

# APHERESIS

**Policy Number:** OUTPATIENT 049.13 T1

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[Instructions for Use](#) ⓘ

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## Related Policies

- [Bone or Soft Tissue Healing and Fusion Enhancement Products](#)
- [Platelet Derived Growth Factors for Treatment of Wounds](#)

## CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General benefits package
Referral Required (Does not apply to non-gatekeeper products)	Yes - Office No - Inpatient, Outpatient
Authorization Required (Precertification always required for inpatient admission)	No - Office Yes - Inpatient, Outpatient
Precertification with Medical Director Review Required	No
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Office, Inpatient, Outpatient

## COVERAGE RATIONALE

### Therapeutic apheresis is proven and medically necessary for treating or managing the following conditions/diagnoses:

- ABO incompatible heart transplantation in children less than 40 months of age (only as second line therapy)
- ABO incompatible major hematopoietic stem cell transplant/bone marrow (only as second line therapy)
- ABO incompatible kidney transplantation (only as second line therapy)
  - Antibody mediated rejection, Living donor (LD) desensitization
  - A<sup>2</sup>/A<sup>2</sup>B into B, deceased donor
- ABO incompatible liver transplantation, desensitized ABOi, deceased donor
- Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome), primary treatment
- Acute liver failure (requiring high volume plasma exchange)
- Age related macular degeneration, dry
- ANCA-associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis; and Microscopic Polyangiitis)
  - Dialysis dependent
  - Diffuse alveolar hemorrhage (DAH)
- Anti-glomerular basement membrane disease (Goodpasture’s syndrome)
  - Dialysis independent
  - DAH
- Cardiac transplantation
  - Recurrent rejection
  - Desensitization

- Chronic inflammatory demyelinating polyneuropathy
- Coagulation factor inhibitors, autoantibody via Immunoabsorption (IA)
- Cutaneous T-cell lymphoma; mycosis fungoides; Sézary syndrome, erythrodermic
- Familial hypercholesterolemia
  - Homozygous
  - Heterozygous (only as second line therapy)
- Focal segmental glomerulosclerosis, recurrent in transplanted kidney (only as second line therapy)
- Graft-versus-host disease
  - Acute skin and non skin
  - Chronic, skin (only as second line therapy)
- Hereditary hemochromatosis
- Hyperleukocytosis, symptomatic
- Hyperlipoproteinemia
- Hyperviscosity in monoclonal gammopathies
- Idiopathic dilated cardiomyopathy, NYHA class II-IV, via IA
- Inflammatory bowel disease, via Adsorptive Cytophoresis
- Lung transplantation, bronchiolitis obliterans syndrome
- Multiple sclerosis
  - Acute CNS inflammatory, demyelinating
  - Relapsing form with steroid resistant exacerbations (only as second line therapy)
- Myasthenia gravis
- Neuromyelitis optica spectrum disorders, acute (Devic's syndrome) (only as second line therapy)
- N-methyl D-aspartate receptor antibody encephalitis
- Paraproteinemic polyneuropathies via Therapeutic Plasma Exchange (TPE)
  - Anti-MAG
  - Multifocal motor
  - IgG/IgA
  - IgM
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS exacerbation)
- Peripheral vascular diseases
- Polycythemia vera; erythrocytosis
- Progressive multifocal leukoencephalopathy associated with natalizumab
- Pruritus due to hepatobiliary diseases
- Renal transplantation, ABO compatible
  - Antibody mediated rejection
  - Desensitization, living donor
- Rheumatoid arthritis, refractory (only as second line therapy)
- Sickle cell disease
  - Acute stroke or multiorgan failure
  - Acute chest syndrome, severe (only as second line therapy)
  - Primary or secondary stroke prevention
  - Prevention of transfusional iron overload
- Systemic lupus erythematosus nephritis
- Thrombotic microangiopathy, complement mediated
  - MCP mutations
- Thrombotic microangiopathy, Shiga toxin mediated
  - Absence of severe neurological symptoms
- Thrombotic thrombocytopenic purpura
- Vasculitis
  - Behet's disease (adsorption granulocytapheresis)
  - Idiopathic PAN (TPE)
  - EGPA (TPE)
- Wilson's disease, fulminant

**Therapeutic apheresis including plasma exchange, Plasmapheresis, or photopheresis is unproven and not medically necessary for treating or managing the following conditions/diagnoses, including but not limited to:**

- ABO incompatible liver transplantation, antibody mediated rejection
- Acute disseminated encephalomyelitis
- Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome), after IVIG
- Amyloidosis, systemic
- Amyotrophic lateral sclerosis
- ANCA-associated rapidly progressive glomerulonephritis, dialysis independent (Granulomatosis with polyangiitis; and Microscopic Polyangiitis)

