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Clinical UM Guideline

Subject:	Therapeutic Apheresis		
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Description

This document addresses therapeutic apheresis, a procedure by which blood is removed from the body, separated into components, manipulated and returned to the individual. There are multiple pheresis procedures that are performed. The therapeutic apheresis procedures addressed in this document utilize devices approved by the United States (U.S.) Food & Drug Administration (FDA) and include the following subcategories:

- plasmapheresis/plasma exchange,
- cytapheresis (specifically, erythrocytapheresis, leukocytapheresis, platelet apheresis, red blood cell (RBC) exchange and thrombocytapheresis),
- low-density lipid (LDL) apheresis,
- selective high-density lipid (HDL) delipidation and therapeutic apheresis and
- immunoadsorption (IA)

Clinical Indications

Medically Necessary:

I. Plasmapheresis or plasma exchange is considered **medically necessary** for any of the following conditions listed in alphabetical order below:
   A. Acute inflammatory demyelinating polyradiculoneuropathy / Guillain-Barre syndrome
   B. Anti-glomerular basement membrane disease (Goodpasture's syndrome) when the individual is dialysis-independent or there is evidence of diffuse alveolar hemorrhage (DAH)
   C. Atypical hemolytic uremic syndrome (aHUS) with Factor H autoantibodies or complement gene mutation

D. Autoimmune hemolytic uremic syndrome- severe cold agglutin disease~~,~~ when there has been an inadequate response to or failure of medical therapy
E. Catastrophic antiphospholipid syndrome (CAPS)
F. Chronic inflammatory demyelinating polyneuropathy when **all** of the following criteria are met:
   1. There is muscle weakness or sensory dysfunction caused by neuropathy in more than one limb; **and**
   2. Nerve conduction studies (NCS) or diagnostic criteria confirm evidence of a demyelinating neuropathy; **and**
   3. Other polyneuropathies such as IgM neuropathy, hereditary neuropathy, and diabetic neuropathy have been ruled out
G. ~~-~~Cryoglobulinemia, symptomatic/severe, when there has been an inadequate response to or failure of medical therapy
~~H. H.E.L.L.P syndrome of pregnancy (hemolysis, elevated liver enzymes, low platelets)~~
~~I.~~H. Hyperviscosity syndromes associated with monoclonal gammopathies (such as, ~~-~~multiple myeloma and Waldenström's macroglobulinemia)
~~J.~~I. Multiple myeloma cast nephropathy (acute renal failure secondary to multiple myeloma)~~,~~ when there has been an inadequate response to or failure of medical therapy
~~K.~~J. Multiple sclerosis (MS)-acute attack/ relapse~~,~~ when there has been an inadequate response to or failure of medical therapy
~~L.~~K. Myasthenia ~~gravis moderate-severe disease (myasthenic crisis, unstable or refractory disease, unstable disease activity pre-thymectomy)~~gravis, acute short-term treatment
~~M.~~L. *N*-methyl D-aspartate receptor antibody encephalitis
~~N.~~M. Neuromyelitis optica spectrum disorders, acute disease/relapse (excluding maintenance therapy)~~,~~ when there has been an inadequate response to or failure of medical therapy
~~O.~~N. Paraproteinemic demyelinating neuropathies/ chronic acquired demyelinating polyneuropathies; associated with IgA, IgG or IgM monoclonal gammopathy of undetermined significance (MGUS) (excluding multiple myeloma, anti-myelin-associated glycoprotein (MAG) neuropathy or multifocal motor neuropathy (MMN))
~~P.~~O. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) exacerbation~~,~~ when there has been an inadequate response to or failure of medical therapy
~~Q. Progressive multifocal leukoencephalopathy (nataluziamab associated)~~
~~R. Sydenham's chorea~~

~~S.~~P. Systemic lupus erythematosus - for individuals with severe or life-threatening symptoms when conventional therapy has failed to prevent clinical deterioration
~~T.~~Q. Thrombotic microangiopathy secondary to ticlopidine or malignancy
~~U.~~R. Thrombotic Thrombocytopenic Purpura (TTP)
~~V.~~S. Transplantation when any of the following are met:
1. Hematopoietic stem cell transplant
   a. ABO incompatible; **or**
   b. Human leukocyte antigen (HLA) incompatibility with haplo-type transplant
2. Solid organ transplantation for any of the following:
   a. Heart transplantation recipients who are in the operating room experiencing a hyper-acute rejection episode; **or**
   b. Liver transplantation from a live donor with ABO incompatibility; **or**
   c. Ren-al transplant recipients who are post-transplant and experiencing recurrent focal and segmental glomerulosclerosis (FGS) or experiencing a humoral or antibody mediated rejection; **or**
   d. Renal transplantation in highly sensitive kidney transplant candidates (high PRA protocols) to reduce the number of antibodies reactive against human lymphocyte antigens (HLA); **or**
   e. Renal transplantation, from a live donor with ABO incompatibility or positive cross-match, where a non-reactive live or cadaveric donor is unavailable; **or**

~~W.~~T. Vasculitis anti-neutrophil cytoplasmic antibodies (ANCA) including granulomatosis with polyangiitis, microscopic polyangiitis and renal limited vasculitis, which associated with rapidly progressive glomerulonephritis and a creatinine level of 5.7 mg/dl or greater, or diffuse alveolar hemorrhage
~~X.~~U. Voltage gated potassium channel antibodies~~,~~ when there has been an inadequate response to or failure of medical therapy
~~Y.~~V. Wilson's disease – fulminant

II. Low-density lipid (LDL) apheresis or lipoprotein apheresis is considered **medically necessary** for individuals with any of the following:
A. Homozygous familial hypercholesterolemia;
B. Severe, refractory heterozygous familial hypercholesterolemia who have failed a 6-month trial of diet therapy and maximum tolerated combination drug therapy AND who meet either of the following FDA-approved indications:

1. Functional hypercholesterolemic heterozygotes with low-density lipoprotein (LDL) that is greater than 300 mg/dL; **or**
2. Functional hypercholesterolemic heterozygotes with LDL that is greater than 200 mg/dL and documented coronary artery disease

C. Lipoprotein (a) hyperlipoproteinemia~~.~~ when there has been an inadequate response to or failure of medical therapy

III. Cytapheresis:

A. Erythrocytapheresis (or phlebotomy) is considered **medically necessary** as a treatment for any of the following:
1. Hereditary hemochromatosis
2. Polycythemia vera
~~3. Symptomatic secondary polycythemia~~
~~4.~~3. Porphyra cutanea tarda

B. Leukocytapheresis is considered **medically necessary** for symptomatic hyperleukocytosis~~leukemias with leukostasis~~

~~B.~~C. Lymphapheresis is considered **medically necessary** when used to collect autologous T-cells for chimeric antigen receptor (CAR) T cell therapy when the criteria within the specific CAR-T therapy document are met.

~~C.~~D. Thrombocytapheresis is considered **medically necessary** for essential thrombocytosis (symptomatic, when the platelet count is greater than 1,000,000/mm^3)

~~D.~~E. Red blood cell exchange is considered **medically necessary** as treatment for any of the following:
1. Babesiosis:
a. Severe
~~b.~~ In the high-risk population
~~2.~~b. ~~Severe malaria~~
~~3.~~2. Sickle cell disease, acute:
a. Acute stroke
b. Acute severe, chest syndrome
~~c. Multi-organ failure syndrome~~
~~d. Pre-procedure preparation (surgery or hematopoietic stem cell transplant)~~
~~e.~~c. Pregnancy

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. ~~Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to implement a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member's card.~~

~~Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan's or line of business's members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.~~

~~4.~~3. Sickle cell disease, chronic exchange or non-acute:
   a. Stroke prophylaxis (primary or secondary)
   ~~b. Iron overload~~

