



BlueShield  
of Northeastern New York

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# Protocol

## Plasma Exchange (Plasmapheresis)

(Formerly Therapeutic Apheresis)  
(80202)

Effective May 1, 2005

**Contracts Affected:**  
**All Community Blue HMO**  
**\*\*\*Senior Blue/Medicare PPO**  
**Traditional Blue**

*The following protocol contains medical necessity criteria for Plasma Exchange (Plasmapheresis) services rendered on or after May 1, 2005 for BlueShield of Northeastern New York (BlueShield) contracts. If these criteria are not met, reimbursement will be denied and the patient cannot be billed. **Prior approval is not required.** Please note that payment for covered services is subject to the limitations noted in the above-referenced contracts and the patient's eligibility at the time the services are rendered.*

### Description

The terms therapeutic apheresis, plasmapheresis, and plasma exchange 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.

Plasma exchange (PE), in which the plasma is isolated, then discarded and replaced with a substitution fluid such as albumin, is frequently done in conjunction with plasmapheresis. Plasma exchange is a nonspecific therapy, since the entire plasma is discarded. Extracorporeal immunoabsorption using protein A columns involves a pheresis procedure that specifically removes circulating immune complexes. This technology is addressed in policy Extracorporeal Immunoabsorption Using Protein A Columns. 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 re-infusing it into the patient. The following 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 2 general categories: 1) acute self-limited diseases, in which PE is used to acutely lower the circulating pathogenic substance; and 2) chronic diseases, in which there is ongoing production of pathogenic autoantibodies. Because PE does not address underlying pathology, and, due to the phenomenon of rebound antibody production, its use in chronic diseases has been more controversial than in acute self-limited diseases.

## **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-Barré syndrome*

Guillain-Barré syndrome is an acute demyelinating neuropathy whose severity is graded on a scale of 1-5. PE is reserved for those patients with grades 3–5 disease who do not initially respond to prednisone.

#### *Rapidly progressive glomerulonephritis (RPGN) including Goodpasture's syndrome*

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 response is noted; the length of treatment averages about once a 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, occasionally in conjunction with a single infusion of intravenous immunoglobulin (IVIG). PE has been occasionally used in emergency situations. PE does not appear to have a role in chronic ITP.

#### *HELLP syndrome of pregnancy*

The HELLP 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, 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 in association with a high titer of anti-platelet alloantibodies. Due to its rapid effect, PE is considered the initial treatment of choice.

#### *Acute fulminant CNS demyelination*

Multiple sclerosis and other idiopathic inflammatory demyelinating diseases may present with an acute fulminant onset, which may proceed to severe cognitive dysfunction, hemiplegia, paraplegia, or quadriplegia.

## **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 progressive 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 an Appendix to this policy.

### *Paraproteinemic polyneuropathy*

A monoclonal immunoglobulin (paraprotein) is found in the serum or urine of approximately 10% of patients with idiopathic polyneuropathy, typically occurring in the context of a monoclonal gammopathy of undetermined significance (MGUS). In addition, approximately 25% of patients with CIDP may have a monoclonal gammopathy. The gammopathy is typically an IgM (in which it is often directed against myelin-associated proteins or the ganglioside GM-1) or less commonly IgG or IgA.

### *Multiple sclerosis*

Multiple sclerosis (MS) is an inflammatory demyelinating disease, the etiology of which has remained frustratingly elusive; both environmental and genetic factors are thought to play a role. Laboratory abnormalities suggest that MS is an immune-mediated disease. 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 are characterized by 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. The Lambert-Eaton myasthenic syndrome (LEMS), characterized by proximal muscle weakness of the lower extremities and associated most frequently with small cell lung cancer, is the most common paraneoplastic syndrome. Although presence of LEMS should prompt a search for a lung primary tumor, the syndrome may also occur idiopathically. Other syndromes include paraneoplastic sensory neuropathy, encephalomyelitis, cerebellar degeneration, or opsoclonus/myoclonus (related to the presence of anti-Hu antibody, or in the case of cerebellar degeneration, anti-Purkinje cell antibodies). 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.