- Anti-glomerular basement membrane disease, dialysis dependent, without DAH (Goodpasture's syndrome)
- Aplastic anemia; pure red cell aplasia
- Atopic (neuro-) dermatitis (atopic eczema), recalcitrant
- Autoimmune hemolytic anemia; warm autoimmune hemolytic anemia (WAIHA); cold agglutinin disease
- Babesiosis
- Burn shock resuscitation
- Cardiac neonatal lupus
- Cardiac transplantation
  - Antibody mediated rejection
  - Rejection prophylaxis
- Catastrophic antiphospholipid syndrome
- Chronic focal encephalitis (Rasmussen's encephalitis)
- Coagulation factor inhibitors
  - Alloantibody (via IA)
  - Autoantibody (via TPE or IA)
- Complex regional pain syndrome
- Cryoglobulinemia
- Cutaneous T-cell lymphoma; mycosis fungoides; Sézary syndrome, non-erythrodermic
- Dermatomyositis/polymyositis
- Erythropoietic porphyria, liver disease
- Focal segmental glomerulosclerosis, native kidney, steroid resistant
- Hashimoto's encephalopathy
- HELLP syndrome
- Hematopoietic stem cell transplantation, HLA desensitized [major or minor HPC(A)]
- Hemolytic uremic syndrome
- Hemophagocytic lymphohistiocytosis
- Henoch-Schonlein purpura
- Heparin induced thrombocytopenia and thrombosis
- Hyperleukocytosis, prophylaxis
- Hypertriglyceridemic pancreatitis
- Immune thrombocytopenia
- Immunoglobulin A nephropathy
- Inflammatory bowel disease, via Extracorporeal Photopheresis
- Lambert-Eaton myasthenic syndrome
- Lung transplantation
  - Antibody mediated rejection
  - Desensitization
- Malaria
- Multiple sclerosis (unless noted above as proven)
- Myeloma cast nephropathy
- Nephrogenic systemic fibrosis
- Neuromyelitis optica spectrum disorders, maintenance
- Overdose, venoms, and poisoning
- Paraneoplastic neurologic syndromes
- Paraproteinemic polyneuropathy, multiple indications (unless noted above as proven)
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (Sydenham's chorea, severe)
- Pemphigus vulgaris
- Phytanic acid storage disease (Refsum's disease)
- Post transfusion purpura
- Prevention of RhD alloimmunization after RBC exposure
- Psoriasis
- Red cell alloimmunization in pregnancy
- Renal transplantation, ABO compatible, desensitized, deceased donor
- Scleroderma (systemic sclerosis)
- Sepsis with multiorgan failure
- Sickle cell disease, non-acute (unless noted above as proven)
- Stiff-person syndrome
- Sudden sensorineural hearing loss
- Systemic lupus erythematosus, severe
- Thrombocytosis
- Thrombotic microangiopathy (unless noted above as proven)
- Thyroid storm

- Toxic epidermal necrolysis
- Vasculitis (unless noted above as proven)
- Voltage gated potassium channel antibodies

There is insufficient evidence to conclude that apheresis, plasma exchange, Plasmapheresis, Immunoabsorption, or photopheresis is beneficial for health outcomes such as decreased morbidity and mortality rates in individuals with disorders other than those listed as medically necessary.

**Note:** Please see [Description of Services](#) section for information regarding all apheresis-based procedures.

## APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

CPT Code	Description
0342T	Therapeutic apheresis with selective HDL delipidation and plasma reinfusion
36511	Therapeutic apheresis; for white blood cells
36512	Therapeutic apheresis; for red blood cells
36513	Therapeutic apheresis; for platelets
36514	Therapeutic apheresis; for plasma pheresis
36516	Therapeutic apheresis; with extracorporeal immunoabsorption, selective adsorption or selective filtration and plasma reinfusion
36522	Photopheresis, extracorporeal

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

## DESCRIPTION OF SERVICES

Therapeutic Apheresis is a procedure in which the blood of a patient is passed through an extracorporeal medical device which separates components of blood to treat a disease. It is a general term which includes all Apheresis based procedures (Schwartz, et al., 2016):

**Adsorptive Cytapheresis:** A therapeutic procedure in which blood of the patient is passed through a medical device, which contains a column or a filter that selectively adsorbs activated monocytes and granulocytes, allowing the remaining leukocytes and other blood components to be returned to the patient.

**Apheresis:** A procedure in which blood of the patient or donor is passed through a medical device which separates one or more components of blood and returns the remainder with or without extracorporeal treatment or replacement of the separated component.

**B2 Microglobulin Column:** The B2 microglobulin Apheresis column contains porous cellulose beads specifically designed to bind to B2 microglobulin as the patient's blood passes over the beads.

**Erythrocytapheresis:** A procedure in which blood of the patient or donor is passed through a medical device which separates red blood cells from other components of blood. The red blood cells are removed and replaced with crystalloid or colloid solution, when necessary.

**Extracorporeal Photopheresis (ECP):** A therapeutic procedure in which the buffy coat is separated from the patient's blood, treated extracorporeally with a photoactive compound (e.g., psoralens) and exposed to ultraviolet A light then subsequently reinfused to the patient during the same procedure.

**Filtration Selective Removal:** A procedure which uses a filter to remove components from the blood based on size. Depending on the pore size of the filters used, different components can be removed. Filtration-based instruments can

be used to perform plasma exchange or LDL Apheresis. They can also be used to perform donor Plasmapheresis where plasma is collected for transfusion or further manufacture.

**High-Volume Plasma Exchange (HVP):** HVP is defined as an exchange of 15% of ideal body weight (representing 8–12 L); patient plasma was removed at a rate of 1–2 L per hour with replacement with plasma in equivalent volume.