IV. Immunoadsorption is considered **medically necessary** for individuals with any of the following:
   A. Thrombotic Thrombocytopenic Purpura (TTP); **or**
   ~~B. Moderate to severe rheumatoid arthritis in adult patients with long-standing disease who have failed or are intolerant to disease-modifying antirheumatic drugs such are methotrexate, hydroxychloroquine, sulfasalazine, gold, azathioprine, D-penicillamine, etanercept, infliximab and leflunomide.~~
   ~~C.~~B. Acute inflammatory demyelinating polyradiculoneuropathy / Guillain-Barre syndrome
   ~~D.~~C. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) when **all** of the following criteria are met:
      1. Muscle weakness or sensory dysfunction caused by neuropathy is present in more than one limb; **and**
      2. Evidence of a demyelinating neuropathy is confirmed by nerve conduction studies (NCS) or diagnostic criteria; **and**
      3. Other polyneuropathies (for example IgM neuropathy, hereditary neuropathy or diabetic neuropathy) have been ruled out
   ~~E.~~D. Myasthenia gravis, acute short-term treatment ~~moderate-severe disease (myasthenic crisis, unstable or refractory disease, unstable disease activity pre-thymectomy)~~
   ~~F.~~E. N-methyl D-aspartate receptor antibody encephalitis
   ~~G.~~F. Renal transplant recipients who are ABO compatible who are experiencing antibody mediated rejection (AMR) or require desensitization (living donor)
   ~~H.~~G. Renal transplant recipients who are ABO incompatible and require desensitization (living donor)
   ~~I.~~H. Renal transplant recipients who are post-transplant and experiencing recurrent focal segmental glomerulosclerosis (FSGS)

Not Medically Necessary:

I. Pla~~a~~smapheresis or plasma exchange is considered **not medically necessary** when the criteria for plasmapheresis or plasma exchange above are not met and for all other indications.

II. Low-density lipid apheresis or lipoprotein apheresis is considered **not medically necessary** when the criteria for low-density lipid apheresis or lipoprotein apheresis above are not met and for all other indications.

~~I. including, but not limited to:~~
~~A. Acute disseminated encephalomyelitis~~
~~B. Acute liver failure~~
~~C. Amyloidosis, systemic~~
~~D. Amyotrophic lateral sclerosis (ALS)~~
~~E. Anti-glomerular basement membrane disease (Goodpasture's syndrome) when the individuals is dialysis-dependent and there is no evidence of diffuse alveolar hemorrhage (DAH)~~
~~F. Aplastic anemia~~
~~G. Autoimmune hemolytic anemia (AHA) - warm autoimmune hemolytic anemia (WAHA)~~
~~H. Burn shock resuscitation~~
~~I. Chronic fatigue syndrome~~
~~J. Chronic focal encephalitis (Rasmussen encephalitis)~~
~~K. Coagulation factor inhibitors, alloeb and autoantibody~~
~~L. Dermatomyositis~~
~~M. Heart (cardiac) transplantation - for desensitization, positive cross-match due to donor specific HLA antibody or antibody mediated rejection~~
~~N. Hemolytic Uremic Syndrome (aHUS), with MCP mutations~~
~~O. Hemolytic Uremic Syndrome associated with infection (such as shiga toxin or Streptococcus pneumonae)~~
~~P. Henoch-Schonlein purpura~~
~~Q. Heparin induced thrombocytopenia~~
~~R. Hypertriglyceridemic pancreatitis~~
~~S. Immune complex rapidly progressive glomerulonephritis~~
~~T. Immune thrombocytopenia, refractory~~
~~U. Immunoglobulin A nephropathy - crescentic and chronic progressive~~
~~V. Inclusion body myositis~~
~~W. Lambert-Eaton myasthenic syndrome~~
~~X. Liver transplantation - desensitization from a deceased donor and for humor rejection~~
~~Y. Lung transplant allograft rejection (antibody mediated rejection)~~

~~Z. Lupus nephritis~~
~~AA. Multiple sclerosis that is chronic progressive or secondary progressive multiple sclerosis~~
~~AB. Nephrogenic systemic fibrosis~~
~~AC. Neuromyelitis optica ([NMO], also known as Devic's disease), when used as maintenance therapy~~
~~AD. Overdose of drugs or poisoning – envenomation and mushroom~~
~~AE. Paraneoplastic neurological syndromes~~
~~AF. Paraproteinemic demyelinating polyneuropathy associated with multiple myeloma, anti-myelin-associated glycoprotein (MAG) neuropathy or multifocal motor neuropathy (MMN)~~
~~AG. Pemphigus vulgaris~~
~~AH. Phytanic acid storage disease (Refsum's Disease) when used to rapidly lower plasmic phytanic acid levels during acute attacks~~
~~AI. POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes)~~
~~AJ. Polymyositis~~
~~AK. Post transfusion purpura~~
~~AL. Psoriasis~~
~~AM. Red cell alloimmunization in pregnancy, prior to intrauterine transfusion availability~~
~~AN. Schizophrenia~~
~~AO. Scleroderma (progressive systemic sclerosis)~~
~~AP. Sepsis with multi-organ failure~~
~~AQ. Stiff-person syndrome~~
~~AR. Sudden sensorineural hearing loss~~
~~AS. Thrombotic microangiopathy, for drugs other than ticlopidine: for example, clopidogrel, cyclosporine, gemcitabine, quinine, or tacrolimus~~
~~AT. Thyroid storm~~
~~AU. Toxic epidermal necrolysis~~

~~II. Low-density lipid apheresis or lipoprotein apheresis is considered **not medically necessary** when the criteria for low-density lipid apheresis or lipoprotein apheresis above are not met and for all other indications including, but not limited to:~~
~~A. Peripheral vascular disease (PVD)~~
~~B. Phytanic Acid Storage Disease (Refsum Disease)~~
~~C. Sudden sensorineural hearing loss~~

III. Selective high-density lipid (HDL) delipidation and therapeutic apheresis is considered **not medically necessary** for all indications.

IV. Cytapheresis is considered **not medically necessary** when the criteria for cytapheresis above are not met and for all indications.

~~IV. including, but not limited to:~~
~~A. Dermatomyositis~~
~~B. Hyperleukocytosis, (asymptomatic)~~
~~C. Inclusion body myositis~~
~~D. Polymyositis~~
~~E. Psoriasis~~

V. Thrombocytapheresis is considered **not medically necessary** when the criteria for thrombocytopheresis above are not met and for all other indications.

VI. Red blood cell exchange is considered **not medically necessary** when the criteria for red blood cell exchange above are not met and for all other indications.

VII. Adsorptive cytapheresis is considered **not medically necessary** when the criteria for adsorptive cytaphere~~i~~sis above are not met and for all other indications.

VIII. Immunoadsorption pheresis is considered **not medically necessary** when the criteria for immunoadsorption pheresis above are not met and for all other indications.~~, including, but not limited to:~~
~~A. Autoimmune diseases other than rheumatoid arthritis~~
~~B. Chronic focal encephalitis (Rasmussen Encephalitis)~~
~~C. Coagulation factor inhibitors alloantibody and autoantibody~~
~~D. Cryoglobulinemia, symptomatic or severe~~
~~E. Immune thrombocytopenia, refractory~~
~~F. Multiple sclerosis – acute CNS inflammatory demyelinating disease~~
~~G. Paraneoplastic neurological syndromes~~

~~H. Paraproteinemic demyelinating neuropathies associated with IgA, IgG or IgM monoclonal gammopathy~~
~~I. Pemphigus vulgaris~~
~~J. Treatment of cancer~~

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Plasmapheresis, plasma exchange

CPT

36514	Therapeutic apheresis; for plasma pheresis

ICD-10 Procedure

6A550Z3	Pheresis of plasma, single
6A551Z3	Pheresis of plasma, multiple

ICD-10 Diagnosis

~~A81.2~~	~~Progressive multifocal leukoencephalopathy~~
B95.0-B95.1	Streptococcus group A/B, as the cause of diseases classified elsewhere [PANDAS]
C88.0	Waldenström macroglobulinemia
C90.00-C90.02	Multiple myeloma
D47.2	Monoclonal gammopathy
D59.0-D59.1	Autoimmune hemolytic anemias
D59.3	Hemolytic uremic syndrome
D68.61	Antiphospholipid syndrome
D89.1	Cryoglobulinemia
D89.89	Other specified disorders involving the immune mechanism, not elsewhere classified [when specified as PANDAS]

