



Louisiana

Plasma Exchange (PE)

Policy # 00249

Original Effective Date: 03/19/2010

Current Effective Date: 11/21/2018

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.

Note: Hematopoietic Cell Transplantation for Autoimmune Diseases is addressed separately in medical policy 00050.

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 Diseases

- 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 Conditions

- 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 Conditions

- 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;

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- 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.
- 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.*
- N-methyl-D-aspartate receptor antibody encephalitis;
- Progressive multifocal leukoencephalopathy associated with natalizumab.

Renal Diseases

- Anti-glomerular basement membrane (GBM) 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;
 - 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 [RPGN] (Wegener's granulomatosis or GPA without renal failure);
- Aplastic anemia;
- Asthma;

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- 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 (ITP); refractory or non-refractory;
- Inclusion body myositis;
- Lambert-Eaton myasthenic syndrome (LEMS);
- Multiple sclerosis (MS); 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);
- Stiff person syndrome;
- 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).

Policy Guidelines

Patients receiving plasma exchange (PE) as a treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) should meet the diagnostic criteria for CIDP, which were established by the American Academy of Neurology in 1991 and have not been updated since. The use of PE in patients with acute, life-threatening complications of chronic autoimmune diseases, such as rheumatoid arthritis and

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systemic lupus erythematosus, may need to be considered on an individual basis. An example of such a situation would be the development of a severe vasculitis, for which it is hypothesized that the use of PE can acutely lower the level of serum autoantibodies until an alternative long-term treatment strategy can be implemented. However, in these situations, the treatment goals and treatment duration with PE need to be clearly established before 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.

Background/Overview

TERMINOLOGY

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

Apheresis is a procedure in which blood of the patient or donor is passed through a medical device that separates out one or more components of blood and returns remainder with or without extracorporeal treatment or replacement of the separated component.

Plasmapheresis is a procedure in which blood of a patient or the donor is passed through a medical device that separates plasma from the other components of blood and the plasma is removed (ie, <15% of total plasma volume) without the use of replacement solution.

Plasma exchange is a therapeutic procedure in which blood of the patient is passed through a medical device that separates plasma from other components of blood, the plasma is removed, and it is replaced with a replacement solution such as colloid solution (eg, albumin and/ or plasma) or a combination of crystalloid/colloid solution.

This evidence review addresses only PE as a therapeutic apheresis procedure.

PLASMA EXCHANGE

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 a symptomatic therapy, because it does not remove the source of the pathogenic factors. Therefore the success of PE depends 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.

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Applications

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, because of the phenomenon of rebound antibody production, its use in chronic diseases has been more controversial than in acute self-limited diseases.

Also, plasmapheresis has been used in the setting of solid organ transplantation. It has been used as a technique to desensitize high-risk patients before transplant and also as a treatment of antibody-mediated rejection reaction occurring after transplant. Before 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 antibody-mediated rejection, plasmapheresis is often used in combination with intravenous immunoglobulin or anti-CD20 therapy (ie, rituximab).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The U.S. Food and Drug Administration 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).

Product code for therapeutic exchange plasma: 57DI-65.

Centers for Medicare and Medicaid Services (CMS)

The national coverage determination for apheresis (therapeutic pheresis), 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 (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);

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- 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.”

Rationale/Source

Assessment of efficacy for therapeutic intervention involves a determination of whether an 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. The following is a summary of the key literature to date.

AUTOIMMUNE DISEASES

One potential type of evidence in support of the clinical effectiveness of plasma exchange (PE) in treating autoimmune diseases is the identification of a pathogenic component of plasma that is reliably eliminated by plasmapheresis. Although many laboratory abnormalities are associated with autoimmune connective tissue diseases, it is unclear which, if any, cause the clinical manifestations of the disease. Furthermore, it is 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.

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Systemic Lupus Erythematosus

A 2016 systematic review by Kronbichler et al found 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, and 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 an 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 hypothesized that the acute lowering of pathogenic autoantibodies with plasmapheresis might result in their rebound production and 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 outcomes.

Multiple Sclerosis

Several RCTs of PE in patients with multiple sclerosis (MS) 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 MS to PE or sham treatments; there was no statistical difference in improvement rates 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 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 assessing 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 were not provided, 19 underwent plasmapheresis, with 27% reporting a moderate to marked response. However, the improvement after plasmapheresis was only transient, even when marked. Patients also received other therapies (eg, various chemotherapy regimens for the underlying lung cancer). Also, 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.