**Immunoadsorption (IA):** A therapeutic procedure in which plasma of the patient, after separation from the blood, is passed through a medical device which has a capacity to remove immunoglobulins by specifically binding them to the active component (e.g., Staphylococcal protein A) of the device.

**LDL Apheresis:** The selective removal of low-density lipoproteins from the blood with the return of the remaining components. A variety of instruments are available which remove LDL cholesterol based on charge (dextran sulfate and polyacrylate), size (double-membrane filtration), precipitation at low pH (HELP), or immunoadsorption with anti-Apo B-100 antibodies.

**Leukocytapheresis (LCP):** A procedure in which blood of the patient or the donor is passed through a medical device which separates white blood cells (e.g., leukemic blasts or granulocytes), collects the selected cells, and returns the remainder of the patient's or the donor's blood with or without the addition of replacement fluid such as colloid and/or crystalloid solution. This procedure can be used therapeutically or in the preparation of blood components.

**Plasmapheresis:** A procedure in which blood of the patient or the donor is passed through a medical device which separates plasma from other components of blood and the plasma is removed (i.e., less than 15% of total plasma volume) without the use of colloid replacement solution. This procedure is used to collect plasma for blood components or plasma derivatives.

**Platelet Apheresis:** A procedure in which blood of the donor is passed through a medical device which separates platelets, collects the platelets, and returns the remainder of the donor's blood. This procedure is used in the preparation of blood components (e.g., Apheresis platelets).

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

**Rheopheresis:** A therapeutic procedure in which blood of the patient is passed through a medical device which separates high-molecular-weight plasma components such as fibrinogen,  $\alpha_2$ -macroglobulin, low-density lipoprotein cholesterol, and IgM to reduce plasma viscosity and red cell aggregation. This is done to improve blood flow and tissue oxygenation. LDL Apheresis devices and selective filtration devices using two filters, one to separate plasma from cells and a second to separate the high-molecular-weight components, are used for these procedures.

**Therapeutic Plasma Exchange (TPE):** A therapeutic procedure in which blood of the patient is passed through a medical device which separates 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 a combination of crystalloid/colloid solution.

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

Therapeutic Apheresis does not include stem cell collection or harvesting for use in bone marrow/stem cell transplantation. It is usually performed in an outpatient facility and usually requires several hours to complete. In some clinical situations, plasma exchange may be performed daily for at least 1 week.

## CLINICAL EVIDENCE

The American Society for Apheresis (ASFA) (Schwartz, et al., 2016) has reviewed therapeutic apheresis outcomes and published practice guidelines. The guidelines included analysis based on the quality of the evidence as well as the strength of recommendation derived from the evidence. ASFA categorizes disorders as noted below:

- 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. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

ASFA recognized that categories alone are difficult to translate into clinical practice. Thus, they adopted a system to assign recommendation grades for therapeutic apheresis to enhance the clinical value of ASFA categories. The grading recommendation are adopted from Guyatt et al., 2008; Szczepiorkowski et al., 2010 and Schwartz et al., 2016:

- Grade 1A: Strong recommendation, high-quality evidence
- Grade 1B: Strong recommendation, moderate quality evidence
- Grade 1C: Strong recommendation, low-quality or very low-quality evidence
- Grade 2A: Weak recommendation, high quality evidence
- Grade 2B: Weak recommendation, moderate quality evidence
- Grade 2C: Weak recommendation, low-quality or very low-quality evidence

### **Sickle Cell Disease**

Red blood cell exchange or erythrocytapheresis is being increasingly used for transfusion therapy in sickle cell disease (SCD). Many of the studies performed to evaluate this therapy are retrospective studies with small patient population.

Hulbert et al. (2006) conducted a retrospective cohort study of 137 children with sickle cell anemia (SCA) and strokes to test the hypothesis that exchange transfusion at the time of stroke presentation more effectively prevents second strokes than simple transfusion. Children receiving simple transfusion had a 5-fold greater relative risk of second stroke than those receiving exchange transfusions. Interpretation of these findings is limited due to the retrospective design of the study.

Velasquez et al. (2009) retrospectively reviewed red cell exchange (RCE) for the management of acute chest syndrome (ACS) in 44 patients with SCD. Clinical Respiratory Score (CRS) was assigned retrospectively to assess respiratory distress (0 = no distress, > 6 = severe). Median admission CRS of 2, progressed to 4 before RCE and declined to 2 within 24 hr. afterwards. Median day of RCE was day 2 (IQR 1-3) and the main indication was worsening respiratory distress. No patient developed venous thrombosis, alloantibodies or other complications from RCE. According to the authors, RCE appears to be a safe and effective treatment for patients with SCD and ACS. The small study population limits the validity of the conclusion of this study.

Turner et al. (2009) evaluated the efficacy of exchange transfusion (XC) versus simple transfusion (ST) for treatment of sickle cell anemia acute chest syndrome (ACS). Twenty patients who received XC for ACS were compared with 20 patients who received ST. Cohorts were similar with regard to age; sex; prior ACS episodes; echocardiogram results; and antibiotic, bronchodilator, and hydroxyurea use. Maximum temperature recorded was higher in the XC group, but lactate dehydrogenase (LDH), WBCs, and indirect bilirubin were comparable. Admission Hb levels were higher for XC (XC 8.6 g/dL vs. ST 7.4 g/dL,  $p = 0.02$ ) and XC had higher peak Hb levels during hospitalization. No differences were demonstrable in postprocedure length of stay (XC 5.6 days vs. ST 5.9 days) or total length of stay (XC 8.4 days vs. ST 8.0 days). A total of 10.3 +/- 3.0 units were transfused for XC compared to 2.4 +/- 1.2 units for ST. Based on postprocedure length of stay or total length of stay, the authors could not detect a difference in the efficacy of XC compared to ST in populations despite red blood cell product usage fourfold higher in the XC group. According to the authors, there is a need for an adequately powered, randomized trial to examine the true risk-benefit ratio of XC in ACS.