E83.01	Wilson's disease
F42.8	Other obsessive-compulsive disorder [specified as PANDAS]
G04.81	Other encephalitis and encephalomyelitis [specified as NMDA receptor antibody encephalitis]
G13.1	Other systemic atrophy primarily affecting central nervous system in neoplastic disease [limbic encephalopathy, voltage gated potassium channel (VGKC) antibody syndrome)
G35	Multiple sclerosis
G36.0	Neuromyelitis optica [Devic]
G37.0-G37.9	Other demyelinating diseases of central nervous system
G60.8	Other hereditary and idiopathic neuropathies [Morvan's disease, VGKC antibody syndrome]
G61.0	Guillain-Barre syndrome
G61.81-G61.89	Other inflammatory polyneuropathies
G70.00-G70.01	Myasthenia gravis
G71.19	Other specified myotonic disorders [neuromyotonia, VGKC antibody syndrome]
~~I02.0-I02.9~~	~~Rheumatic chorea [Sydenham's chorea]~~
M31.0	Hypersensitivity angiitis [Goodpasture's syndrome]
M31.1	Thrombotic microangiopathy [includes TTP]
M31.31	Wegener's granulomatosis with renal involvement
M31.7	Microscopic polyangiitis
M32.0-M32.9	Systemic lupus erythematosus (SLE)
N01.0-N01.9	Rapidly progressive nephritic syndrome
N03.0-N03.9	Chronic nephritis syndrome
N04.0-N04.9	Nephrotic syndrome
N17.0-N17.9	Acute kidney failure
N18.1-N18.9	Chronic kidney disease
N19	Unspecified kidney failure
~~O14.20-O14.25~~	~~HELLP syndrome~~
T86.00-T86.09	Complications of bone marrow transplant
T86.10-T86.19	Complications of kidney transplant
T86.21	Heart transplant rejection
T86.40-T86.49	Complications of liver transplant

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T86.5	Complications of stem cell transplant
Z94.0	Kidney transplant status
Z94.1	Heart transplant status
Z94.4	Liver transplant status
Z94.81	Bone marrow transplant status
Z94.84	Stem cells transplant status

Low density lipid apheresis, lipoprotein apheresis and immunoadsorption pheresis

CPT

36516	Therapeutic apheresis; with extracorporeal immunoadsorption, selective adsorption or selective filtration and plasma reinfusion
0342T	Therapeutic apheresis with selective HDL delipidation and plasma reinfusion **Note:** apheresis with selective HDL delipidation is considered Not Medically Necessary for all indications

HCPCS

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

ICD-10 Diagnosis

E78.00	Pure hypercholesterolemia, unspecified
E78.01	Familial hypercholesterolemia
G04.81	Other encephalitis and encephalomyelitis [specified as NMDA receptor antibody encephalitis]
G61.0	Guillain-Barre syndrome
G61.81-G61.9	Other inflammatory polyneuropathies
G70.00-G70.01	Myasthenia gravis
~~M05.00-M05.9~~	~~Rheumatoid arthritis with rheumatoid factor~~
~~M06.00-M06.09~~	~~Rheumatoid arthritis without rheumatoid factor~~
~~M06.80-M06.9~~	~~Other specified and unspecified rheumatoid arthritis~~
M31.1	Thrombotic microangiopathy [TTP]

N01.0-N01.9	Rapidly progressive nephritic syndrome
N03.0-N03.9	Chronic nephritis syndrome
N04.0-N04.9	Nephrotic syndrome
N17.0-N17.9	Acute kidney failure
N18.1-N18.9	Chronic kidney disease
N19	Unspecified kidney failure
T86.10-T86.19	Complications of kidney transplant
Z83.42	Family history of familial hypercholesterolemia
Z94.0	Kidney transplant status

Cytapheresis

CPT

36511	Therapeutic apheresis; for white blood cells
36512	Therapeutic apheresis; for red blood cells [red blood cell exchange]
36513	Therapeutic apheresis; for platelets

ICD-10 Procedure

6A550Z0	Pheresis of erythrocytes, single
6A550Z1	Pheresis of leukocytes, single
6A550Z2	Pheresis of platelets, single
6A551Z0	Pheresis of erythrocytes, multiple
6A551Z1	Pheresis of leukocytes, multiple
6A551Z2	Pheresis of platelets, multiple

ICD-10 Diagnosis

~~B50.0-B54~~	~~Malaria~~
B60.0	Babesiosis
C82.00-C82.99	Follicular lymphoma [related to CAR-T cell therapy]
C83.30-C83.39	Diffuse large B-cell lymphoma [related to CAR-T cell therapy]
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma [related to CAR-T cell therapy]
C90.00-C95.92	Leukemias [related to CAR-T cell therapy]

D45	Polycythemia vera
D47.3	Essential (hemorrhagic) thrombocythemia
D57.00-D57.819	Sickle-cell disorders
~~D75.1~~	~~Secondary polycythemia~~
E80.1	Porphyria cutanea tarda
E83.110	Hereditary hemochromatosis
O99.011-O99.03	Anemia complicating pregnancy, childbirth and the puerperium

Discussion/General Information

Description of Pheresis Techniques

The goal of pheresis is the removal of harmful plasma components. Theoretically, decreasing the concentration of the harmful plasma component, will improve the course of the disease. Abnormal components potentially removed with apheresis include toxins, metabolic substances, and plasma components, such as complement or antibodies. Therefore, diseases thought to be caused by these abnormal constituents might best be treated with this form of therapy. Diseases benefiting from these procedures are largely autoimmune or neurological disorders. Pheresis techniques are not intended to be curative treatments for most indications. Rather, they are used to address related symptoms. Depending on the indication, alternative treatments, such as pharmacologic therapy, may be available.

Applications of pheresis can be broadly subdivided into three general categories: acute, self-limited diseases, acute, fulminant exacerbations of chronic diseases, and chronic diseases. In self-limited diseases and acute exacerbations of chronic diseases, therapeutic apheresis is used to acutely lower the circulating pathogenic substance. In chronic diseases, there is ongoing production of pathogenic autoantibodies. Because therapeutic apheresis does not address the underlying pathology, and due to the phenomenon of rebound antibody production, its use in most chronic diseases has been less effective than in acute, self-limiting diseases. For this reason, chronic conditions are not amenable to pheresis treatment. As an example, individuals with chronic progressive or relapsing-remitting multiple sclerosis are unlikely to benefit from pheresis treatment. However, individuals with an acute central nervous system inflammatory demyelinating disease (including the rare proportion of individuals with multiple sclerosis who suffer from this condition) have been found to have a reduction of symptoms.

Pheresis procedures are typically performed in outpatient settings, including blood banks, dialysis centers, hospital clinics and physician's offices. Reinfusion with human plasma may cause anaphylaxis and bleeding complications, and though rare, may require replacement clotting factors. Therefore, pheresis procedures should be performed by appropriately-trained clinicians in a setting that can respond to medical emergencies at all times.

Peer-reviewed, published medical literature and medical society guidelines support the clinical effectiveness and safety of therapeutic pheresis modalities for the indications listed in the policy statements. There is evidence for the accepted indications that the use of this procedure can result in an improvement in symptoms, primarily for acute self-limited conditions, and subsequently for an improvement in quality of life. Evidence is limited regarding the role of therapeutic apheresis to remove specific autoantibodies, proteins and complements in the pathogenesis of many other conditions.

