PLASMA EXCHANGE (PLASMAPHERESIS)
THE801.006

COVERAGE:

**Plasma exchange (PE) and plasmapheresis** may be considered **medically necessary and eligible for coverage** for any of the conditions listed below:

- Myasthenia Gravis in crisis;
- Hyperviscosity Syndromes associated with multiple myeloma, Waldenstrom’s macroglobulinemia, or other conditions;
- Thrombotic Thrombocytopenic Purpura (TTP);
- Hemolytic Uremic Syndrome (HUS);
- Idiopathic Thrombocytopenic Purpura (ITP) in patients with platelet counts less than 100,000/mm³;
- Guillain-Barré syndrome in severely ill patients with rapidly progressing weakness.
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in patients with severe or life-threatening symptoms who have failed to respond to conventional therapy with prednisone or intravenous immunoglobulins (IVIG); (See Appendix for diagnostic criteria for CIDP.)
- Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome of pregnancy;
- Post-transfusion purpura;
- Progressive renal failure due to anti-basement membrane antibodies (i.e., Goodpasture’s syndrome);
- Relapsing or progressive multiple sclerosis that is unresponsive to or the patient is intolerant of high dose corticosteroids. PE should not be considered a first line therapy.

**COVERAGE IS NOT ALLOWED FOR THE FOLLOWING:**

**Investigational** applications of PE include but are not limited to the following conditions:

- Scleroderma (systemic sclerosis);
- Systemic Lupus Erythematosus;
- Polymyositis and Dermatomyositis;
- Pemphigus;
- Amyotrophic Lateral Sclerosis;
- Paraneoplastic Syndromes including Eaton-Lambert syndrome and Paraproteinemic Polyneuropathy;
- Chronic Fatigue Syndrome;
- Regional Enteritis (Crohn’s disease); rapidly progressive Glomerulonephritis, excluding those related to anti-basement membrane immunoglobulins (i.e., Goodpasture’s syndrome);
- Acute Pancreatitis related to hyperlipidemia.
The terms therapeutic apheresis, plasmapheresis, and PE are often used interchangeably, but when properly used denote different procedures. Apheresis is a general term describing removal of blood from a subject; a portion of the blood is separated and retained while the rest is returned to the donor. Plasmapheresis, in which plasma is separated and manipulated in a variety of ways, is probably the most common type of apheresis procedure. However, leukapheresis or lymphocytapheresis also describes apheresis procedures in which the white blood cells are isolated and retained. As another example, peripheral stem cell collection, done in preparation for autologous bone marrow transplant, involves an apheresis procedure in which the critical stem cells are isolated and retained. Extracorporeal immunoabsorbent therapy is another procedure involving pheresis.

PE, in which the plasma is isolated, then discarded and replaced with an allogenic plasma or substitution fluid such as albumin is frequently done in conjunction with plasmapheresis. PE is a nonspecific therapy, since the entire plasma is discarded. Extracorporeal Immunoadsorption using Protein A columns involves a pheresis procedure which specifically removes circulating immune complexes. This technology is addressed in another policy. Low density lipoprotein (LDL) apheresis is another selective procedure in which LDL particles are removed from the plasma while preserving the rest of the plasma and reinfusing it into the patient. This policy refers only to 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. Plasma exchange is essentially a symptomatic therapy, since it does not remove the source of the pathogenic factors. Therefore, the success of PE will depend on whether the pathogenic substances are accessible through the circulation, and whether their rate of production and transfer to the plasma component can be adequately addressed by PE. For example, PE can rapidly reduce levels of serum autoantibodies; however, through a feedback mechanism this rapid reduction may lead to a rebound overproduction of the same antibodies. This rebound production of antibodies is thought to render the replicating pathogenic clone of lymphocytes more vulnerable to cytotoxic drugs. Therefore, PE is sometimes used in conjunction with cyclophosphamide.