Wahl et al. (2012) compared alloimmunization rates between patients receiving simple or exchange chronic transfusions with erythrocytapheresis (ECP). Data were retrospectively collected for 45 SCD patients (n=23 simple, n=22 ECP) on a chronic transfusion program to determine the rate of antibody formation (antibodies formed per 100 units transfused). The 45 patients received 10,949 units and formed 6 new alloantibodies during the study period; therefore, the overall alloimmunization rate was 0.055 alloantibodies per 100 U. The ECP group received significantly more blood. The rate of antibody formation (auto plus allo) was 0.040 antibodies per 100U in the ECP group and 0.171 antibodies per 100U in the simple transfusion group. The alloantibodies formed per 100 units was 0.013 in the ECP group and 0.143 in the simple transfusion group. The authors concluded that chronic ECP should be considered in patients requiring optimal management of HbS levels and iron burden. The authors stated that concerns about increased alloimmunization with ECP may be unjustified.

The National Heart, Lung, and Blood Institute (NHLBI) published a clinical guideline for the management of sickle cell disease (SCD) that includes the following recommendations relative to therapeutic apheresis (2014):

- In children with SCA, screen annually with TCD according to methods employed in the STOP studies, beginning at age 2 and continuing until at least age 16.
- In children with conditional (170–199 cm/sec) or elevated (>200 cm/sec) TCD results, refer to a specialist with expertise in chronic transfusion therapy aimed at preventing stroke.
- In all persons with SCD, perform urgent exchange transfusion—with consultation from hematology, critical care, and/or apheresis specialists—when there is rapid progression of ACS as manifested by oxygen saturation below 90

percent despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates, and/or decline in hemoglobin concentration despite simple transfusion.

- In consultation with a sickle cell expert, perform exchange transfusion in people with SCD who develop acute stroke confirmed by neuroimaging.
- Initiate prompt evaluation, including neurologic consultation and neuroimaging studies, in people with SCD who have mild, subtle, or recent history of signs or symptoms consistent with transient ischemic attack.
- In children and adults who have had a stroke, initiate a program of monthly simple or exchange transfusions.
- In adults and children with SCA, transfuse RBCs to bring the hemoglobin level to 10 g/dL prior to undergoing a surgical procedure involving general anesthesia.
- In adults and children with HbSC or HbSB+ -thalassemia, consult a sickle cell expert to determine if full or partial exchange transfusion is indicated before a surgical procedure involving general anesthesia.
- Administer iron chelation therapy, in consultation with a hematologist, to patients with SCD and with documented transfusion-acquired iron overload.

### **Professional Societies**

#### **American Society for Apheresis (ASFA)**

Regarding sickle cell disease, ASFA states:

- Red blood cell (RBC) exchange is an option for patients with acute ischemic stroke, acute chest syndrome (ACS), or multiorgan failure.
- RBC exchange is also recommended as a prophylaxis for primary or secondary stroke.
- Advantages of RBC exchange over simple transfusion (S-Tx) through randomized controlled clinical trials have not been documented.
- Long-term RBC exchange has the distinctive advantage of preventing or markedly reducing transfusional iron accumulation, but is associated with significantly higher (1.5 to 3 times higher) blood requirements than S-Tx.
- Increased blood donor exposure can potentially increase rates of viral transmission and RBC alloimmunization. Strategies to reduce the risk of alloimmunization include the use of racially- and partial phenotypically-matched RBC. (Schwartz et al., 2016)

#### **Desensitization for Renal Transplants**

Plasmapheresis has been used prior to renal transplants in highly sensitized patients to remove human leukocyte antigen (HLA) antibodies. Desensitization protocols use high dose intravenous immunoglobulin (IVIG) or low dose IVIG with plasmapheresis to convert a positive crossmatch to a negative crossmatch and allow for transplantation. Plasmapheresis may continue after the transplant or be reserved for posttransplant treatment of acute antibody mediated rejection (AMR). Clinical trials have demonstrated that living or deceased donor kidney recipients treated with plasmapheresis and IVIG have beneficial outcomes.