The Guidelines on the Use of Therapeutic Apheresis in Clinical Practice (Eighth special issue) were updated by the American Society for Apheresis (ASFA) in 2019. This guideline is typically updated every 3 years with the most recent evidence. Therapeutic apheresis is a general term which includes all apheresis based procedures used in a therapeutic manner. This involves the individual's blood being passed through an external device which separates blood into components as treatment of a disease. Specific ASFA definitions for the therapeutic modalities addressed in this document include (Padmanabhan, 2019):

> Erythrocytapheresis: Procedure in which blood of the patient or donor is passed through a medical device which separates RBCs from other components of blood. The RBCs are removed and replaced with crystalloid or colloid solution, when necessary.
>
> Immunoadsorption (IA): A therapeutic procedure in which plasma of the patient, after membrane based or centrifugal separation from the blood, is passed through a medical device (adsorber column) which has the capacity to remove immunoglobulins by binding them to the select ligands on the backing matrix surface (membranes or beads) of the adsorber column.
>
> Leukocytapheresis: A procedure in which blood of the patient is passed through a medical device which separates out white blood cells (e.g., leukemic blasts or granulocytes), collects the selected cells and returns remainder of the patient's blood with or without addition of replacement fluid such as colloid and/or crystalloid solution.

Lipoprotein apheresis (LA): Previously known as low density lipid apheresis. The selective removal of lipoproteins from the blood with the return of the remaining components. A variety of methodologies are available and include double filtration plasmapheresis (DFPP), HELP-apheresis, polyclonal-sheep-anti-apoB-immunoadsorption, dextran-sulfate plasma adsorption, dextran-sulfate whole blood adsorption, and polyacrylate whole blood adsorption.

Red blood cell (RBC) Exchange: A therapeutic procedure in which blood of the patient is passed through a medical device which separates RBCs from other components of blood. The patient's RBCs are removed and replaced with donor RBCs and colloid solution.

Therapeutic plasma exchange (TPE): A therapeutic procedure in which blood of the patient is passed through a medical device which separates out plasma from other components of blood. The plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin and/or plasma) or combination of crystalloid/colloid solution.

Thrombocytapheresis: A therapeutic procedure in which blood of the patient is passed through a medical device which separates out platelets, removes the platelets and returns remainder of the patient's blood with or without addition of replacement fluid such as colloid and/or crystalloid solution.

The ASFA utilizes categories and grade of recommendation for various indications. The four categories are (Padmanabhan, 2019):

Category I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
Category II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
Category III	Optimum role of apheresis therapy is not established. Decision making should be individualized.

Category IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. Institutional Review Board (IRB) approval is desirable if apheresis treatment is undertaken in these circumstances.

The Grading Recommendations include the following (Padmanabhan, 2019):

Recommendation	***Description***	***Methodological quality of supporting evidence***
Grade 1A	Strong recommendation, high-quality evidence	Randomized controlled trials (RCTs) without important limitations or overwhelming evidence from observational studies
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Grade 1C	Strong recommendation, low-quality or very low-quality evidence	Observational studies or case series
Grade 2A	Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series

Plasma Pheresis and Plasma Exchange

The ASFA recommends plasmapheresis or plasma exchange as Category I treatment options and the associated levels of evidence range with Grade 1A – 1C recommendations for the following indications (Padmanabhan, 2019):

- Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre Syndrome)
- Anti-glomerular basement membrane disease (Goodpasture's syndrome) when dialysis-independent or evidence of DAH
- ~~Cardiac transplantation when used as a means of desensitization~~
- Chronic inflammatory demyelinating polyneuropathy
- Focal segmental glomerulosclerosis that is recurrent in a transplanted kidney
- Hyperviscosity syndromes in hypergammaglobulinemia
- Liver transplantation from a live donor with ABO incompatibility, desensitization ~~or positive cross-match~~
- Myasthenia gravis, acute, short term ~~moderate to severe and pre-thymectomy~~
- ~~N~~treatment-methyl D-aspartate receptor antibody encephalitis
- Paraproteinemic demyelinating neuropathies associated; Chronic acquired demyelinating polyneuropathies; IgG/IgA/IgM
- Renal transplantation from a live donor with ABO compatibility, ~~i~~desensitization ~~n highly sensitive kidney transplant candidates (high PRA protocols) to reduce the number of antibodies reactive against human lymphocyte antigens (HLA)~~
- Renal transplantation from a live donor with ABO incompatibility, desensitization ~~or positive cross-match~~
- Renal transplant recipients who are post transplant and experiencing an ~~humoral or~~ antibody mediated rejection
- Thrombotic microangiopathy, thrombotic t~~T~~hrombocytopenic Purpura (TTP)
- Vasculitis, ANCA-associated (AAV)for any of the following conditions
  - Microscopic polyangiitis- when creatinine is 5.7 mg/dl or greater
  - Granulomatosis with polyangiitis- when creatinine is 5.7 mg/dl or greater
  - Renal- limited vasculitis- when creatinine is 5.7 mg/dl or greater
  - ~~•~~ Diffuse alveolar hemorrhage
- Wilson~~'s~~ disease – fulminant

In addition to the above ASFA recommendations, published peer-reviewed literature and/or specialty medical societies support the use therapeutic apheresis when there is evidence that a targeted component(s) of the blood or plasma is readily removed with therapeutic apheresis and there is sufficient improvement in clinical symptoms without causing serious adverse effects.

The ASFA recommends plasmapheresis or plasma exchange as Category II treatment options and the associated levels of evidence range with Grade 1A – 1C recommendations for the following indications (Padmanabhan~~Schwarz~~, 2019):

- Cardiac Transplantation, desensitization
- Cryoglobulinemia
- Familial hypercholesterolemia in Homozygotes/ Heterozygotes
- Hematopoietic stem cell transplant – ABO incompatible when specific to the marrow specific hematopoietic progenitor cell (HPC) indication
- Neuromyelitis optica spectrum disorders (NMOSD)-acute attack/relapse
- Multiple sclerosis –acute attack/relapse
- Myeloma Cast Nephropathy
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) exacerbation
- Renal Transplantation, ABO incompatible, antibody mediated rejection
- Voltage-gated potassium channel (VGKC) antibody related diseases

Acute inflammatory demyelinating polyneuropathy (AIDP)/ Guillain-Barre Syndrome (GBS)
The American Academy of Neurology (AAN) (Cortese, 2011) published an updated evidence-based guideline on plasmapheresis in neurologic disorders. Plasmapheresis was recommended in the treatment of "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 (Level B)." In a consensus statement by the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Committee (Donofrio, 2009), treatment of GBS in adults, particularly those who require an aid to walk (disability grade ≥ 2) within 2 weeks of the onset of symptoms with IVIG was recommended. The committee noted based on randomized trials, similar functional

improvements in individuals treated with IVIG or plasmapheresis. Data did not support the combination of IVIG and plasmapheresis to treat GBS.

Chronic inflammatory demyelinating polyneuropathy (CIDP)
CIDP is a rare disorder which typically presents with symmetrical motor function impairment that may or may not be coupled with sensory disturbances. CIDP generally progresses over the course of at least 2 months but may follow a relapsing/remitting course. CIDP affects approximately 5-7 cases per 100,000 individuals and over 50% of affected individuals will be unable to walk without support during the course of the disease. Approximately 10% of these individuals will become persistently disabled or will die. Although the exact etiology is unknown, CIDP is thought to be the result of an autoimmune attack (humoral and cell-mediated) on the peripheral nerves which damages the myelin sheath. This myelin damage is documented by nerve conduction studies or nerve biopsies. CIDP is difficult to diagnose, atypical CIDP can account up to 50% of all cases and several neuropathies share a similar clinical presentation with CIDP. Once the diagnosis is made, prompt treatment is needed to halt inflammatory demyelination, prevent secondary axonal degeneration, and minimize the chances of permanent disability.