Applications of PE can be broadly subdivided into two general categories:

1. Acute self-limited diseases where PE is used to acutely lower the circulating pathogenic substance; and

2. Chronic diseases where 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.

APPLICATIONS:

Acute Self-Limited Conditions:
• **Conditions associated with hyperviscosity**

Serum hyperviscosity is most commonly related to overproduction of immunoglobulins and thus is seen in association with B-cell lymphocyte neoplasms such as multiple myeloma and Waldenstrom’s macroglobulinemia. Symptoms of hyperviscosity include bleeding disorders, retinopathy, and neurologic disorders including stroke. Treatment is principally directed at the underlying disorder, but PE may be used to acutely lower the serum viscosity.

• **Acute exacerbations of myasthenia gravis**

Myasthenia gravis is an autoimmune disease with autoantibodies directed against the postsynaptic membrane of the muscle end-plate. Clinically, the disease is characterized by fatigable weakness of voluntary muscles. Initial treatment focuses on the use of cholinesterase inhibitors to overcome the postsynaptic blockade. Immunosuppressant drugs including corticosteroids and azathioprine are also effective. PE has been used as a short-term therapy in patients with acute exacerbations associated with severe weakness.

• **Guillain-Barre syndrome (GBS)**

Guillain-Barre syndrome (GBS) is an acute demyelinating neuropathy whose severity is graded on a scale of 1-5.

1= minor symptoms  
2= able to walk 5 meters without assistance  
3= able to walk 5 meters with assistance  
4= confined to bed or chair  
5= requiring assisted ventilation for at least part of the day or night.

Loss of reflexes and motor strength, and variable sensory loss characterize GBS. Evidence suggests that nerve injury is immunologically mediated. In studies, significant benefit was demonstrated in those patients with rapidly progressing weakness treated with PE in terms of improvement by at least one disability grade.

• **Rapidly progressive glomerulonephritis (RPGN) including Goodpasture’s syndrome (RPGN)**

RPGN is a general term describing the rapid loss of renal function in conjunction with the finding of glomerular crescents on renal biopsy specimens. There are multiple etiologies of RPGN including vasculitis, the deposition of anti-glomerular basement membrane (GBM) antibodies as seen in Goodpasture’s syndrome, or the deposition of immune complexes as seen in various infectious diseases or connective tissue diseases. RPGN may also be idiopathic. Because many cases of RPGN represent an immune-mediated disease of acute onset, RPGN was an early focus of PE research.

• **Thrombotic thrombocytopenic purpura (TTP)—Hemolytic uremic syndrome (HUS)**

Once considered distinct syndromes, TTP and HUS are now considered different manifestations of the same disease process, i.e., thrombotic
microangiopathy. The classic signs and symptoms include fever, thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, and renal involvement. TTP-HUS may be seen in association with other conditions, such as pregnancy or HIV infection. PE has become the primary treatment for TTP-HUS, although a rationale for its effectiveness is unknown. PE is performed daily until a clinical and laboratory (i.e., increased platelet count and reduction of LDH) response is noted; the length of treatment averages about once month with increasing intervals between PE treatments.

• **Idiopathic thrombocytopenic purpura (ITP)**

ITP is an acquired disease of either adults or children characterized by the development of autoantibodies to platelets. Management of acute bleeding due to thrombocytopenia typically involves immediate platelet transfusion, in conjunction with infusions of intravenous immunoglobulin (IVIG) and corticosteroid treatment. PE has been occasionally used in emergency situations. PE does not appear to have a role in chronic ITP.

• **HELLP syndrome of pregnancy.**

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

• **Post-transfusion purpura**

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

**CHRONIC CONDITIONS**

• **Chronic inflammatory demyelinating polyneuropathy (CIDP)**

CIDP is a symmetric polyneuropathy associated with both motor and sensory deficits. The disease course may present as either a relapsing/fluctuating or slowly progressing disease. PE is reserved for those patients who do not respond to treatment with prednisone. PE may be required on a chronic basis, its frequency titrated according to the durability of the patient’s response. Some of the symptoms of CIDP may overlap with those of chronic fatigue syndrome. However, the American Academy of Neurology has established diagnostic guidelines for CIDP, which are summarized in the Appendix.