### *Stiff Man Syndrome*

Stiff man syndrome is an autoimmune disorder characterized by involuntary stiffness of axial muscles and intermittent painful muscle spasm. Symptoms are related to the autoantibodies directed against glutamic acid decarboxylase in the nervous system. 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.

### *Pemphigus*

Pemphigus is an autoimmune blistering skin disease that is characterized by serum antibodies that bind to squamous epithelia. Clinically, 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 the 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), rheumatoid arthritis (RA), systemic sclerosis (also referred to as scleroderma), polymyositis, and dermatomyositis. Inclusion body myositis is the most commonly acquired inflammatory myopathy in patients over age 50 years, characterized by weakness of the quadriceps, biceps, and triceps. 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, successive randomized controlled trials have not validated the role of PE as a treatment of the chronic phase of these conditions.

## *Plasmapheresis in the Setting of Solid Organ Transplantation*

Acute rejection after transplant can be broadly divided into 2 categories, the more common acute cellular rejection (ACR) related to activation of T cells, and the less common antibody-mediated rejection reaction (AMR) related to the presence of anti-donor antibodies. While ACR typically responds to immunologic therapy directed at T cells, AMR does not, and, as such, has also been referred to as “steroid resistant rejection.” The risk of AMR is related to the presence of preformed allo-antibodies in the recipient due to prior blood transfusions, transplants, or pregnancies. The presence of allo-antibodies is assessed by using a panel reactive antibody (PRA) screen, which combines the recipient’s serum with samples of antigen containing cells taken from 60 individuals representative of the potential donor pool. The percentage PRA is the percentage of positive reactions. Those with a PRA >20% are referred to as “sensitized,” and these patients often have prolonged waiting times to identify a compatible donor. Living donor kidney transplants have also been performed using ABO mismatched donor organs. These recipients are also at risk of AMR. Plasmapheresis has been used as a technique to desensitize high-risk patients prior to transplant, and also as a treatment of AMR occurring after transplant. Prior to transplant, plasmapheresis has been most commonly used to desensitized 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; see policy on Daily Hemodialysis in the Home) or anti-CD20 therapy (i.e., Rituxan).

**Note:** This policy is focused on indications for plasmapheresis that are typically delivered in the outpatient setting. Therefore, this policy does not address plasmapheresis as a treatment of septic shock.

### **Corporate Medical Guideline**

Plasmapheresis and plasma exchange may be considered **medically appropriate** for any of the conditions listed below:

- myasthenia gravis in crisis or as part of preoperative preparation;
- hyperviscosity syndromes associated with multiple myeloma, Waldenstrom’s macroglobulinemia, or other conditions;
- thrombotic thrombocytopenic purpura (TTP);
- hemolytic uremic syndrome (HUS);
- idiopathic thrombocytopenic purpura in emergency situations;
- Guillain-Barré syndrome for severely ill patients who are diagnosed with grades 3–5 disease, which include the ability to walk 5 meters with assistance, confinement to a bed or chair-bound, or requiring assisted ventilation for at least part of the day or night;
- chronic inflammatory demyelinating polyneuropathy (CIDP) for patients with severe or life-threatening symptoms who have failed to respond to conventional therapy with prednisone or intravenous immunoglobulins (IVIG);
- IgA or IgG paraproteinemia polyneuropathy;
- HELLP syndrome of pregnancy;
- post-transfusion purpura;
- progressive renal failure due to anti-basement membrane antibodies (i.e., Goodpasture’s syndrome);
- acute fulminant CNS demyelination, associated with multiple sclerosis or other conditions, such as transverse myelitis, etc.;
- prior to solid organ transplant, treatment of patients at high risk of antibody-mediated rejection, including highly sensitized patients, and those receiving an ABO incompatible organ; and
- following solid-organ transplant, treatment of antibody-mediated rejection.