Complement-mediated thombotic microangiopathy (TMA)
TMA, previously known as Atypical Hemolytic Uremic Syndrome (aHUS) is a rare genetic and chronic blood disease that can lead to renal failure and is associated with increased risk of stroke and death. Prompt diagnosis is essential, as aHUS is aggressive and treatment can be initiated for affected individuals. According to Loirat (2011), the diagnosis of aHUS relies on: 1) no associated disease; 2) investigations for Shiga toxin E. coli infection at onset of aHUS with no evidence of a Shiga-toxin/EHEC positive test (stool culture and polymerase chain reaction for Shiga-toxins; serology for anti-lipopolysaccharides antibodies); and 3) ADAMTS 13 (A Disintegrin-like And Metalloprotease with ThromboSpondin type 1 motif 13) determination as manifestations of aHUS and TTP may overlap. Frequent causes of aHUS involve complement regulatory abnormalities such as factor H mutations and MCP mutations. Plasma exchange can replace mutated circulating complement factors, specifically factor H. However, plasma exchange does not demonstrate similar efficacy for individuals with isolated MCP mutations, and plasma exchange is not recommended to treat MCP aHUS. Based on expert consensus opinion, plasma therapy has demonstrated efficacy as the first-line treatment for aHUS and should be started as early as possible, typically within 24 hours of presentation (Ariceta, 2009; Lapeyraque, 2011; Loirat, 2011; Taylor 2010). However, since the introduction of eculizumab, which has been shown to be effective as a front-line therapy, the role of plasma therapy has become more limited.

Autoimmune Hemolytic Uremic Syndrome – Severe Cold Agglutin Disease
Individuals with autoimmune hemolytic anemia may be classified into warm or cold autoantibody types. Those with cold agglutin disease (CAD) have IgM autoantibodies that target red blood cells when the temperatures are typically between 0–5 degrees Celsius. Avoiding exposure to cold temperatures is the primary treatment. ~~However, for severe disease, immunosuppression with targeted therapy and anti-lymphoma chemotherapy may be used. Specialty input recommends use of plasmapheresis or plasma exchange to treat autoimmune hemolytic uremic syndrome with severe cold agglutin disease.~~ The ASFA notes that most effective is rituximab, which is recommended as first-line therapy (Padmanabhan, 2019).

Catastrophic Antiphospholipid Syndrome (CAPS)
ASFA (Padmanabhan, 2019) defines CAPS as the acute onset of multiple thromboses in at least three organ systems over a period of days or weeks, in individuals with antiphospholipid antibodies. European Forum on Antiphospholipid Antibodies maintains a registry of individuals with CAPS due to the rarity of the disease. Data from the registry documented higher survival rates related to the increased frequency of combination therapy including anticoagulants, glucocorticoids and plasma exchange and/or intravenous immune globulin (Cervera, 2012). Specialty input recommends use of plasmapheresis or plasma exchange to treat CAPS.

Cryoglobulinemia
Cryoglobulins, single or mixed immunoglobulins may precipitate at low temperatures and can deposit in the vessels and tissues of the body. The increase of cryoglobulins can increase the viscosity of the circulating blood and may cause vasculitis and obstruct vessels, causing organ damage. Cryoglobulinemia involves the presence of cryoglobins in the blood and typically occurs concomitantly with other conditions such as viral hepatitis, lymphoproliferative and autoimmune disorders. Treatment is based on the severity of disease and ~~includes~~ addressing the underlying ~~concomitant~~ disorder. Individuals who are asymptomatic do not require treatment and mild symptoms can be treated with cold avoidance and analgesics. More severe cases are treated with immunosuppressive therapy. ~~, suppression of the immune response, and plasmapheresis for severe or life-threatening complications.~~ The AFSA recommendation for plasmapheresis or plasma exchange in severe or symptomatic is a category II with an evidence level of 2A (Padmanabhan, 2019).~~.~~

Hyperviscosity syndromes associated with monoclonal gammopathies

The National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology (NCCN Guidelines® V.3.2019) on multiple myeloma recommend plasmapheresis as an adjunctive therapy for symptomatic hyperviscosity. The guideline also notes, "Institutions differ in their use of plasmapheresis for adjunctive treatment of renal dysfunction." The recommendation to improve renal function by utilizing plasmapheresis is a category 2B recommendation.

Lipoprotein (a) hyperlipoproteinemia
Lipoprotein (a) is recognized as an independent and causal risk factor for atherosclerotic cardiovascular disease (ASCVD). While its physiological function is still unknown, lipoprotein (a) exerts all the atherogenic effects of an LDL-particle. As elevated lipoprotein (a) levels are prevalent in the population, treatment is limited to those with additional comorbidities. While lipoprotein (a) levels are not affected by changes in diet or lifestyle, some existing lipid lowering drugs can reduce lipoprotein (a) levels.

Myeloma Cast Nephropathy
The formation of casts in the distal tubules of the kidneys is thought to be due to an increase in light chain concentrations typically seen with tumor progression (Padmanabhan, 2019). Primary therapy typically involves chemotherapy and intravenous fluid to increase the alkaline levels and to dissolve the light chains. The ASFA recommendation was a category II with a level of evidence 2B. ~~However, specialty input recommended use of plasmapheresis or plasma exchange to treat multiple myeloma cast nephropathy~~.

Multiple Sclerosis – Acute CNS inflammatory demyelinating disease
The ASFA recommends the use of plasmapheresis or plasma exchange to treat acute CNS inflammatory demyelinating disease associated with multiple sclerosis (Padmanabhan, 2019). The AAN has a Level B recommendation for plasmapheresis as adjunctive treatment of exacerbations in relapsing forms of MS. Based on Level A evidence, the AAN states, "Plasmapheresis should not be offered for chronic progressive or secondary progressive MS" (Cortese, 2011).

Neuromyelitis optica spectrum disorders (NMOSD)
NMOSD, also known as Devic's disease, is an inflammatory CNS syndrome, which is distinct from multiple sclerosis. NMOSD targets optic nerves and the spinal cord, causing immune-mediated demyelination and axonal injury. High-dose intravenous methylprednisolone followed by oral dosing is considered first-line therapy. Plasmapheresis therapy is usually limited to those who do not respond adequately to first line therapy

(Padmanabhan, 2019). In addition to methylprednisolone therapy, other pharmacological treatments have shown promise in the treatment of NMOSD (Cree, 2019; Damato, 2016; Pittock, 2019).

PANDAS
Although ASFA (Padmanabhan, 2019) provides a Category II recommendation grade 1B level of evidence for plasmapheresis or plasma exchange as a treatment for PANDAS ~~and Sydenham's chorea~~, there is still conflicting information in the published literature. The AAN guideline on plasmapheresis in neurologic disorders (Cortese, 2011) stated there is "insufficient evidence to support or refute the use of plasmapheresis in the treatment of acute obsessive compulsive disorders (OCD) and tic symptoms in the setting of PANDAS." Swedo and colleagues (2012) proposed a set of diagnostic criteria for Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) as modified from PANDAS criteria. The authors noted this new set of criteria would need to be validated in large trials. In a retrospective review in a large metropolitan area, Gabbay (2008) reported significant over diagnosis of PANDAS and subsequent therapies that included plasma exchange. The AFSA noted that initial treatment include cognitive behavioral therapy and/or anti-obsessional medications (Padmanabhan, 2019).

Sydenham's chorea
ASFA (Padmanabhan, 2019) provides a Category III recommendation grade 2B level of evidence for plasmapheresis or plasma exchange as a treatment for Sydenham's chorea, there is still conflicting information in the published literature. Sydenham's chorea is a pediatric post-infectious autoimmune neuropsychiatric disorder that manifests after an acute bout of rheumatic fever. Symptoms include rapid and jerky, involuntary movements that may affect the face, trunk and extremities, which may prevent independent activities of daily living. Chorea is usually treated with neuroleptics, valproic acid and corticosteroids. Sydenham's chorea is thought to be an autoimmune disorder based on the presence of antibodies that react with neuronal tissue that control motor activity (Garvey, 2005; National Institute of Neurological Disorders and Stroke [NINDS], 2007). The AAN guideline (Cortese, 2011) noted there is "Insufficient evidence to support or refute the use of plasmapheresis in the treatment of Sydenham chorea." The NINDS notes there is no specific treatment for Sydenham's chorea.

Systemic Lupus Erythematosus (SLE) - Severe
Circulating autoantibodies and immune complexes along with complement deposition results in injury to the cell and tissue for individuals with SLE. Immunosuppressive agents and biologic therapies are used to treat SLE.

Specialty input recommends therapeutic plasmapheresis or plasma exchange for those with severe or life-threatening symptoms and conventional therapies have failed to prevent clinical deterioration.