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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 (17%) patients showed a minor improvement in neurologic symptoms.

Rheumatoid Arthritis

In 1983, Dwosh et al reported on 26 patients with chronic rheumatoid arthritis randomized in a crossover design to true or sham PE. The authors concluded that PE had no clinical benefit, despite impressive laboratory changes.

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.

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. This trial 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 was ineffective 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, as well as small-cell lung, colon, or breast cancer. The mainstay of treatment of stiff man syndrome is diazepam. The published literature on plasmapheresis consists of small case series and anecdotal reports. Most of these studies were published in the late 1980s or early 1990s. A small case series of 9 patients was published in 2014, and a smaller case report of 2 patients was published in 2016.

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. They identified 11 studies (total N=156 patients).

Reviewers 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."

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HEMATOLOGIC CONDITIONS

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). Interventions were compared with placebo or supportive therapy or a comparison of two 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 patients) 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 with PE plus 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 plasma infusion group. Reviewers concluded that PE plus FFP is the most effective treatment available for TTP. Seven RCTs included children with HUS. None of the assessed interventions were 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. No RCTs evaluated the effectiveness of any interventions on patients with atypical HUS who have a more chronic and relapsing course. A 2009 review article by Noris and Remuzzi described 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

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.

Post-Transfusion Purpura

Post-transfusion 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.

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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 the 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 the treatment of acute renal failure associated with multiple myeloma using chemotherapy alone vs chemotherapy and PE. Four RCTs were identified; three had full text availability and were included in the data synthesis. None of the RCTs were double-blinded. The trials included 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 no statistically significant difference in 6-month survival outcomes between 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 than in the group receiving chemotherapy alone (RR=2.02; 95% CI, 1.03 to 3.96; p=0.04).

NEUROLOGIC CONDITIONS

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. 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 after the control intervention (RR=1.60; 95% CI, 1.19 to 2.15; $I^2=34%$). 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; $I^2=0%$). 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; $I^2=43%$). 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. The trial 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). The mean (standard deviation [SD]) patient age was 96 months in the PE group and 106 months in the IVIg group. The mean duration of ventilation (the primary outcome) was 11 (1.5) days in the PE group and 13 (2.1) days in the IVIg group (p=0.037).

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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 et al identified 2 randomized trials on PE for chronic inflammatory demyelinating polyradiculoneuropathy. Both trials were considered to be of high quality, but 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 with sham treatment. A pooled analysis of trial data found a statistically significantly greater reduction in impairment after 4 weeks with PE vs sham (mean difference in Neuropathy Impairment Score, 31 points; 95% CI, 16 to 45 points). This 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

Plasmapheresis may be considered medically necessary in patients with acute fulminant central nervous system demyelination; this conclusion 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. 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.

Myasthenia Gravis

Several RCTs have evaluated use of PE in the treatment of myasthenia gravis. 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 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.

A 2017 RCT by Alipour-Faz et al in Iran randomized 24 adults with myasthenia gravis to presurgical treatment with PE (n=12) or IVIG (n=12). Treatments were given 10 to 30 days before thymectomy. All patients completed the trial. Study outcomes were duration of hospitalization, length of postsurgical intensive care unit stay, duration of intubation, duration of surgery, and dose of steroids. Most outcomes

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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 ($p=0.01$).

Paraproteinemic Polyneuropathies

A 1991 randomized, double-blinded trial compared PE with sham treatment in 39 patients who had monoclonal gammopathy of undetermined significance–associated polyneuropathy. After twice weekly PE for 3 weeks, the treatment group reported improvements in neurologic function in the immunoglobulin (Ig) G and IgA groups but not the IgM monoclonal gammopathy of undetermined significance groups. Those from the sham group who later crossed over to the PE group also reported improvement.

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. 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 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 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 as add-on treatment were older and more disabled at baseline. The finding that a

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greater proportion of the more severely ill population had a 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 both 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; 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 a 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), for 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), for 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 in 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 in the PE group (mean, 10.8 and 5.8 years, respectively, $p<0.001$).

