm/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 the 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 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 SC (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 2 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 1 month. The secondary outcome variable was chorea severity at 1 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 9 or higher was required for study entry. Baseline medications to control choreatic symptoms were discontinued 1 week prior to 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). The between-group differences were not statistically significant. Larger studies are needed to confirm these clinical observations.

**Clinical Input Received through 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.
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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 PE in patients with renal failure associated with ANCA-associated vasculitis or other diagnoses.

Summary
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.

References
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03/05/2010 Medical Policy Committee approval
03/19/2010 Medical Policy Implementation Committee approval. New policy.
03/03/2011 Medical Policy Committee review
03/16/2011 Medical Policy Implementation Committee approval. Added “post-transfusion purpura” as eligible for coverage into the hematologic section. Deleted “ANCA-associated rapidly progressive glomerulonephritis (Wegener’s granulomatosis)” from investigational statement since it belongs in the eligible for coverage section only. Deleted unnecessary language ("manifestations other than nephritis; nephritis") from systematic lupus erythematosus bullet in the investigational statement.
03/01/2012 Medical Policy Committee review
03/21/2012 Medical Policy Implementation Committee approval. Added a new investigational indication. SLE
03/07/2013 Medical Policy Committee review
03/20/2013 Medical Policy Implementation Committee approval. Two indications moved from investigational to eligible for coverage. New indication added to renal and transplantation sections. New investigational indication added.
03/06/2014 Medical Policy Committee review
03/19/2014 Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015 Medical Policy Committee review
09/23/2015 Medical Policy Implementation Committee approval. Added neuromyelitis optica to list of INV conditions.
09/08/2016 Medical Policy Committee review
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09/21/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update
04/09/2017 Medical Policy Committee review
04/19/2017 Medical Policy Implementation Committee approval. Added neuromyelitis optica to coverage statement and removed it from investigational indications.

Next Scheduled Review Date: 04/2018

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|             | D69.51 D69.59 D75.1 D89.1  
|             | G35 G36.0 G60.9-G61.0 G61.81  
|             | G70.00-G70.01 M30.1 M31.0-M31.1 M31.30-M31.31  

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B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other
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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant
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3. Reference to federal regulations.

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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the
patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific
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