**Investigational** applications of plasma exchange include, but are not limited to, the following conditions because it is unproven outside the investigational setting:

- rheumatoid arthritis;
- scleroderma (systemic sclerosis);

- systemic lupus erythematosus;
- polymyositis and dermatomyositis;
- inclusion body myositis;
- pemphigus;
- Guillain-Barré syndrome, grades 1–2;
- chronic progressive or relapsing remitting multiple sclerosis;
- amyotrophic lateral sclerosis;
- paraneoplastic syndromes including Lambert-Eaton myasthenic syndrome;
- paraproteinemic polyneuropathy including monoclonal gammopathy of undetermined significance (MGUS);
- chronic fatigue syndrome;
- regional enteritis (Crohn's disease);
- rapidly progressive glomerulonephritides, excluding those related to anti-basement membrane immunoglobulins (i.e., Goodpasture's syndrome);
- asthma; and
- stiff man syndrome.

*For explanation of experimental and investigational refer to the Technology Assessment Protocol.*

**\*\*\* Senior Blue/Medicare PPO \*\*\***

For Senior Blue/Medicare PPO Apheresis is **medically appropriate** 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 pruritus of cholestatic liver disease;
- Plasma exchange in the treatment of Goodpasture's Syndrome;
- Plasma exchange in the treatment of glomerulonephritis associated with antglomerular 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-Barré Syndrome; and
- Treatment of last resort for life threatening systemic lupus erythematosus (SLE) when conventional therapy has failed to prevent clinical deterioration.

## Settings

When Apheresis meets medical criteria, it is covered only when performed in a hospital setting (either inpatient or outpatient) or in a non-hospital setting, e.g., a physician directed clinic when the following conditions are met:

- A physician (or a number of physicians) is present to perform medical services and to respond to medical emergencies at all times during patient care hours;
- Each patient is under the care of a physician; and
- All non-physician services are furnished under the direct, personal supervision of a physician.

Prior approval is not required. BlueShield fully expects that only appropriate and medically necessary services will be rendered. BlueShield reserves the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures.

## References

1. Shumak KH, Rock GA. Therapeutic plasma exchange. *N Engl J Med* 1984; 310(12):762-71.
2. Lewis EJ, Hunsicker LG, Lan SP, et al. A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. *N Engl J Med* 1992; 326(21):1373-9.
3. Danieli MG, Palmieri C, Salvi A, et al. Synchronized therapy and high-dose cyclophosphamide in proliferative lupus nephritis. *J Clin Apheresis* 2002; 17(2):72-7.
4. Dwosh IL, Giles AR, Ford PM, et al. Plasmapheresis therapy in rheumatoid arthritis. A controlled, double-blind, crossover trial. *N Engl J Med* 1983; 308(19):1124-9.
5. Miller FW, Leitman SF, Cronin ME, et al. Controlled trial of plasma exchange and leukapheresis in polymyositis and dermatomyositis. *N Engl J Med* 1992; 326(21):1380-4.
6. Guillaume JC, Roujeau JC, Morel P, et al. Controlled study of plasma exchange in pemphigus. *Arch Dermatol* 1988; 124(11):1659-63.
7. Khatri BO, McQuillen MP, Harrington GJ, et al. Chronic progressive multiple sclerosis: double-blind controlled study of plasmapheresis in patients taking immunosuppressive drugs. *Neurology* 1985; 35(3):312-9.
8. Weiner HL, Dau PC, Khatri BO, et al. Double-blind study of true vs. sham plasma exchange in patients treated with immunosuppression for acute attacks of multiple sclerosis. *Neurology* 1989; 39(9):1143-9.
9. Canadian Cooperative Multiple Sclerosis Study Group. The Canadian cooperative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis. *Lancet* 1991; 337(8739):441-6.
10. Couser WG. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanisms, and therapy. *Am J Kidney Dis* 1988; 11(6):449-64.
11. Cole E, Cattran D, Magil A, et al. A prospective randomized trial of plasma exchange as additive therapy in idiopathic crescentic glomerulonephritis. The Canadian Apheresis Study Group. *Am J Kidney Dis* 1992; 20(3):261-9.
12. Tim RW, Massey JM, Sanders DB. Lambert-Eaton myasthenic syndrome: electrodiagnostic findings and response to treatment. *Neurology* 2000; 54(11):2176-8.
13. Sanders DB, Massey JM, Sanders LL, et al. A randomized trial of 3, 4-diaminopyridine in Lambert-Eaton myasthenic syndrome. *Neurology* 2000; 54(3):603-7.
14. Anderson NE, Rosenblum MK, Posner JB. Paraneoplastic cerebellar degeneration: clinical-immunological correlations. *Ann Neurol* 1988; 24(4):559-67.
15. Vicari AM, Folli F, Pozza G, et al. Plasmapheresis in the treatment of stiff-man syndrome. *N Engl J Med* 1989; 320(22):1499.

