Clinical Policy: Plasmapheresis, Plasma Exchange, Therapeutic Apheresis

Reference Number: HNCA.CP.MP.322
Effective Date: 8/16
Last Review Date: 8/19

Coding Implications

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

This policy describes the medical necessity guidelines for plasmapheresis based on the guidelines from the American Society for Apheresis. In this procedure, whole blood is removed from the body, its cellular elements are separated from the plasma by centrifugation or filtration, and the cells suspended in saline or some other plasma substitute are reinfused. This depletes the body's own plasma without depleting its cells.

Policy/Criteria

I. It is the policy of Health Net of California that plasmapheresis, plasma exchange and therapeutic apheresis are **medically necessary** for any of the following indications:

- **A.** ABO incompatible bone marrow transplants;
- **B.** ABO incompatible solid organ transplant (i.e., Kidney, Heart etc);
- **C.** Acute disseminated encephalomyelitis where conventional treatment has failed;
- **D.** ANCA-associated rapidly progressive glomerulonephritis (Wegener's Granulomatosis) with renal failure;
- **E.** Catastrophic antiphospholipid antibody syndrome (Hughe's Syndrome) unresponsive to conventional therapy (aspirin, warfarin, heparin);
- ~~**F.**~~ Chronic inflammatory demyelinating polyneuropathy (CIDP), also known as chronic relapsing polyneuropathy who have not responded to conventional therapy;
- **G.** Chronic demyelinating gammopathy;
- **H.** Cold Agglutinin disease (life threatening due to fulminant hemolysis);
- **I.** Symptomatic thrombocytosis, or when platelet count is ≥ 1,000,000/cu.mm (cytapheresis);
- **J.** Guillain-Barré syndrome, for severely ill patients who are diagnosed with grade 3-5 disease;
- **K.** Multiple Sclerosis (i.e., Acute CNS inflammatory demyelinating disease unresponsive to steroids);
- **L.** Myasthenia gravis in acute crisis because of a sudden worsening of symptoms, as in an impending respiratory crisis, which fails to respond to all other treatments (e.g., cholinesterase inhibitors, corticosteroids, immunosuppressant drugs, IVIG, and/or thymectomy) or needs rapid improvement of strength before surgery or irradiation;
- **M.** Hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome of pregnancy;
- **N.** Hyperglobulinemias, including (but not limited to) multiple myelomas, severe/symptomatic cryoglobulinemia, primary (Waldenstrom's) macroglobulinemia, and hyperviscosity syndromes;

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O. Idiopathic Thrombocytopenic Purpura in emergency situations;
P. IgA and IgG paraproteinemia with polyneuropathy, including MGUS;
Q. Leukemia (Leukapheresis) (for acute debulking only);
R. Myeloma cast nephropathy (acute renal failure secondary to multiple myeloma);
S. Neuromyelitis optica (Devic's syndrome);
T. Phytanic Acid Storage Disease when used to rapidly lower plasmic phytanic acid levels during acute attacks (Refsum's disease);
U. Post renal transplant recurrent focal and segmental glomerulosclerosis (FGS) or acute humoral rejection;
V. Progressive renal failure due to antiglomerular basement membrane antibodies and pulmonary hemorrhage (Goodpasture's syndrome) (i.e., dialysis independent; Diffuse alveolar hemorrhage);
W. Renal transplantation from live donor with ABO incompatibility or positive cross-match, where a suitable non-reactive live or cadaveric donor is unavailable;
X. Renal transplantation in highly sensitive kidney transplant candidates (high PRA protocols) to reduce the number of antibodies reactive against human lymphocyte antigens;
Y. Severe hypercholesterolemia in person's refractory to diet and maximum drug therapy who are homozygous for familial hypercholesterolemia (LDL apheresis, also known as heparin-induced extracorporeal LDL precipitation or dextra sulfate adsorption) with LDL levels greater than 500 mg/dL, or persons heterozygous for familial hypercholesterolemia with LDL levels > 300 mg/dl or > 200 mg/dL with documented history of coronary artery disease;
Z. Sickle cell disease (therapeutic cytopheresis);
AA. Solid organ transplant: prior to transplant as a treatment for patients at high-risk of antibody mediated rejection or following transplant as a treatment of antibody mediated rejection;
BB. Systemic lupus erythematosus, severe, for refractory or critically ill patients (e.g.,cerebritis, diffuse alveolar hemorrhage);
CC. Systemic vasculitis (life threatening rheumatoid, polyateritis nodosa, Wegener's granulomatosis, microscopic vasculitis) unresponsive to conventional therapy;
DD. Thrombotic microangiopathy: drug associated (i.e., Ticlopedine/Clopidogrel);
EE. Thrombotic thrombocytopenic purpura /Hemolytic Uremic Syndrome or microangiopathic hemolytic;
FF. Wilson's disease, fulminant hepatic failure with hemolysis (bridge to liver transplant)
GG. Pemphigus vulgaris that is resistant to standard therapy (e.g. dapsone, corticosteroids, immunosuppressants such as azathioprine or cyclosporine);
HH. Babesiosis, with a high grade parasitemia, severe anemia or hepatic, pulmonary, or renal compromise (red blood cell exchange);
II. Recurrence of focal and segmental glomerulosclerosis in the kidney allograft;
JJ. Treatment of transverse myelitis when corticosteroid treatment has failed.