Thrombotic Microangiopathy (TMA)
TMA is a rare medical condition involving small blood vessel damage from blood clots, usually as a result of other complex and serious illnesses. There are various syndromes such as HUS and TTP that involve TMA as a component of the specific syndrome, but are classified separately based on additional clinical indications (Loriat, 2011).

Transplantation
Approximately 20% of individuals waiting for cadaveric renal transplantation have high cytotoxic antibody titers rendering them at high risk for hyperacute and acute allograft rejection. Plasma exchange and immunoadsorption have been utilized as a means of removing these antibodies prior to transplantation resulting in significant reductions in the level of antibodies. When used in individuals with recurrent FSGS, pheresis induced a decrease in urinary protein. Additionally, randomized controlled trials have been conducted establishing the efficacy of plasma exchange in the treatment of biopsy proven acute antibody mediated renal allograft rejection The literature on pheresis for the treatment of chronic rejection is limited to a few uncontrolled studies with modest and transient results.

Voltage-gated potassium channel (VGKC) antibody related diseases
Dysfunction of the VGKC antibodies, which are important in the control of membrane excitability in the nervous system, is associated with a variety of neurological conditions, including limbic encephalitis, acquired neuromyotonia (NMT), LGI1/CASPR2- antibody mediated encephalitis (AME), and Morvan's syndrome (MVS). Affected individuals present with a variety of symptoms, delaying diagnosis in many individuals. Immunotherapy, including steroids and immunosuppressive drugs, as well as symptomatic treatment, are typical first-line treatments. The AFSA notes that due to a high variability in presentation and treatment response associated with VGKC antibody related disease, individualized treatment is warranted.

Other Indications
Additional ASFA indications for plasma pheresis or plasma exchange were of lower levels of evidence and/or the optimum role of therapy could not be established; or the evidence demonstrated the therapy could be ineffective or

harmful. These indications are listed by categories:

Plasmapheresis or plasma exchange treatment options with Category I-II recommendation and levels of evidence ranging from Grade 2A – 2C include the following indications (Padmanabhan, 2019):

- Acute disseminated encephalomyelitis (ADEM)
- Lambert-Eaton myasthenic syndrome
- Myasthenia gravis; long-term management
- Overdose of drugs or poisoning – mushroom
- Phytanic acid storage disease (Refsum's disease)
- Steroid-responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto's Encephalopathy)
- Systemic lupus erythematosus (SLE)
- Thrombotic microangiopathy, factor H autoantibody mediated or associated with Ticlopidine
- Thyroid storm
- Vasculitis, Hepatitis B polyarteritis nodosa

Plasmapheresis or plasma exchange treatment options with Category III recommendations and levels of evidence ranging from Grade 1B – 2C were provided for the following indications (Padmanabhan, 2019):

- Acute liver failure
- Anti-glomerular basement membrane disease (Goodpasture's syndrome) when the individual is dialysis-dependent and there is no evidence of DAH
- ~~Aplastic anemia~~
- Autoimmune hemolytic anemia, warm (WAHA), ~~when condition is~~ severe
- Burn shock resuscitation
- Cardiac neonatal lupus
- Chronic focal encephalitis (Rasmussen encephalitis)
- Coagulation factor inhibitors
- Complex regional pain syndrome, chronic
- Dilated cardiomyopathy, idiopathic
- Erythropoietic protoporphyria liver disease

- Focal segmental glomerulosclerosis (FSGS); steroid resistant in native kidney
- Heart (cardiac) transplantation; antibody mediated rejection (AMR)
- Hematopoietic stem cell transplantation, ABO incompatible with pure red blood cell aplasia or HLA desensitization
- Hemophagocytic lymphohistiocytosis; hemophagocytic syndrome; macrophage activating syndrome
- ~~Henoch-Schonlein purpura~~
- Heparin induced thrombocytopenia and thrombosis
- Hypertriglyceridemic (HTG) pancreatitis
- Rapidly progressive glomerulonephritis; ANCA-associated and ~~dialysis independent~~independent creatinine of less than 5.7 mg/dl
- Immune thrombocytopenia, refractory
- Immunoglobulin A nephropathy – crescentic and chronic progressive
- Liver transplantation – desensitization from a deceased donor or antibody mediated rejection
- Lung transplantation – antibody mediated rejection or desensitization
- Multiple sclerosis that is chronic ~~progressive~~
- Neuromyelitis optica spectrum disorders (NMOSD); maintenance treatment
- Nephrogenic systemic fibrosis
- Overdose of drugs or poisoning – envenomation
- Paraneoplastic syndromes
- Paraproteinemic demyelinating ~~polyneuropath~~neuropathies~~y~~ or chronic acquired demyelinating polyneuropathies; associated with multiple myeloma or anti myelin-associated glycoprotein neuropathy
- Pemphigus vulgaris
- Post transfusion purpura
- Progressive multifocal leukoencephalopathy (PML); natalizumab associated
- Pruritus related to hepatobiliary disease; treatment resistant
- Red cell alloimmunization in pregnancy, ~~prior to intrauterine transfusion availability~~prevention and treatment
- Renal cell transplantation; ABO compatible for desensitization with a deceased donor
- Scleroderma (progressive systemic sclerosis)

- Sepsis with multi-organ failure
- Stiff-person syndrome
- Sudden sensorineural hearing loss
- Thrombotic microangiopathy
  - coagulation mediated
  - complement factor gene mutations mediated
  - clopidogrel associated
  - infection associated
  - transplantation associated
- ~~Thyroid storm~~
- Toxic epidermal necrolysis, refractory
- Vasculitis, Behcet's disease
- Vasculitis, IgA (Henoch-Schonlein purpura)

Plasmapheresis or plasma exchange treatment options with Category IV recommendations were provided for the following indications (Padmanabhan, 2019):

- Amyloidosis, systemic
- Amyotrophic lateral sclerosis
- Hemolytic Uremic Syndrome associated with infection (Shiga toxin), absence of severe neurologic symptoms
- Inclusion body myositis
- POEMS syndrome
- Psoriasis
- Schizophrenia
- Thrombotic microangiopathy, drug (gemcitabine or quinine) related

Immune thrombocytopenia
Immune thrombocytopenia has a widely accepted abbreviation, ITP, and is also known as "immune thrombocytopenic purpura and idiopathic thrombocytopenic purpura." The most recent name "immune thrombocytopenia" is based on an international work group to standardize the terminology and definitions of ITP

(Neunert, 2011; Rodeghiero, 2009). The 2011 evidence-based practice guideline for ITP does not include any form of therapeutic apheresis as a recommended treatment (Neunert, 2011).

Lupus Nephritis
The ASFA lists the use of plasmapheresis or plasma exchange treatment options with a Category IV recommendation and level of evidence Grade 1B. This recommendation was based on a controlled study that showed no benefit of adding therapeutic plasmapheresis or plasma exchange to prednisone and cyclophosphamide for individuals with severe lupus nephritis, these findings were supported by smaller, later trials. (Schwartz, 2016). While a 2010 RCT suggested that adjunctive IA and TPE were equally effective in reducing systemic lupus erythrematosus Disease Activity Index (SLEDAI) scores, the ASFA did not change their recommendation. American College of Rheumatology (ACR) guidelines for screening, treatment and management of lupus nephritis do not include the use of plasmapheresis or plasma exchange as treatment modalities (Hahn, 2012). Similarly, the Joint European League Against Rheumatism and European Renal Association-European dialysis and Transplant Association (EULAR/ERA-EDTA) (Bertsias, 2012) do not include the use of plasmapheresis or plasma exchange as a recommended treatment for the management of adult or pediatric lupus nephritis.

Phytanic Acid Storage Disease (Refsum's disease)
Refsum Disease, or phytanic acid storage disease, is a rare genetic disease where individuals lack the enzyme to break down phytanic acid found in certain foods. This excess phytanic acids accumulate in the brain, blood and other tissues, with can cause blindness and arrhythmias in the heart. Avoidance of foods such as dairy products, beef, lamb, and fatty fish (e.g., tuna, cod and haddock) is the primary treatment. When there is excessive buildup of phytanic acid, plasma exchange has been utilized with some improvement in symptoms, but vision and hearing problems persisted (NINDS, 2011).

