Apheresis (Therapeutic Pheresis)

MEDICAL POLICY NUMBER: 305

Effective Date: 11/1/2022
Last Review Date: 8/2022
Next Annual Review: 8/2023

INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☒ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

First-Line Therapy, Alone Or In Conjunction With Other Therapies

I. Apheresis (therapeutic pheresis) may be considered **medically necessary** when used as a first-line therapy, alone or in conjunction with other therapies, as part of treatment for any of the following indications (A.- T.):

A. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome)
B. Acute liver failure (note: requires high volume TPE)
C. Anti-Glomerular Basement Membrane Disease (Anti-GBM, Goodpasture Syndrome) in dialysis independent patients or when diffuse alveolar hemorrhage (DAH) is present
D. Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
E. Focal Segmental Glomerulosclerosis (FSGS) recurrent in kidney transplant
F. Symptomatic hyperviscosity in hypergammaglobulinemia due to symptomatic disease or as prophylactic for rituximab
G. Acute myasthenia gravis
H. n-methyl D-aspartate receptor antibody encephalitis
I. Paraproteinemic demyelinating neuropathies or chronic acquired demyelinating polyneuropathies due to immunoglobulin G (IgG), immunoglobulin A (IgA) or immunoglobulin M (IgM)
J. Thrombotic microangiopathy
K. Thrombotic thrombocytopenic purpura (TTP; severe ADAMTS13 deficiency)
L. ABO incompatible liver transplantation; live donor liver transplant
M. ABO compatible kidney transplantation and antibody mediated rejection

N. Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis in microscopic polyangiitis, granulomatous polyangiitis, and renal limited vasculitis in the setting of either rapidly progressive glomerulonephritis or diffuse alveolar hemorrhage.
O. Wilson's disease presenting as fulminant hepatic failure with hemolysis.
P. Cutaneous T-cell lymphoma (e.g. Mycosis fungoides, Sezary syndrome).
Q. Hereditary hemochromatosis
R. Polycythemia vera.
S. Acute sickle cell disease-related stroke
T. Stroke prophylaxis in patients with non-acute sickle cell disease.

II. Apheresis (therapeutic pheresis) is considered **investigational and not covered** when used as a first-line therapy, alone or in conjunction with other therapies when criterion I. above is not met.

Second-Line Therapy, Alone Or In Conjunction With Other Therapies

III. Apheresis (therapeutic pheresis) for the treatment of familial hypercholesteremia may be considered **medically necessary** following failure of appropriate lifestyle changes and maximal use of statin agents, with or without the use of ezetimibe, for any of the following indications (A.-D.):

A. Functional homozygotes with an LDL cholesterol greater than 500mg/dl;
B. Functional heterozygotes with no known cardiovascular disease but a LDL cholesterol greater than 300mg/dl;
C. Functional heterozygotes with known cardiovascular disease and a LDL cholesterol greater than 200mg/dl;
D. Pregnancy, when the physician feels usual therapy is inadequate to assure uteroplacental perfusion.

IV. Apheresis (therapeutic pheresis) may be considered **medically necessary** when used as a second-line therapy, alone or in conjunction with other therapies, as part of treatment for any of the following indications:

A. Severe symptomatic cryoglobulinemia
B. Acute attack/relapse of multiple sclerosis
C. Acute attack/relapse of neuromyelitis optica spectrum disorders (NMOSD)
D. Pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections (PANDAS)
E. Desensitization for cardiac transplantation
F. Rejection prophylaxis for cardiac transplantation
G. Cellular/recurrent rejection for cardiac transplantation
H. Major ABO incompatible hematopoietic cells obtained from bone marrow as part of hematopoietic stem cell transplantation
I. ABO incompatible, antibody-mediated rejection as part of renal transplantation
J. Voltage-gated potassium channel (VGKC) antibody-related disease
K. Bronchiolitis obliterans syndrome as part of lung transplantation
L. Vasculitis (e.g. Behcet's disease)

M. Idiopathic dilated cardiomyopathy (NYHA II-IV)
N. Acute graft-versus-host disease
O. Chronic graft-versus-host disease
P. Lipoprotein (a) hyperlipoproteinemia: Progressive atherosclerotic cardiovascular disease
Q. Peripheral vascular disease
R. Severe sickle cell disease (e.g. acute chest syndrome)

V. Apheresis (therapeutic pheresis) is considered **investigational and not covered** when used as a second-line therapy, alone or in conjunction with other therapies, when criterion IV. above is not met.