II. It is the policy of Health Net of California that plasmapheresis, plasma exchange, and therapeutic apheresis may be considered medically necessary on a case by case basis for use in the treatment of any of the following:

Plasmapheresis

- **A.** ABO incompatible liver transplantation, perioperative
- **B.** Acute liver failure
- **C.** AIDS
- **D.** ANCA-associated rapidly progressive glomerulonephritis (i.e., dialysis independent)
- **E.** Aplastic anemia
- **F.** Cardiac allograft rejection (treatment of antibody mediated rejection)
- **G.** Chronic progressive or relapsing-remitting muscular sclerosis in absence of acute fulminant onset
- **H.** Chronic focal encephalitis (Rassmussen's Encephalitis);
- **I.** Dilated cardiomyopathy NYHA II-IV
- **J.** Acute pancreatitis related to hyperlipidemia to lower markedly elevated triglyceridelevels acutely in patients with associated severe pancreatitis (i.e.,hypertriglyceridemic pancreatitis)
- **K.** Immune complex rapidly progressive glomeruonephritis
- **L.** LAK cells for reinfusion with Interleukin II
- **M.** Lambert-Eaton myasthenia syndrome
- **N.** Multiple myeloma
- **O.** Nephrogenic systemc fibrosis
- **P.** Overdose, venoms and poisoning (invenomation, monoclonal antibody with PML, other compounds)
- **Q.** Paraneoplastic neurological syndromes
- **R.** Paraproteinemic polyneuropathy (except for asymptomatic monoclonal gammopathy of unknown significance
- **S.** Pediatric autoimmune neuropsychiatric disorders associated with streptoccal infections (exacerbation) and Sydenhams Chorea when symptoms are severe and other therapies have failed to reduce symptom severity
- **T.** Post transfusion purpura
- **U.** Pure red cell aplasia unresponsive to steroid and immunosuppressive therapy
- **V.** Red cell alloimmunization in pregnancy until intrauterine transfusion can safely be administered
- **W.** Scleroderma (progressive systemic sclerosis)
- **X.** Severe bullous pemphigoid
- **Y.** Sepsis with multi-organ failure
- **Z.** Thyroid storm
- **AA.** Treatment of antibody mediated rejection
- **BB.** Autoimmune hemolytic anemia

III. It is the policy of Health Net of California that plasmapheresis, plasma exchange and therapeutic apheresis are not medically necessary for any of the following indications because there is inadequate scientific evidence in the medical literature validating their effectiveness:

- **A.** Amyloidosis, systemic
- **B.** Amyotrophic lateral sclerosis
- **C.** Asthma
- **D.** Burn shock resuscitation