Yuan et al. (2010) evaluated the efficacy of plasmapheresis plus low-dose IVIG in highly sensitized patients waiting for a deceased-donor renal transplant. Thirty-five highly sensitized patients (HLA class I panel reactive antibody greater than 50%) received plasmapheresis, plus low-dose IVIG treatment. In 25 patients (group 1), a positive T- and/or B-cell cytotoxicity crossmatch became negative by plasmapheresis plus low-dose IVIG treatment. Two patients did not receive renal transplants due to persistent positive crossmatch. Eight patients already had a negative crossmatch before desensitization. During the same time, 32 highly sensitized patients (group 2), without desensitization, had a negative crossmatch and received deceased-donor renal transplants. Group 1 showed a numerically higher rate of acute rejection (32.0% vs. 21.9%) and AMR (20.0% vs. 9.4%), but the difference was not statistically significant. Comparable mean serum creatinine levels at 24 months were observed. No difference in Kaplan-Meier graft survival was found between group 1 and group 2 after follow-up of 52 +/- 26 months. The authors concluded that desensitization with plasmapheresis plus low-dose IVIG enables successful deceased-donor renal transplant in highly sensitized patients with a positive crossmatch. AMR occurred predominantly in recipients with donor-specific antibodies of high titers.

Meng et al. (2009) determined the percentage of panel reactivity and specificity of anti-HLA immunoglobulin (IgG) antibodies in 73 presensitized renal allograft recipients who underwent cadaveric renal transplantation compared with 81 unsensitized recipients who received cadaveric renal transplantation (control group). Sensitized patients had higher rates of graft rejection and graft loss. A total of 20 out of the 73 patients received pre-transplantation plasmapheresis (PP) and/or immunoadsorption (IA) and of these, 10 achieved negative panel reactive antibodies (PRAs). Graft rejection rate was 18% in unsensitized group, 41% in non-PP and/or IA sensitized group, and 20% in PP and/or IA sensitized group. Graft loss rate was 5% in unsensitized group, 21% in non-PP and/or IA sensitized group, and 15% in PP and/or IA sensitized group (20% positive PRA at transplant and 10% negative PRA at transplant). The authors concluded that pre-transplant PRA preparations might improve the access of presensitized patients to renal donors.

Montgomery et al. (2011b) used mathematical simulations verified by actual data from several national kidney-paired donation (KPD) programs to evaluate which donor/recipient phenotypes are likely to benefit from each transplant modality. They found that pairs that are easy to match are likely to receive compatible kidneys in a KPD. Those who

are hard to match may be better served by desensitization with high-dose IVIG or plasmapheresis and low-dose IVIG. The phenotype which is both hard to match and hard to desensitize due to board and strong HLA reactivity are most likely to be transplanted by a hybrid modality utilizing desensitization after identifying a more immunologically favorable donor in a KPD. The authors state that recent outcomes from desensitization in which starting donor-specific antibody strength is low have been very good. For broadly sensitized patients with a high-strength cross-match, searching for a better donor in a KPD pool can facilitate a safer and more successful desensitization treatment course.

Montgomery et al. (2011a) used a protocol that included plasmapheresis and the administration of low-dose IVIG to desensitize 211 human leukocyte antigen (HLA)-sensitized patients who underwent live-donor renal transplantation (treatment group). The rates of death were compared between the group undergoing desensitization treatment and 2 carefully matched control groups of patients on a waiting list for kidney transplantation who continued to undergo dialysis (dialysis-only group) or who underwent either dialysis or HLA-compatible transplantation (dialysis-or-transplantation group). In the treatment group, Kaplan-Meier estimates of patient survival were 90.6% at 1 year, 85.7% at 3 years, 80.6% at 5 years, and 80.6% at 8 years, as compared with rates of 91.1%, 67.2%, 51.5%, and 30.5%, respectively, for patients in the dialysis-only group and rates of 93.1%, 77.0%, 65.6%, and 49.1%, respectively, for patients in the dialysis-or-transplantation group. The authors concluded that live-donor transplantation after desensitization provided a significant survival benefit for patients with HLA sensitization, as compared with waiting for a compatible organ. By 8 years, this survival advantage more than doubled. According to the authors, plasmapheresis does not result in a durable reduction in HLA antibody unless the patient undergoes transplantation within several days after the last treatment. This factor accounts for the paucity of reports of protocols that use plasmapheresis to desensitize patients who are on the waiting list for a transplant from a deceased donor.

### **Pediatric ABO-Incompatible Heart Transplantation**

Dipschand et al. (2010) conducted a non-randomized prospective observational single institution study comparing clinical outcomes over 10 years of the largest cohort of ABO-incompatible recipients. ABO-incompatible (n=35) and ABO-compatible (n=45) infant heart transplantation recipients ( $\leq 14$  months old, 1996-2006) showed no important differences in pretransplantation characteristics. In 7 patients, donor-specific isohemagglutinin titers were elevated at the time of transplantation, but were significantly reduced using intraoperative plasma exchange. Only 2 of the 7 required treatment for AMR (which occurred early posttransplantation, was easily managed and did not recur in follow-up). Occurrence of graft vasculopathy (11%), malignancy (11%) and freedom from severe renal dysfunction were identical in both groups. Survival was identical (74% at 7 years post-transplantation). The researchers concluded that ABO-blood group incompatible heart transplantation has excellent outcomes that are indistinguishable from those of the ABO-compatible population and there is no clinical justification for withholding this lifesaving strategy from all infants listed for heart transplantation. Further studies into observed differing responses in the development of donor-specific isohemagglutinins and the implications for graft accommodation are warranted.