VI. Apheresis (therapeutic pheresis), as a first- or second-line therapy is considered **investigational and not covered**, including but not limited to the following indications:

A. Catastrophic Antiphospholipid Antibody Syndrome (CAPS)
B. Hypertriglyceridemic pancreatitis
C. HELLP syndrome (Hemolysis, elevated liver enzymes, low platelets, syndrome)
D. Heparin-Induced Thrombocytopenia (HIT)
E. Hyperleukocytosis
F. Thrombotic Microangiopathy, Hemolytic Uremic Syndrome

VII. Selective high-density lipoprotein (HDL) delipidation and apheresis is considered **investigational and not covered** for the treatment of all indications, including but not limited to acute coronary syndrome.

Link to Evidence Summary

POLICY CROSS REFERENCES

None

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

DOCUMENTATION REQUIREMENTS

- For the treatment of familial hypercholesterolemia, the need for therapeutic apheresis must be clearly documented in the medical records for each visit including all of the following:
  - Pharmacologic agents that are/have been used

- What lifestyle changes have been made
- The actual findings and symptoms reported in the case of patients intolerant of statins.
- Notes are properly signed by the treating provider and dated for the date of service.

- Apheresis may be covered only when performed in a hospital setting (either inpatient or outpatient) or in a nonhospital 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 nonphysician services are furnished under the direct, personal supervision of a physician.

DEFINTIONS

Apheresis

Apheresis (also known as pheresis or therapeutic pheresis) is a medical procedure utilizing specialized equipment to remove selected blood constituents (plasma, leukocytes, platelets, or cells) from whole blood. The remainder is retransfused into the person from whom the blood was taken.

Apheresis is an autologous procedure, in which blood is taken from the patient, processed, and returned to the patient as part of a continuous procedure. (This is distinct from the procedure in which a patient donates blood preoperatively and is transfused with the donated blood at a later date).

High-Density Lipid (HDL) Apheresis

Apheresis with selective HDL delipidation involves the selective removal of cholesterol from HDL, also called delipidation, converting alpha HDL to prebeta-like HDL, which is then infused into the patient. It is proposed that this infusion may reduce atherosclerosis in individuals at high-risk for cardiovascular disease.

BACKGROUND

Treatment modalities for apheresis (therapeutic pheresis) include but are not limited to the following:

- Therapeutic plasma exchange
- Extracorporeal photopheresis
- Erythrocytapheresis
- Red blood cell exchange

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

Criteria for apheresis are largely based on clinical practice guidelines published through June 2022. As such, the evidence review was limited to addressing apheresis with high-density lipid apheresis.

High-Density Lipid (HDL) Apheresis

Several randomized controlled trials reported that high-density lipoprotein did not produce plaque regression in statin-treated patients following an acute coronary syndrome.[1-4] No improved net clinical health outcomes were reported in patients receiving therapeutic apheresis combined with selective HDL delipidation. Moreover, it is unclear whether acute regression of atherosclerotic burden will be associated with decreased clinical cardiovascular events.

CLINICAL PRACTICE GUIDELINES

American Society for Apheresis

In 2019, the American Society for Apheresis published guidelines addressing the use of therapeutic apheresis in clinical practice.[5] The guidelines include four categories that were developed based on the quality of evidence and the resultant strength of investigators' recommendations. The guidelines do not address HDL lipid apheresis. Authors concluded that apheresis could be utilized as a primary treatment option for the following conditions:

- ABO compatible kidney transplantation and antibody mediated rejection (AMR) (Grade 1B)
- ABO compatible kidney transplantation with elevated human leukocyte antigens (HLA) (Grade 1B)
- ABO incompatible kidney transplantation; live donor (Grade 1B)
- ABO incompatible liver transplantation; live donor liver transplant (Grade 1C)
- Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) (Guillain-Barré Syndrome), primary treatment (Grade 1A)
- Anti-glomerular basement membrane disease (Anti-GBM) (Goodpasture's syndrome) in dialysis independent patients (Grade 1B) or when diffuse alveolar hemorrhage (DAH) is present (Grade 1C)
- Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) rapidly progressive
- Glomerulonephritis (RPGN); (granulomatosis with polyangiitis [e.g., Wegner's] and microscopic Polyangiitis [MPA]) in dialysis dependent patients (Grade 1A) or when diffuse alveolar hemorrhage (DAH) is present (Grade 1C)
- Catastrophic antiphospholipid syndrome (CAPS) (Grade 2C)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (Grade 1B)
- Recurrent focal segmental glomerulosclerosis in transplanted kidney (Grade 1B)

- Hyperviscosity syndrome in monoclonal gammopathies (e.g., Waldenström's Macroglobulinemia, multiple myeloma) (Grade 1B-C)
- Myasthenia gravis (acute, short-term treatment) for moderate-severe disease including myasthenic crisis, unstable or refractory disease, unstable disease activity pre-thymectomy (Grade 1B)
- *n*-methyl D-aspartate receptor antibody encephalitis (Grade 1C)
- Paraproteinemic polyneuropathy associated with immunoglobulin G (IgG), immunoglobulin A (IgA) or immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance (e.g., MGUS) (Grade 1B)
- Thrombotic microantiopathy (TMA), complement mediated secondary to Factor H antibodies (Grade 2C)
- Thrombotic microangiopathy (TMA), drug associated secondary to ticlopidine (Grade 2B)
- Thrombotic thrombocytopenic purpura (TTP) (Grade 1A)
- Wilson's disease presenting as fulminant hepatic failure with hemolysis (Grade 1C)

Authors recommended apheresis as an acceptable adjunct therapy for the conditions listed below:

- ABO incompatible kidney transplantation; humoral rejection (Grade 1B)
- Acute central nervous system (CNS) inflammatory demyelinating disease (Grade 1A)
- Acute disseminated encephalomyelitis, steroid refractory (ADEM) (Grade 2C)
- Cardiac Transplantation, Desensitization (Grade 1C)
- Cold Agglutinin Disease [CAD], Severe (Grade 2C)
- Cryoglobulinemia, Symptomatic/Severe (Grade II 2A)
- Familial Hypercholerserolemia (Grade 1B)
- Hashimoto's Encephalopathy (HE); Steroid Responsive Encephalopathy Associated with Autoimmune Thyroiditis (Grade 2C)
- Lambert-Eaton Myasthenic Syndrome (LEMS) (Grade 2C)
- Mushroom Poisoning (Grade 2C)
- Myasthenia Gravis (long-term treatment) (Grade 2B)
- Myeloma Associated with Acute Renal Failure (Myeloma Cast Nephropathy) (Grade 2B)
- Neuromyelitis Optica Spectrum Disorders (NMSOD), Acute (Grade 1B)
- Pediatric Postinfectious Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) (Grade 1B), Sydenham's Chorea (SC) (III Grade 2B)
- Phytanic Acid Storage Disease (Refsum's Disease) (Grade 2C)
- Post-Transfusion Purpura (III Grade 2C)
- Systemic Lupus Erythematosus (SLE), Severe without Nephritis (Grade 2C)
- Thyroid Storm (II Grade 2C)
- Vasculitis (Hepatitis B Virus [HBV] Polyarteritis Nodosa [PAN]) (Grade 2C)
- Voltage Gated Potassium Channel Antibody-Related Diseases (Grade 1B)

<u>American Academy of Neurology</u>

In 2011 (reaffirmed 2016), the American Academy of Neurology published clinical practice guidelines addressing the use of plasmapheresis for the treatment of neurologic disorders.[6] Investigators issued the following recommendations:

- Plasmapheresis is established as effective and should be offered in severe acute inflammatory demyelinating polyneuropathy (AIDP)/Guillain-Barre´ syndrome (GBS) and in the short-term management of chronic inflammatory demyelinating polyneuropathy (Class I studies, Level A).
- Plasmapheresis is established as ineffective and should not be offered for chronic or secondary progressive multiple sclerosis (MS) (Class I studies, Level A).
- Plasmapheresis is probably effective and should be considered for mild AIDP/GBS, as second-line treatment of steroid-resistant exacerbations in relapsing forms of MS, and for neuropathy associated with immunoglobulin A or immunoglobulin G gammopathy, based on at least one Class I or 2 Class II studies (Level B).
- Plasmapheresis is probably not effective and should not be considered for neuropathy associated with immunoglobulin M gammopathy, based on one Class I study (Level B).
- Plasmapheresis is possibly effective and may be considered for acute fulminant demyelinating CNS disease (Level C).
- Evidence is insufficient to support or refute the use of plasmapheresis for myasthenia gravis, pediatric autoimmune neuropsychiatric disorders associated with streptococcus infection, and Sydenham chorea (Class III evidence, Level U).

EVIDENCE SUMMARY

Clinical practice guidelines from the American Society for Apheresis and the American Academy of Neurology support the use of apheresis (therapeutic pheresis) for the treatment of a variety of indications, as either a first- or second-line treatment. Evidence reported in studies published to date is insufficient to support the use of apheresis for other indications, including but not limited to hypertriglyceridemic pancreatitis, heparin-induced thrombocytopenia and hyperleukocytosis. Additional studies are also needed to support the clinical utility of apheresis with selective HDL delipidation.

BILLING GUIDELINES AND CODING

CODES*		
CPT	0342T	Therapeutic apheresis with selective HDL delipidation and plasma reinfusion
	36511	Therapeutic apheresis; for white blood cells
	36512	Therapeutic apheresis; for red blood cells [red blood cell exchange]
	36513	Therapeutic apheresis; for platelets
	36514	Therapeutic apheresis; for plasma pheresis
	36516	Therapeutic apheresis; with extracorporeal immunoadsorption, selective adsorption or selective filtration and plasma reinfusion
	36522	Photopheresis, extracorporeal

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES

1. Waksman R, Torguson R, Kent KM, et al. A first-in-man, randomized, placebo-controlled study to evaluate the safety and feasibility of autologous delipidated high-density lipoprotein plasma infusions in patients with acute coronary syndrome. *J Am Coll Cardiol.* 2010;55(24):2727-2735.
2. Subedi BH, Joshi PH, Jones SR, Martin SS, Blaha MJ, Michos ED. Current guidelines for high-density lipoprotein cholesterol in therapy and future directions. *Vascular health and risk management.* 2014;10:205.
3. Nicholls SJ, Andrews J, Kastelein JJP, et al. Effect of Serial Infusions of CER-001, a Pre-β High-Density Lipoprotein Mimetic, on Coronary Atherosclerosis in Patients Following Acute Coronary Syndromes in the CER-001 Atherosclerosis Regression Acute Coronary Syndrome Trial: A Randomized Clinical Trial. *JAMA Cardiology.* 2018;3(9):815-822. https://doi.org/10.1001/jamacardio.2018.2121
4. Nicholls SJ, Puri R, Ballantyne CM, et al. Effect of Infusion of High-Density Lipoprotein Mimetic Containing Recombinant Apolipoprotein A-I Milano on Coronary Disease in Patients With an Acute Coronary Syndrome in the MILANO-PILOT Trial: A Randomized Clinical Trial. *JAMA Cardiology.* 2018;3(9):806-814. https://doi.org/10.1001/jamacardio.2018.2112
5. Padmanabhan A, Connelly-Smith L, Aqui N, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue. *Journal of Clinical Apheresis.* 2019;34(3):171-354. https://onlinelibrary.wiley.com/doi/abs/10.1002/jca.21705
6. Cortese I, Chaudhry V, So Y, Cantor F, Cornblath D, Rae-Grant A. Evidence-based guideline update: plasmapheresis in neurologic disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 2011;76(3):294-300.

POLICY REVISION HISTORY

2/2023	Updated to new template