- **E.** Chronic fatigue syndrome
- **F.** Coagulation factor inhibitors
- **G.** Diarrhea-Associated Pediatric Hemolytic Uremic Syndrome or typical HUS
- **H.** Guillain-Barré syndrome, grades 1-2
- **I.** Hashimoto's encephalopathy
- **J.** Immune thrombocytopenic purpura
- **K.** Inclusion body myositis
- **L.** Lupus Nephritis
- **M.** Multifocal motor neuropathy
- **N.** Necrobiotic xanogranulomatous skin disorder
- **O.** Parkinson's disease
- **P.** Acute obsessive-compulsive disorder and tics in PANDAS
- **Q.** POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes)
- **R.** Polymyositis and dermatomyositis unless unresponsive to conventional therapy
- **S.** Psoriasis
- **T.** Pulmonary alveolar proteinosis
- **U.** Rapidly progressive glomerulonephritis, excluding those related to anti-basement membrane immunoglobulins (e.g., Goodpasture's syndrome)
- **V.** Raynaud's phenomenon
- **W.** Regional enteritis (Crohn's disease)
- **X.** Refractory rheumatoid arthritis
- **Y.** Rheumatoid arthritis except for life-threatening vasculitis
- **Z.** Schizophrenia
- **AA.** Stiff man syndrome
- **BB.** Thrombotic microangiopathy: drug associated (i.e., Gemcitabine and Quinine)
- **CC.** Alzheimer's Disease
- **DD.** High density lipoprotein (HDL) delipidation and plasma re-infusion for acute coronary syndrome

Background

The terms therapeutic apheresis, plasmapheresis and plasma exchange are often used interchangeably, but actually refer to different procedures.

Apheresis is an extracorporeal medical technology in which the blood of a patient is passed through an apparatus that separates out one particular constituent and returns the remainder to the circulation. 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.

Plasmapheresis is generally performed to remove and discard harmful substances (e.g., toxins or autoantibodies), which have accumulated in the plasma. It is hypothesized that removal of these factors can be therapeutic in certain situations.

Plasmapheresis

Plasma exchange (PE) is a procedure in which the plasma is separated from the blood, discarded in total, and replaced with a substitution fluid such as albumin or with donated plasma from a healthy person. This also is generally performed to remove toxins or autoantibodies that have accumulated in the plasma. Rapidly reducing specific autoantibodies may sometimes lead to a rebound overproduction of the same antibodies. This rebound production of antibodies is thought to make the replicating pathogenic cells more vulnerable to cytotoxic drugs. For this reason, it is often performed to enhance the effectiveness of cytotoxic drugs (e.g., cyclophosphamide). The number of treatments needed varies greatly depending on the particular disease and the person's general condition. 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. An average course of plasma exchanges is six to 10 treatments over two to 10 weeks.

Applications of plasma exchange can be subdivided into 2 general categories: 1) acute self-limited diseases in which apheresis are used to acutely lower the circulating pathogenic substance; and 2) chronic diseases, in which there is ongoing production of pathogenic autoantibodies. The applications of plasma exchange seen in acute self-limited conditions are many. Serum hyper viscosity is most commonly related to overproduction of immuno-globulins and thus is seen in association with B-cell lymphocyte neoplasm’s such as multiple myeloma and Waldenström's macroglobulinemia, a cancer of the B lymphocytes that causes overproduction of monoclonal macroglobulin (IBM antibody). This hyperviscosity interferes with blood flow through small blood vessels, which leads to many of the symptoms of the disease. 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 by removing or reducing the high concentration of IgM.

Severe hypertriglyceridemia with an accumulation of chylomicrons and triglyceride figures >1000 mg/dL can cause acute pancreatitis, a potentially fatal complication. When standard therapies fail to achieve favorable clinical and metabolic outcomes, selected patients with HTG-induced pancreatitis may be referred for plasmapheresis, or plasma exchange (PE), to remove serum lipids, primarily triglycerides. Studies done by Ramirez-Bueno et al. (2015) Gubensek et al. (2014), and Stafanuti et al. (2011), have been done to determine the efficacy of this procedure, however there is a lack of long-term outcomes. The peer-reviewed literature, confirms the need for randomized clinical trials to compare conventional treatment versus plasmapheresis in patients with severe hypertriglyceridemic pancreatitis.