Issitt et al. (2012) performed a retrospective analysis of all elective ABO-incompatible heart transplants performed at a single center from January 2001 - January 2011. Data included underlying conditions and demographics of the patients, the isohemagglutinin titer before and after plasma exchange, and survival figures to date. Twenty-one patients (ages 3-44 months) underwent ABO-incompatible heart transplantation. All patients underwent a "3 times" plasma exchange before transplantation, requiring exchange volumes of up to 3209 mL. Isohemagglutinin titers that were as high as 1:32 preoperatively were reduced to a range of 0-1:16 posttransplantation. One patient expired from causes unrelated to organ rejection. The authors concluded that through the use of a combination of adult reservoir/pediatric oxygenator and extracorporeal circuit, ABO-incompatible plasma exchange transfusions can be undertaken safely using a simplified "3 times" method, reducing the circulating levels of isohemagglutinins while providing minimal circuit size. This allows ABO-incompatible heart transplantation in a broader patient population than reported previously.

### **Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Sydenham's Chorea**

Sigra et al. (2018) conducted a systematic review of published peer reviewed literature which addressed treatment for PANDAS and related disorders. Twelve studies (N = 529) as well as 240 case reports were identified. Treatments evaluated in these studies included IVIG, TPE, antibiotics, cognitive behavior therapy, and tonsillectomy. The authors determined that the studies generally had a high risk of bias and the results were inconclusive. Further rigorous research is needed.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and Sydenham's Chorea (SC) are pediatric post-infectious autoimmune neuropsychiatric disorders. Both share an array of neuropsychiatric symptoms and both may have a shared etiopathogenesis. Because of the possible role of antineuronal antibodies in the pathogenesis, antibody removal by therapeutic plasma exchange (TPE) may be effective. However, the mechanism for the benefit of TPE is not clear, as there is a lack of relationship between therapeutic response and the rate of antibody removal. (Szczepiorkowski et al., 2010)



Eighteen patients were entered into a randomized controlled trial designed to determine if IVG or plasma exchange would be superior to prednisone in decreasing the severity of chorea. Mean chorea severity for the entire group was significantly lower at the 1-month follow-up evaluation (overall 48% improvement). Although the between-group differences were not statistically significant, clinical improvements appeared to be more rapid and robust in the IVIG and plasma exchange groups than in the prednisone group (mean chorea severity scores decreased by 72% in the intravenous immunoglobulin group, 50% in the plasma exchange group, and 29% in the prednisone group). According to the authors, larger studies are required to confirm these clinical observations and to determine if these treatments are cost-effective for this disorder. (Garvey, 2005)

Studies failed to provide convincing evidence that plasma exchange is effective for treating pediatric autoimmune neuropsychiatric disorders associated with streptococcus infection and Sydenham chorea. Additional studies are needed to determine if plasma exchange is a useful for treating these conditions.

### **Rheumatoid Arthritis**

In a single institution observational study, Kitagaichi et al. evaluated the efficacy of treatment on 85 individuals with rheumatoid arthritis (RA) using leukocytapheresis (LCAP) and drug therapy initiated between 2006 and 2015. Participants received LCAP once a week for up to 5 weeks. The clinical response was evaluated at the completion of the series and again 4 weeks later using the American College of Rheumatology (ACR) criteria and the 28-joint disease activity score (DAS28) of the European League Against Rheumatism (EULAR). Marked decreases were seen in tender joint count, swollen joint count, and CRP level, and the DAS28-CRP was significantly improved from before to after LCAP. The authors concluded that leukocytapheresis is a safe and worthy therapy for individuals with intractable RA where there is drug allergy or other complications. ACR20 response was 61%, and efficacy persisted to 4 weeks after LCAP completion. (2016)

Roth (2004) conducted a noninterventional prospective study on 91 patients with RA who qualified for ProSORBA column apheresis therapy (PCT) per the package insert and completed the 12 prescribed treatments. An initial baseline assessment was performed prior to first treatment and then up to 4 additional assessments were performed at weeks 9, 16, 20, and 24. Criteria from the ACR (ACR20) were noted in order to assess response rate, and commercial adverse event (AE) reporting was used to record serious/unanticipated AEs. There was a ACR20 (or greater) response rate of 53.8% in these patients with previously refractory RA. The individual criteria showed a much greater improvement than reflected by ACR20; for example, this response included a 52% improvement in joint tenderness, 40% improvement in swelling, 42% improvement in patient's pain, 38% improvement in patient's global response, and 48% improvement in physician's global scores (76% of responders had measured ACR20 by Week 16 and 100% by Week 24). Some patients stated that they felt improvement began closer to the 6th week. Most responders were concurrently taking biologics or DMARD, e.g., methotrexate and etanercept, despite previously inadequate RA response to those medications. The author concluded that this postmarketing study of PCT used commercially in 59 rheumatology practice settings supports the safety and efficacy of this treatment regime in selected patients with refractory RA and compares favorably with the initial sham controlled clinical trial. PCT is a relatively underutilized choice for the management of active, aggressive RA.

Furst et al. (2000) conducted a double-blind, randomized, placebo controlled study to determine the efficacy of the ProSORBA Immunoabsorption Column in patients with refractory RA. Ninety nine patients received 12 weekly procedures after being randomized to the active treatment arm or to the sham treatment arm (apheresis only). Evaluations were double-blinded and occurred at baseline and periodically for 24 weeks thereafter. Primary efficacy was assessed at 7 and 8 weeks after the completion of 12 treatments (at trial weeks 19 and 20) using the ACR definition of improvement, and results from the assessments at weeks 19 and 20 were averaged. Analysis of patients who completed all treatments and follow-up indicated that 15 of 36 (41.7%) ProSORBA-treated patients responded compared to 5 of 32 (15.6%) sham-treated patients. Common AEs included joint pain, fatigue, joint swelling, and hypotension. There was no significant increase in AEs in ProSORBA-treated patients compared to sham-treated patients. The authors concluded that immunoabsorption therapy was proven to be a new alternative in patients with severe, refractory disease.