16. Brashear HR, Phillips LH. Autoantibodies to GABAergic neurons and response to plasmapheresis in stiff-man syndrome. *Neurology* 1991; 41(10):1588-92.
17. Harding AE, Thompson PD, Kocen RS, et al. Plasma exchange and immunosuppression in the stiff man syndrome. *Lancet* 1989; 2(8668):915.
18. Ellingsen I, Florvaag E, Andreassen AH, et al. Plasmapheresis in the treatment of steroid-dependent bronchial asthma. *Allergy* 2001; 56(12):1202-5.
19. Weinshenker BG, O'Brien PC, Petterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol* 1999; 46(6):878-86.
20. Dyck PJ, Low PA, Windebank AJ, et al. Plasma exchange in polyneuropathy associated with monoclonal gammopathy of undetermined significance. *N Engl J Med* 1991; 325(21):1482-6.
21. Jordan SC, Vo AA, Nast CC, et al. Use of high-dose human intravenous immunoglobulin therapy in sensitized patients awaiting transplantation: the Cedars-Sinai experience. *Clin Transpl* 2003:193-8.
22. Montgomery RA, Zachary AA. Transplanting patients with a positive donor-specific crossmatch: a single center's perspective. *Pediatr Transpl* 2004; 8(6):535-42.
23. Tanabe K, Takahashi K, Sonda K, et al. Long-term results of ABO-incompatible living kidney transplantation: a single-center experience. *Transplantation* 1998; 65(2):224-8.
24. Winters JL, Gloor JM, Pineda AA, et al. Plasma exchange conditioning for ABO-incompatible renal transplantation. *J Clin Apher* 2004; 19(2):79-85.
25. Shishido S, Hasegawa A. Current status of ABO-incompatible kidney transplantation in children. *Pediatr Transpl* 2005; 9(2):148-54.
26. Jordan SC, Vo AA, Tyan D, et al. Current approaches to treatment of antibody-mediated rejection. *Pediatr Transpl* 2005; 9(3):408-15.
27. Lehrich RW, Rocha PN, Reinsmoen N, et al. Intravenous immunoglobulin and plasmapheresis in acute humoral rejection: experience in renal allograft transplantation. *Hum Immunol* 2005; 66(4):350-8.
28. Ibernón M, Gil-Vernet S, Carrera M, et al. Therapy with plasmapheresis and intravenous immunoglobulin for acute humoral rejection in kidney transplantation. *Transplant Proc* 2005; 37(9):3743-5.
29. Shah A, Nadasdy T, Arend L, et al. Treatment of C4d-positive acute humoral reaction with plasmapheresis and rabbit polyclonal antithymocyte globulin. *Transplantation* 2004; 77(9):1399-405.
30. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment of plasmapheresis. *Neurology* 1996; 47(3):840-3.
31. Smith JW, Weinstein R and the AABB Hemapheresis Committee. Therapeutic apheresis: a summary of current indication categories endorsed by the AABB and the American Society of Apheresis. *Transfusion* 2003; 43(6):820-2.
32. CMS NCD for Apheresis (Therapeutic Pheresis) 110.14, 7/30/92.

**Last Review Date**

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**Next Review Date**

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