Because plasmapheresis 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. However, based on the peer-reviewed literature, plasmapheresis is a widely accepted component in the management of acute rejection, with most experience related to kidney trans-plantation due to its higher volume and use in living donors. It is accepted as standard therapy for transplant recipients at high risk for antibody mediated rejection (AMR). As a treatment of AMR, plasmapheresis is often used in combination with IVIG or anti-CD20 therapy.

American Gastroenterological Association (AGA)
The AGA published a medical position statement on acute pancreatitis to guide clinicians in the management of patients with both mild and severe forms of acute pancreatitis. However, the guidelines do not refer to apheresis or plasmapheresis as possible treatment options for acute pancreatitis. [20]

American Society for Apheresis (ASFA)
The ASFA recommends the following Category I indications for therapeutic plasma exchange: [1, 2]

Specialty	Condition
Neurology	Acute Guillain–Barré Syndrome
	Chronic inflammatory demyelinating polyneuropathy
	Myasthenia gravis
	Polyneuropathy associated with paraproteinaemias (PANDAS-i.e., pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection).
Hematology	Thrombotic thrombocytopenic purpura
	Atypical haemolytic uraemic syndrome (autoantibody to factor H)
	Hyperviscosity syndromes (paraproteinaemias)
	Severe/symptomatic cryoglobulinaemia
Renal	Goodpasture's syndrome (anti-glomerular basement membrane antibodies)
	Antineutrophil cytoplasmic antibody (ANCA)-associated rapidly progressive glomerulonephritis
	Recurrent focal segmental glomerular sclerosis
	Antibody-mediated renal transplant rejection
Metabolic	Familial hypercholesterolaemia (homozygous)
	Fulminant Wilson's disease

American Academy of Neurology (AAN)
The AAN completed an evidence-based guideline update from the Therapeutics and Technology Assessment Subcommittee regarding plasmapheresis in neurologic disorders made the following recommendations:

1. Plasmapheresis should be offered in the treatment of acute inflammatory demyelinating polyneuropathy/Guillain-Barre´syndrome (AIDP/GBS) severe enough to impair independent walking or to require mechanical ventilation (Level A). Plasmapheresis should be considered in the treatment of milder clinical presentations of AIDP/GBS (Level B). The guideline notes that IV immunoglobulin (IVIg) is an alternative treatment used in patients with AIDP/ GBS. There is insufficient evidence to demonstrate the superiority of one treatment over the other.

2. Plasmapheresis should be offered as a short-term treatment for patients with chronic inflammatory demyelinating neuropathy (CIDP). (Level A). The guideline notes that steroids, IVIg, and immunosuppressants have also been used in the treatment of CIDP.

3. Plasmapheresis should be considered in polyneuropathy associated with IgA and IgG monoclonal gammopathy of undetermined Significance (MGUS) (Level B).

4. Plasmapheresis should not be considered in the treatment of polyneuropathy associated with IgM MGUS (Level B).

5. Because of the lack of randomized controlled studies with masked outcomes, there is insufficient evidence to support or refute the efficacy of plasmapheresis in the treatment of myasthenic crisis (Level U) or myasthenia gravis (MG) prethymectomy (Level U). The guideline notes that despite the fact that the use of plasmapheresis in myasthenic crisis and MG prethymectomy receives a Level U recommendation, plasmapheresis is used at many medical centers for these indications.

6. Plasmapheresis should be considered for the adjunctive treatment of exacerbations in relapsing forms of MS (Level B). Plasmapheresis may be considered in the treatment of fulminant CNS demyelinating diseases that fail to respond to high-dose corticosteroid treatment (Level C). Plasmapheresis should not be offered for chronic progressive or secondary progressive MS (Level A). The guideline states that no studies on the efficacy of plasmapheresis compared to other treatment options in MS are available.