### **High Density Lipoprotein (HDL) Delipidation**

Low levels of HDL are associated with increased risk of cardiovascular disease. Researchers posit that plasma selective delipidation converts alpha-HDL to pre-beta-like HDL, the most effective form of HDL for lipid removal from arterial plaques. However, there is a paucity of clinical evidence regarding HDL delipidation for various cardiac disease indications, including acute coronary syndrome (ACS). A search of the peer-reviewed medical literature identified one placebo-controlled RCT (n=28). (Waksman et al., 2010) This study sought to determine whether serial autologous infusions of selective HDL delipidated plasma are feasible and well tolerated in patients with ACS. Patients undergoing cardiac catheterization were randomized to either 7 weekly HDL selective delipidated or control plasma apheresis/reinfusions. Patients underwent intravascular ultrasound (IVUS) evaluation of the target vessel. All reinfusion sessions were tolerated well by all patients. The levels of prebeta-like HDL and alphaHDL in the delipidated plasma converted from 5.6% to 79.1% and 92.8% to 20.9%, respectively. The IVUS data demonstrated a numeric

and non-significant trend toward regression in the total atheroma volume in the delipidated group compared with an increase of total atheroma volume in the control group. Study results demonstrated that serial autologous infusions of selective HDL delipidated plasma is clinically feasible and well tolerated. Study limitations included small study population and lack of appropriate blinding methods. The study may not have been sufficiently powered to detect differences between treatment and controls. Additional well-designed studies are necessary to determine the ability of HDL delipidation and plasma reinfusion to improve patient-relevant clinical outcomes, such as the reduction of cardiovascular events and increased overall survival.

There is a clinical trial registered but not yet recruiting on HDL Acute Lipid Optimization in Homozygous Familial Hypercholesterolemia. For more information, please go to [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### **Inflammatory Bowel Disease**

A large-scale, prospective, observational study was performed by Yokoyama et al. (2014) which enrolled patients from 116 medical facilities in Japan with active ulcerative colitis (UC) treated with leukocytapheresis. Out of 847 patients, 623 were available for efficacy analysis. 80.3% of the patients had moderate to severe disease activity, and 67.6% were steroid refractory. Concomitant medications, 5-aminosalicylic acids, corticosteroids, and thiopurines were administered to 94.8%, 63.8%, and 32.8% of the patients, respectively. In addition, infliximab and tacrolimus were concomitantly used in 5.8% and 12.3%, respectively. Intensive leukocytapheresis ( $\geq 4$  leukocytapheresis sessions within the first 2 weeks) was used in  $>70\%$  of the patients. Adverse events were seen in 10.3%, which were severe in only 5 patients. Any concomitant medications did not increase the incidence of adverse events. The authors concluded that that leukocytapheresis, including intensive procedure, is a safe and effective therapeutic option for active UC. However, this study did not translate research data into clinical guidelines that can be used to improve physician decision-making and patient care.

Eberhardson et al. conducted a randomized, double-blind, placebo-controlled trial to evaluate safety, tolerability, and immunological response when selectively removing circulating CCR9-expressing monocytes via leukapheresis in individuals with moderate to severe UC. Fourteen individuals made up the active treatment group, and 8 were in the placebo group. Participants were treated every second day with leukapheresis during 5 sessions. No major safety concerns were raised and the procedure was well tolerated. Eight of 14 patients (57.1%) in the active treatment group responded compared with 3 of 8 (37.5%) in the placebo group. The authors concluded that this trial demonstrated that activated monocytes could be removed from UC patients safely and efficaciously via leukapheresis. With this being the first trial of its kind in humans, further studies with larger participant groups are needed.

The National Institute for Health and Care Excellence (NICE) published a report in 2009 on the efficacy and safety of Extracorporeal Photopheresis (ECP) for Crohn's disease. The evidence base consisted primarily of 1 case-series study with 28 patients. The results of the study indicated that ECP leads to improved quality of life, reduction in bowel motion frequency and abdominal cramps, reduced steroid use, and reduction in inflammatory markers. Two of the 28 patients included in the study discontinued treatment due to adverse events. NICE recommended that ECP should not be used outside the context of research for Crohn's disease for both adults and children.