Stiff Person (Man) Syndrome
Also known as Stiff-Man Syndrome, the classic features of this syndrome include painful muscular spasms associated with muscular stiffness, often times impairing the ability to walk. This syndrome is a rare, chronic but usually not progressive disorder. Published literature includes case reports with mixed results (Padmanabhan, 2019).

Lipoprotein apheresis

Low-density apheresis
Low-density lipoprotein (LDL) apheresis describes a variety of technologies used to acutely remove lipoprotein LDL from the plasma. The individual initially undergoes an apheresis procedure to isolate the plasma. The LDLs are then selectively removed from the plasma by either immunoadsorption, heparin-induced extracorporeal LDL precipitation (also referred to as HELP), or dextran sulfate adsorption. In immunoadsorption, polyclonal antihuman apoB antibodies from sheep selectively bind and remove LDL. (ApoB is the protein moiety of low-density lipoprotein.) In HELP, LDL and other particles containing ApoB are precipitated by heparin at an acidic pH. Dextran sulfate adsorption removes LDL by binding the positively charged apoB to dextran sulfate particles bound to cellulose. LDL apheresis is a selective procedure in which only pathogenic low-density lipoproteins are removed. The plasma is then returned to the individual. Examples of two LDL-apheresis systems currently FDA-approved for use in the United States are the Heparin-Induced Extracorporeal LDL Cholesterol Precipitation (H.E.L.P.) Futura Apheresis system (B. Braun Avitum AG., Bethlehem, PA) and the LipoSorber® system (Kaneka Pharma America Corporation, New York, NY).

The ASFA recommends lipoprotein apheresis as Categories I-II treatment options and the associated level of Grade 1A (strong recommendation, high-quality evidence) (Padmanabhan, 2019). A single session of lipoprotein apheresis has been shown to decrease cholesterol levels by 60-70% (Padmanabhan, 2019). There are various recommendations for individual selection criteria, however, there is a lack of evidence to support the initiation of treatment at specific LDL levels.

Familial hypercholesterolemia is an autosomal, co-dominant inherited disorder of lipoprotein metabolism that features mutations in the LDL-receptor gene. Due to reduced or absent LDL receptors, low-density lipoprotein cholesterol (LDLc) is not effectively cleared by the liver, resulting in very high plasma concentration in the circulating blood. LDLc deposits can be found in the tendons (tendon xanthomas) and arterial walls, and may be associated with an increased risk of early onset of atherosclerosis and premature coronary heart disease (CHD.) The estimated frequency is 1:500 for heterozygotes, and 1:1,000,000 for homozygotes. Recommendations noting individual selection criteria regarding when treatment should be initiated vary between sources.

Individuals with homozygous hypercholesterolemia are treated aggressively to prevent or slow the progression of cardiovascular disease (CVD) due to the prolonged high lipid level exposure since birth (Robinson, 2013). Statins and other agents along with diet and lifestyle modifications are recommended to lower TC. In addition, a new class of drugs, proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors were recently approved by the FDA to treat

familial hypercholesterolemia have been shown to aggressively lower LDL levels. LDL apheresis may be used to selectively lower LDLc to optimal levels.

High-density lipid (HDL) apheresis
Autologous apheresis with selective HDL delipidation and infusion of selected preβ-HDL is being evaluated as a method to reduce atherosclerosis in individuals at high-risk for cardiovascular disease (CVD). The selective removal of cholesterol from HDL (α-HDL), also called delipidation, involves exposing the plasma to organic solvents in the proprietary collection device and the process of returning the resulting small form of HDL (β-HDL). A randomized, placebo-controlled study examined the safety of a device called LS PDS-2 (Lipid Sciences Plasma Delipidation System-2; Life Sciences, CA) that does not have U.S. Food & Drug Administration approval at this time. A total of 28 individuals with acute coronary syndrome (ACS) who were scheduled for diagnostic cardiac catheterization were enrolled and 26 participants completed all of the treatments and visits. Treatment involved HDL selected apheresis once every 7 days, for a total of 7 treatments. Fourteen individuals randomized to the treatment arm completed the 7-week selective HDL delipidation treatment period and 12 individuals assigned to the control arm completed the placebo treatment period. Preβ-HDL was evaluated by electrophoresis and quantitative analysis. On average, preβ-HDL was increased by 28 times in post-delipidated plasma compared to baseline volume. Intravascular ultrasound (IVUS) of the target vessel was performed and a non-significant reduction in the volume of the atheroma was reported in the delipidated group versus the placebo group. Fifteen of the participants had 1 or more adverse events, with a total of 38 reported adverse events. Hypotension was the most common adverse event. The authors noted limitations to the study included a small sample size and majority of the participants on the trial were also on statin therapy. Additionally, the authors noted "It is not clear whether acute regression of atherosclerotic burden will be associated with decreased clinical cardiovascular events." (Waksman, 2010). The evidence does not support that there are improved net clinical health outcomes in individuals treated with therapeutic apheresis combined with selective HDL delipidation. Subedi and associates (2014) notes that further evaluation regarding the association between HDL and ASCVD is needed. The 2019 ASFA guidelines do not address HDL lipid apheresis.

Cytapheresis
Erythrocytapheresis
The ASFA recommends erythrocytapheresis with Category I and the associated Grade 1B level of evidence (strong recommendations, moderate quality evidence) treatment options were listed for the following indications (Padmanabhan, 2019):

- Hereditary hemochromatosis
- Polycythemia vera

The ASFA notes management of individuals with low risk polycythemia vera (PV) include maintaining hematocrit ≤ 45% with phlebotomy and low dose aspirin. Individuals with high risk are treated with phlebotomy, aspirin and other cytoreductive agents. Cytapheresis is recommended to correct hyperviscosity as an alternative to emergent large-volume phlebotomy (Padmanabhan, 2019).

Specialty input recommends use of erythrocytapheresis to treat symptomatic secondary polycythemia vera and porphyria cutanea tarda. Porphyria is a group of rare disorders where the process of heme production is affected. Porphyria cutanea tarda is the most common type of porphyria.

Leukocytapheresis
Symptomatic hyperleukocytosis manifests itself with a variety of symptoms including confusion, somnolence, dizziness, headache, coma, parenchymal hemorrhage, hypoxemia, diffuse alveolar hemorrhage, and respiratory failure. Induction chemotherapy with aggressive supportive care is considered the definitive treatment.
~~Leukocytapheresis with Category II recommendations were provided for the following indications (Padmanabhan, 2019):~~

- ~~Hyperleukocytosis - Symptomatic~~

Leukocytapheresis with Category III recommendations were provided for the following indications (Padmanabhan, 2019):

- Hyperleukocytosis – prophylaxis or secondary

Leukocytapheresis with Category IV recommendations were provided for the following indications (Padmanabhan, 2019):

- Inclusion body myositis

RBC exchange
The ASFA recommends RBC exchange with Category I-II and the associated Grade 1A -2C level of evidence treatment options were listed for the following indications (Padmanabhan, 2019):

- Babesiosis, severe
- Sickle cell disease, acute:
  - Acute stroke
  - Acute severe, chest syndrome
- Sickle cell disease, non-acute:
  - Stroke prophylaxis
  - Pregnancy
  - Recurrent vaso-occlusive pain crisis

RBC exchange with Category III and an associated Grade 2B or 2C level of evidence was listed for the following indications (Padmanabhan, 2019):

- Erythropoietic protoporphyria, liver disease
- Malaria
- Red cell alloimmunization, prevention and treatment; Exposure to RhD^+ RBCs
- Transplantation, hematopoietic stem cell, minor ABO incompatible; hematopoietic progenitor cell, apheresis

Additional indications were recommended by specialty input using RBC exchange for the following indications:

- Babesiosis in the high-risk population
- Severe malaria
- Sickle cell disease
  - ~~Multi-organ failure syndrome~~
  - ~~Pre-procedure preparation for hematopoietic stem cell transplant or surgery~~
  - Pregnancy
  - Primary or secondary stroke prophylaxis