7. There is insufficient evidence to support or refute the use of plasmapheresis in the treatment of acute obsessive compulsive disorder (OCD) and tic symptoms in the setting of PANDAS (Level U).

8. There is insufficient evidence to support or refute the use of plasmapheresis in the treatment of Sydenham chorea (Level U). [5]

AAN Classification of Recommendations

A	Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies)
B	Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)
C	Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
U	Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

American Association for the Study of Liver Diseases (AASLD)

Plasmapheresis

The AASLD recommends: treatment for Wilson's Disease to acutely lower serum copper and to limit further hemolysis should include albumin dialysis, continuous hemofiltration, plasmapheresis, or plasma exchange. [12]

American Society of Hematology

American Society of Hematology recommends the use of plasma exchange in HELLP syndrome if thrombocytopenia, hemolysis, or renal failure continues to worsen 48 to 72 hours postpartum. [15]

American Family Physician (AMF)

The AMF notes that the use of plasma exchange with Guillain-Barré Syndrome has been shown to improve short-term and long-term outcomes. [18]

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2015, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT® Codes	Description
36514	Therapeutic apheresis; for plasmapheresis

HCPCS Codes	Description
S2120	Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation

ICD-10-CM Diagnosis Codes that Support Coverage Criteria

ICD-10-CM Code	Description
C88.0	Waldenstrom macroglobulinemia
C90.00-C90.01	Multiple myeloma
C90.10-C90.12	Plasma cell leukemia
C91.00-C91.92	Lymphoid leukemia
C92.00-C92.92	Acute Myeloid leukemia

Plasmapheresis

ICD-10-CM Code	Description
C93.00-C93.92	Monocytic leukemia
C94.00-C94.82	Other leukemias of specified cell type
C95.00-C95.92	Leukemias of unspecified cell type
D47.3	Essential (hemorrhagic) thrombocythemia
D58.0-D59.9	Hemolytic anemias
D69.0-D69.6	Purpura and other hemorrhagic conditions
G04.00	Acute disseminated encephalitis and encephalomyelitis, unspecified
G04.01	Postinfectious acute disseminated encephalitis and encephalomyelitis (postinfectious ADEM)
G25.82	Stiff-man syndrome
G35-G37.9	Demyelinating diseases of central nervous systems
G60.0-G65.2	Polyneuropathies and other disorders of the peripheral nervous system
G70.00-G73.7	Diseases of myoneural junction and muscle
L10.0-L14	Bullous disorders
M05.20-M05.29	Rheumatoid vasculitis with rheumatoid arthritis
M05.60-M05.69	Rheumatoid arthritis with involvement of other organs and systems
M05.70-M05.9	Rheumatoid arthritis with rheumatoid factor without organ or system involvement
M06.00-M06.9	Other rheumatoid arthritis
M08.00-M08.99	Unspecified juvenile rheumatoid arthritis
M31.1	Thrombotic microangiopathy
M32.10-M32.9	Systemic lupus erythematosus, organ or system involvement unspecified
M33.00-M33.99	Dermatopolymyositis
N01.0-N01.9	Rapidly progressive nephritic syndrome with glomerulonephritis
N05.0-N05.9	Unspecified nephritic syndrome
N08	Glomerular disorders in diseases classified elsewhere
O14.10-O14.13	Severe pre-eclampsia
O14.20-O14.23	HELLP syndrome
T86.10-T86.19	Complications of kidney transplant

Reviews, Revisions, and Approvals	Date	Approval Date
Policy adopted from Health Net NMP# 322 Plasmapheresis	8/16	
Added these to medically necessary or may be medically necessary on a case by case basis indications: pemphigus vulgaris, babesiosis, recurrence of focal and segmental glomerulosclerosis in the kidney allograft and transverse myelitis if other treatments have failed. Added Alzheimers and high density lipoprotein (HDL) delipidation and plasma re-infusion for acute coronary syndrome to investigational section. Updated references	8/17	
Minor wording changes, updated codes	8/18	8/18
Wording changes, updated references and codes, removed redundant categories	8/19	8/19

References

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical

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This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and

Plasmapheresis

LCDs should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.