Four clinical trials studying therapeutic apheresis and inflammatory bowel disease have been completed but results have not yet been published. For more information, please go to [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### **Professional Societies**

#### ***American Academy of Neurology (AAN)/MS Council for Clinical Practice***

The Therapeutics and Technology Assessment Subcommittee of the AAN and the MS Council for Clinical Practice Guidelines issued a report on disease-modifying therapies in MS. The subcommittee concluded that "on the basis of consistent class I, II, and III studies, plasma exchange is of little or no value in the treatment of progressive MS." The AAN guideline also states that on the basis of a single small Class I study, it is considered possible that plasma exchange may be helpful in the treatment of severe acute episodes of demyelination in previously non-disabled individuals. (Goodin et al., 2002)

A guideline from the AAN assessing the role of plasmapheresis in the treatment of neurologic disorders states that plasmapheresis is established as effective for severe acute inflammatory demyelinating polyneuropathy (AIDP)/Guillain-Barré syndrome (GBS) as well as in the short-term management of chronic inflammatory demyelinating polyneuropathy. 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. Plasmapheresis is established as ineffective and should not be offered for chronic or secondary progressive MS. Plasmapheresis is probably not effective and should not be considered for neuropathy associated with immunoglobulin M gammopathy (IgM). Plasmapheresis is possibly effective and may be considered for acute fulminant demyelinating CNS disease. There is insufficient evidence to support or refute the use of plasmapheresis for myasthenia gravis, pediatric autoimmune neuropsychiatric disorders associated with streptococcus infection, and Sydenham chorea. (Cortese et al., 2011. Updated 2016)

The AAN evidence based guidelines on the clinical evaluation and treatment of transverse myelitis state that plasma exchange may be considered in patients who fail to improve after corticosteroid treatment. (Scott, et al., 2011. Reaffirmed 2016)

### **European Federation of Neurological Societies (EFNS)**

In a guideline for the treatment of MS relapses, the EFNS states that patients with inflammatory demyelination, including patients with MS, who have not responded to treatment with methylprednisolone may benefit from plasma exchange treatment, but only about one-third of treated patients are likely to respond. This treatment regimen should probably be restricted to a subgroup of patients with severe relapses (level B recommendation). A randomized, controlled study specifically addressing the effect of plasma exchange in patients with severe relapses of MS not responding to methylprednisolone treatment would be desirable. (Sellebjerg et al., 2005)

### **National Institute of Neurological Disorders and Stroke (NINDS)**

The Neuromyelitis Optica (NMO) information page states that relapses and attacks of NMO (also known as Devic Syndrome) are often treated with corticosteroids and plasma exchange. (National Institutes of Health, May 2017)

### **National Institute for Health and Care Excellence (NICE)**

NICE clinical guidelines on the management of MS in adults do not address any type of therapeutic apheresis. (2014)

### **National Comprehensive Cancer Network (NCCN)**

Guidelines on acute myeloid leukemia indicate that leukapheresis is not recommended in the routine management of patients with a high WBC in acute promyelocytic leukemia (APL). However, in life threatening cases with leukostasis that is not responsive to other modalities, leukapheresis can be considered with caution. (NCCN,2017)

### **Additional Search Terms**

Photoimmune therapy, photoimmunotherapy

## **U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Devices for therapeutic apheresis are regulated by the FDA as Class II or III devices depending on whether they rely on centrifugation or filtration of blood. Devices that separate blood cells from plasma by filtration are Class III devices that are subject to the most extensive regulations enforced by the FDA.

For additional information, search product code LKN (separator, automated, blood cell and plasma, therapeutic) at the following website: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmnm.cfm>. (Accessed March 22, 2018)

The FDA has granted premarket approval (PMA) to one extracorporeal photopheresis (ECP) device, the UVAR Photopheresis System (Therakos, Inc., Exton, PA, USA). This system is currently only approved for the palliative treatment of skin manifestations resulting from cutaneous T-cell lymphoma (CTCL), which are unresponsive to other treatments. Therakos now markets a second generation of the system under the name UVAR XTS. The UVAR XTS system utilizes the photoactive drug, UVADEX (8-methoxsalen), also manufactured by Therakos and approved by FDA for the same indication. For additional information, search product code LNR at the following website: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>. (Accessed March 22, 2018)

UVADEX was granted Orphan Drug Status "for use in conjunction with the UVAR photopheresis [system] to treat diffuse systemic sclerosis" in June 1993 and "for use in conjunction with the UVAR photopheresis system to treat graft versus host disease [GVHD]" in October 1998. In addition, UVADEX was granted Orphan Drug Status "for the prevention of acute rejection of cardiac allografts" in May 1994. Additional information is available at the following website: <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>. (Accessed March 22, 2018)

### **Additional Medical Products**

Haemonetics Therapeutic Plasma Exchange Set, Fresenius P1r Plasma Treatment Set, Cobe Spectra™ Blood Component Separator, Plasma Separation System, Heparin-Induced Extracorporeal Lipoprotein Precipitation (H.E.L.P.) System, Liposorber LA-15 System, LDL-Therasorb, Prosorba.

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2018T0136X]

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**POLICY HISTORY/REVISION INFORMATION**

Date	Action/Description
11/01/2018	<ul style="list-style-type: none"> <li>• Reorganized policy template:               <ul style="list-style-type: none"> <li>○ Simplified and relocated <i>Instructions for Use</i></li> <li>○ Removed <i>Benefit Considerations</i> section</li> </ul> </li> <li>• Updated coverage rationale; modified language to clarify the listed services are:               <ul style="list-style-type: none"> <li>○ Proven <b>and</b> medically necessary (as described)</li> <li>○ Unproven <b>and</b> not medically necessary (as described)</li> </ul> </li> <li>• Archived previous policy version OUTPATIENT 049.12 T1</li> </ul>

**INSTRUCTIONS FOR USE**

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.