Thrombocytapheresis
Thrombocytapheresis with Category II with "weak recommendation, low-quality or very low-quality evidence" or Category III recommendations were provided for the following indications (Padmanabhan, 2019):

- Thrombocytosis – symptomatic, prophylactic or secondary

Immunoadsorption Pheresis
Immunoadsorption pheresis with Category II 1B or 2B recommendations were provided for the following indications (Padmanabhan, 2019):

- Cryoglobulinemia, symptomatic or severe
- Dilated cardiomyopathy, idiopathic; New York
- Multiple sclerosis, acute attack/relapse

Immunoadsorption pheresis with Category III recommendations were provided for the following indications (Padmanabhan, 2019):

- ~~Acute CNS inflammatory demyelinating disease, associated with multiple sclerosis~~
- Atopic (neuro-) dermatitis (atopic eczema), recalcitrant
- Coagulation factor inhibitors ~~alloantibody and autoantibody~~
- Immune thrombocytopenia, refractory
- Multiple sclerosis, chronic
- Paraneoplastic neurological syndromes
- ~~Paraproteinemic demyelinating neuropathies associated with IgA, IgG or IgM monoclonal gammopathy~~
- Pemphigus vulgaris

The ACR 2002 Update of the Rheumatoid Arthritis Guidelines note use of Staphylococcal protein A immunoadsorption column, "should be considered only for patients with refractory rheumatoid arthritis in whom treatment with several disease modifying anti-rheumatic drugs (DMARDs) has failed." This recommendation was based on the improvement in 31.9% of the participants treated with the immunoadsorption column compared to 11.4% who received sham treatment in a randomized, multicenter trial (Felson, 1999). The 2015 ACR guidelines do not mention IA for the treatment of RA. There have been a few other older studies which support use of IA in the treatment of RA (Furst, 2000; Poullin, 2005).

The peer-reviewed medical literature supports the clinical effectiveness and safety of immunoadsorption for the indications listed in the policy statements. Most studies to date have supported the use of this procedure for individuals with hemolytic uremic syndrome and TTP resulting in a reduction of symptoms. Furthermore, the safety and efficacy of immunoadsorption has been well established in individuals with HUS, TTP, in post kidney

transplant recipients with recurrent focal and segmental glomerulosclerosis (FGS). The current research does not support the benefits of immunoadsorption in other immune-related disorders.

Based on the data from the published studies and specialty consensus input, therapeutic apheresis modalities are considered medically necessary for selected indications. Conditions which have been evaluated by the AFSA and have been found to be lacking data showing the efficacy or clinical utility of apheresis or conditions which have not been evaluated by the AFSA and there is a lack of published data showing improved clinical outcomes associated with apheresis when compared to alternative treatments are considered not medically necessary.

Definitions

Antibodies: Immunoglobulins (a specialized immune protein) produced as a result of the introduction of an antigen into the body.

Autoimmune disease: An illness occurring when the body tissues are attacked by its own immune system; as a result, individuals with these diseases frequently have unusual antibodies circulating in their blood that target their own body tissues.

Bullous pemphigoid: A disease characterized by tense blistering eruptions of the skin, generally caused by antibodies abnormally accumulating in a layer of the skin.

Cerebritis: Inflammation of the brain.

Cryoglobulinemia: The presence of abnormal proteins called cryoglobulins that, by definition, have the unusual properties of precipitating from the blood serum when it is chilled and re-dissolving upon rewarming.

Cytapheresis: Subtype of therapeutic apheresis in which the white blood cells are isolated and retained (leukapheresis or lymphocytopheresis) or red blood cells are isolated and retained (erythrocytapheresis).

Guillain-Barre: A condition that usually occurs after an infection; the signs and symptoms include loss of sensation in the arms and legs and increasing weakness.

Heterozygotes: A person possessing two different forms of a particular gene, one inherited from each parent.

Homozygotes: A person who has two identical forms of a particular gene, one inherited from each parent.

Immune complex: A combination of an antibody (immunoglobulin), and an antigen (the target that the antibody is attacking).

Immune thrombocytopenic purpura: A condition in which antibodies destroy the cells in the body that is responsible for blood clotting (platelets).

Immunoglobulin: A protein produced by plasma cells and lymphocytes; immunoglobulins are an essential part of the body's immune system which attach to foreign substances, such as bacteria, and assist in destroying them.

Myocarditis: Inflammation of the heart muscle.

Nephritis: Inflammation of the kidney.

Pemphigus vulgaris: An autoimmune disease of the skin, with blistering.

Polymyositis: A chronic inflammatory disease of muscle that begins when white blood cells spontaneously invade muscles, which may result in severe muscle pain, tenderness and weakness.

PRA: Panel reactive antibodies.

Pure red cell aplasia: A condition where an individual has an inability to produce red blood cells.

Regional enteritis: Also called Crohn's disease, a chronic inflammatory disease of the intestine primarily in the small and large intestines but which can occur anywhere in the digestive system between the mouth and the anus.

Scleroderma: A disease of connective tissue resulting in formation of scar tissue in the skin and at times other organs of the body.

Segmental glomerulosclerosis: An illness that occurs when scar tissue forms in some of the glomeruli (structures involved in the filtration of blood) of the kidney.

Thymectomy: Removal of the thymus gland.

Vasculitis: A general term for a group of uncommon diseases characterized by inflammation of the blood vessels.

Waldenström's macroglobulinemia: A disease where abnormal white blood cells produce excessive amounts of antibodies; bleeding and enlarged liver and spleen may be seen.

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Revised	05/14/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Added requirement that medical treatments must have been tried and failed prior to therapeutic apheresis to medically necessary category II indications, with the exception of symptomatic hyperleukocytosis. -Removed the following medically necessary indications: H.E.L.L.P Syndrome of

		pregnancy, progressive multifocal leukoencephalopathy (natalziamab associated), Ssydenham's chorea, symptomatic secondary polycythemia, severe malaria, multi organ failure syndrome, pre-procedure preparation for surgery or hematopoietic stem cell transplant, iron overload and moderate to severe rheumatoid arthritis. Removed examples from the not medically necessary statements. Updated Discussion, References, and Coding section.
Revised	11/07/2019	Medical Policy & Technology Assessment Committee (MPTAC) review. Added diagnostic criteria to the condition chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) when treated by plasmapheresis or immunoadsorption. Updated Discussion/General Information and References sections.
Revised	08/22/2019	MPTAC review. Added medically necessary indications for acute inflammatory demyelinating polyradiculoneuropathy/Guillain-Barre syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, myasthenia gravis, N-methyl D-aspartate receptor antibody encephalitis and renal transplant recipients. Revised the medically necessary indication for anti-neutrophil cytoplasmic antibodies vasculitis. Added not medically necessary indications for red blood cell exchange and adsorptive cytapheresis when criteria are not met. Clarified not medically necessary statements. Removed clarifying not medically necessary statement regarding immunoadsorption. Clarified term Low-density lipid (LDL) apheresis as also lipoprotein apheresis. Clarified several medically necessary indications based on 2019 ASFA indications. Updated Description, References, Websites and Coding sections.
Reviewed	11/08/2018	MPTAC review.
Reviewed	10/31/2018	Hematology/Oncology Subcommittee review. Updated Discussion/General Information and References sections.
Reviewed	03/22/2018	MPTAC review. Updated References section.
New	11/02/2017	MPTAC review. Initial document development.
New	11/01/2017	Hematology/Oncology Subcommittee review. Initial document development. Moved content of MED.00113 Therapeutic Apheresis to new clinical utilization management guideline document with the same title. Added

medically necessary indications for N-methyl D-aspartate receptor antibody encephalitis, progressive multifocal leukoencephalopathy and apheresis as a component of CAR-T therapy. Revised medically necessary indications for polyneuropathy, glomerulonephritis, neuromyelitis optica disorders and paraproteinemic demyelinating neuropathies. Updated Coding section with 01/01/2018 CPT descriptor change for code 36516 and removed code 36515 deleted 12/31/2017.