• **Multiple sclerosis**

Multiple sclerosis (MS) is an inflammatory demyelinating disease, the etiology of which has remained frustratingly elusive with both environmental and genetic factors thought to play a role. Laboratory abnormalities suggest that MS is an immune-mediated
disease. Classic features of multiple sclerosis include weakness and paraparesis, visual impairment, diplopia, nystagmus, dysarthria, intention tremor, ataxia, bladder dysfunction, and emotional lability. PE has been used primarily as a technique to either shorten the duration of an acute attack or to reduce the number of acute attacks.

- **Paraneoplastic neuromuscular syndromes**

Paraneoplastic neuromuscular syndromes refer to the production of tumor antibodies that cross react with the patient’s nervous system tissues. In many cases, the paraneoplastic syndrome may be the initial manifestation of the tumor, and in other instances the symptoms of the syndrome are more disabling than the tumor itself. Eaton Lambert syndrome, characterized by generalized motor weakness and associated most frequently with small cell lung cancer, is the most common paraneoplastic syndrome. Other syndromes include paraneoplastic sensory neuropathy and paraneoplastic encephalomyelitis; both are related to the presence of anti-Hu antibody. Paraproteinemic immunoglobulin M can also be associated with a demyelinating polyneuropathy. Although treatment of the underlying primary tumor is the cornerstone of treatment, PE has also been investigated due to the presence of circulating autoantibodies.

- **Pemphigus**

Pemphigus is an autoimmune blistering skin disease that is characterized by serum antibodies that bind to squamous epithelia. It is characterized by flaccid bullae that rupture and leave areas of denuded skin, creating serious problems of secondary infection and fluid balance. Steroids or other immunosuppressants are the most common forms of treatment, but high doses of steroids can produce significant side effects. PE has been investigated in patients refractory or intolerant to steroids or other immunosuppressant therapies.

- **Autoimmune connective tissue diseases**

This family of diseases includes systemic lupus erythematosus (SLE), systemic sclerosis (also referred to as scleroderma), polymyositis, and dermatomyositis. When PE first became available during the 1970s and early 1980s, there was considerable interest and enthusiasm for the use of PP/PE for these autoimmune diseases. However, since that time there have been successive randomized controlled trials that have not validated the role of PE as a treatment of the chronic phase of these conditions.

RATIONAL:

**Chronic Autoimmune Diseases**

Over the past 10 years, randomized trials of PE have been conducted and, in general, have shown a lack of effectiveness as a treatment of chronic autoimmune diseases. On the basis of a randomized controlled trial, Lewis and colleagues reported that PE had no benefit in patients with SLE and glomerulonephritis compared to a standard therapy regimen of prednisone and cyclophosphamide. Finally, 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. Guillaume and colleagues reported on a study of 40 patients with pemphigus randomized to receive either prednisone 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.

Another potential type of evidence in support of the clinical effectiveness of PE 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, is the cause of the clinical manifestations of the disease. Furthermore, it is not known to what extent plasma levels parallel clinical disease. For example, in the controlled trials cited above, 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.

**Multiple sclerosis (MS)**

There have been several controlled, randomized trials of PE in patients with MS that have reported inconclusive results. Khatri 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 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. More recent studies published in the Annals of Neurology have shown that plasma exchange leads to functionally important neurological recovery in an important proportion of severely disabled patients with acute attacks of idiopathic inflammatory demyelinating disease. A Mayo Clinic study reported that 42% of people with MS and related conditions treated with plasma exchange experienced moderate to marked improvement, including, in some, recovery of full function of their arms and legs and return of speech.

**Rapidly progressive glomerulonephritis (RPGN)**

PE has long been considered a treatment alternative in immune-mediated RPGN. However, there have been a few controlled clinical trials published, and interpretation is difficult due to small numbers 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.

**DISCLAIMER:**
State and federal law, as well as contract language, including definitions and specific inclusions/exclusions, takes precedence over Medical Policy and must be considered first in determining coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Any benefits are subject to the payment of premiums for the date on which services are rendered. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

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