Limitations of the Bonnan and the Merle studies include possible patients overlap between studies, and lack of randomization, which might have led to baseline between-group differences in factors that affected outcomes. Also, both studies were subject to bias due to use of historical controls, ie, patients in the latter 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; collectively, the patients experienced 871 acute attacks. Various first-line treatments of NMO attacks were used, most commonly high-dose IV steroids

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(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 (eg, lack of randomization, use of historical control groups), and findings need to be confirmed in well-designed and conducted randomized trials.

N-methyl-D-aspartate Receptor Antibody Encephalitis

A 2017 review by the American Society for Apheresis has stated that, if left untreated, *N*-methyl-D-aspartate receptor antibody encephalitis can lead to decline in the autonomic function and, ultimately, to death. The review indicated that approximately 50% of patients respond to one of several first-line immunotherapies, which includes PE. There is little published evidence. A 2015 retrospective evaluation of 14 patients with anti-*N*-methyl-D-aspartate receptor antibody encephalitis found improvement in the modified Rankin Scale score in 7 of 10 patients treated with PE, compared with 3 of 10 patients treated with corticosteroids.

Progressive Multifocal Leukoencephalopathy Associated With Natalizumab

As noted in the 2017 American Society for Apheresis review (discussed above) progressive multifocal leukoencephalopathy is a potentially fatal side effect of natalizumab, a treatment option for relapsing MS. If progressive multifocal leukoencephalopathy is suspected, natalizumab should be stopped immediately. Also, PE, which was shown in a small 2009 study of 12 patients to reduce serum natalizumab concentration by 92% in a week, can be used to quickly remove natalizumab from the bloodstream and reduce the consequences of progressive multifocal leukoencephalopathy.

RENAL DISEASES

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, few controlled clinical trials have been 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. 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.

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Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

In 2011, Walsh et al published a meta-analysis of studies on PE in adults diagnosed with idiopathic renal vasculitis or RPGN. 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 a 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. This multicenter RCT was conducted on behalf of the European Vasculitis Study Group. The trial investigated whether the addition of PE was more effective than the addition of IVMP. 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 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. The 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 trial results, 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

Plasmapheresis has been extensively used in solid organ transplantation, 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; 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-CD20 (ie, 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

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combination with other therapies, such as IVIg or anti-CD20. 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

Acute Liver Failure

One controlled study, an unblinded RCT published in 2016 by Larsen, evaluated high-volume PE in patients with acute liver failure. Patients with a diagnosis of acute liver failure 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 (8-12 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. The 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 vs 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 vs 36 [40%] in the standard care group, p=0.03). Limitations of the study included its lack of blinding and measurement of the survival outcome only at hospital discharge, a period of several weeks, and longer term outcomes were not reported. Also, the PE protocol and transplantation criteria in Denmark, where the study was conducted, may differ from those in the United States.

Asthma

Some researchers have assessed the use of plasmapheresis in patients with severe, steroid-dependent asthma. However, 1 small crossover trial (N=4), published in 2001, did not suggest treatment effectiveness. No subsequent controlled studies have been published.

Sepsis

In 2014, Rimmer et al published a systematic review and meta-analysis of the literature on PE for treatment of sepsis and septic shock. Reviewers identified 4 RCTs comparing PE with usual care (total N=194 patients). All 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

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was 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 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 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. Children (N=30) with clear evidence of a strep infection as the trigger of their obsessive-compulsive disorder 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 showed 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. 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. The 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.

SUMMARY OF EVIDENCE

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.

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Louisiana

Plasma Exchange (PE)

Policy # 00249

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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. |

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09/08/2016 Medical Policy Committee review
 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.
 11/02/2017 Medical Policy Committee review
 11/15/2017 Medical Policy Implementation Committee approval. N-methyl-D-aspartate receptor antibody encephalitis and progressive multifocal leukoencephalopathy associated with natalizumab added to the Neurological Conditions that are eligible for coverage.
 11/08/2018 Medical Policy Committee review
 11/21/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 Next Scheduled Review Date: 11/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT)^{®†}, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code			
CPT	36456, 36514			
HCPCS	No codes			
ICD-10 Diagnosis	C88.0	D58.8	D59.3	D69.49
	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
	O14.10-O14.13	O14.20	O14.22-O14.23	

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- 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:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- 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 evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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