

# Apheresis (for Kentucky Only)

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[Instructions for Use](#)

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**Related Policy**

- [Prolotherapy and Platelet Rich Plasma Therapies \(for Kentucky Only\)](#)

## Application

This Medical Policy only applies to the state of Kentucky.

## Coverage Rationale

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

- Acute inflammatory demyelinating polyneuropathy, primary treatment
- Acute liver failure (requiring High Volume Therapeutic Plasma Exchange (TPE-HV))
- Anti-glomerular basement membrane disease
  - Dialysis independent
  - Diffuse alveolar hemorrhage
- Chronic acquired demyelinating polyneuropathies
  - IgG/IgA/IgM related
  - Anti-myelin-associated glycoprotein
- Chronic inflammatory demyelinating polyneuropathy
- Cryoglobulinemia, second line therapy
- Cutaneous T-cell lymphoma; erythrodermic mycosis fungoides; Sézary syndrome
- Dilated cardiomyopathy, idiopathic, New York Heart Association Class II-IV, via Immunoabsorption
- Erythrocytosis, polycythemia vera
- Familial hypercholesterolemia
  - Homozygotes, lipoprotein apheresis
  - Homozygotes, lipoprotein apheresis; second line therapy
  - All patients via therapeutic Plasma Exchange (TPE)
- Focal segmental glomerulosclerosis, recurrent in transplanted kidney, second line therapy
- Graft-versus-host disease
  - Acute
  - Chronic, second line therapy
- Hereditary hemochromatosis

- Hypertriglyceridemic pancreatitis, severe
- Hyperviscosity in hypergammaglobulinemia
- Inflammatory bowel disease, ulcerative colitis/Crohn's disease via [Adsorptive Cytapheresis](#)
- Lipoprotein(a) hyperlipoproteinemia
- Multiple sclerosis, acute attack or relapse, second line therapy
- Myasthenia gravis, acute
- Myeloma cast nephropathy, second line therapy
- Neuromyelitis optica spectrum disorders, acute or relapse, second line therapy
- N-methyl D-aspartate receptor antibody encephalitis
- Pediatric autoimmune neuropsychiatric disorders, PANDAS/PANS exacerbation
- Peripheral vascular diseases
- Progressive multifocal leukoencephalopathy associated with natalizumab
- Pruritus due to hepatobiliary diseases, treatment resistant
- Rheumatoid arthritis, refractory, second line therapy
- Sickle cell disease
  - Acute stroke or multiorgan failure
  - Acute chest syndrome, severe, second line therapy
  - Stroke prophylaxis
  - Individuals requiring chronic transfusion (receiving transfusions once every 5 weeks or more frequently)
- Thrombotic microangiopathy, thrombotic thrombocytopenic purpura (TTP)
- Transplantation, heart, second line therapy
  - Cellular rejection
  - Recurrent rejection
  - Desensitization
  - In children less than 40 months of age, ABO incompatible
  - Rejection prophylaxis via therapeutic Plasma Exchange
- Transplantation, hematopoietic stem cell, ABO incompatible, second line therapy
  - Hemopoietic progenitor cells collected from marrow (HPC(M))
  - Hemopoietic progenitor cells collected by apheresis (HPC(A))
- Transplantation, Kidney, ABO compatible
  - Antibody mediated rejection
  - Desensitization/prophylaxis living donor
- Transplantation, Kidney, ABO incompatible, second line therapy
  - Antibody mediated rejection
  - Desensitization, living donor
- Transplantation, Liver, desensitization, ABO incompatible, living donor, via therapeutic Plasma Exchange
- Transplantation, Lung
  - Bronchiolitis obliterans syndrome
  - Chronic lung allograft dysfunction
- Vasculitis, Antineutrophil cytoplasmic antibodies (ANCA) -associated
  - Microscopic polyangiitis
  - Granulomatosis with polyangiitis
- Voltage gated potassium channel antibody-related diseases
- Wilson's disease, fulminant

**Due to insufficient evidence of efficacy, [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:**

- Acute disseminated encephalomyelitis (ADEM)
- Acute liver failure and acute fatty liver of pregnancy (requiring TPE)
- Acute toxins, venoms and poisons
- Age related macular degeneration, dry
- Alzheimer's disease (mild or moderate)
- Amyloidosis, systemic, dialysis related

- ANCA-associated rapidly progressive glomerulonephritis, dialysis independent (Granulomatosis with polyangiitis; and Microscopic Polyangiitis)
- Anti-glomerular basement membrane disease, dialysis dependent, without diffuse alveolar hemorrhage
- Atopic dermatitis, recalcitrant
- Autoimmune dysautonomia
- Autoimmune hemolytic anemia; severe warm autoimmune hemolytic anemia (WAIHA); severe cold agglutinin disease
- Babesiosis, severe
- Burn shock resuscitation
- Cardiac neonatal lupus
- Catastrophic antiphospholipid syndrome/Hemolytic uremic syndrome
- Chronic acquired demyelinating polyneuropathies, CANOMAD/CANDA
- Chronic focal encephalitis
- Coagulation factor deficiency and inhibitors
- Complex regional pain syndrome
- Cryoglobulinemia
- Cutaneous T-cell lymphoma; mycosis fungoides, non-erythrodermic
- Dilated cardiomyopathy, idiopathic, New York Heart Association Class II-IV, via TPE
- Erythropoietic protoporphyria, liver disease
- Focal segmental glomerulosclerosis, steroid resistant in native kidney via TPE or lipoprotein apheresis for all types
- Hemophagocytic lymphohistiocytosis
- Heparin induced thrombocytopenia and thrombosis
- Hyperleukocytosis
- Hypertriglyceridemic pancreatitis, prevention of relapse
- Idiopathic inflammatory myopathies, including anti-synthetase-syndrome, clinically amyopathic dermatomyositis and immune-mediated necrotizing myopathies
- IgA nephropathy
- Immune checkpoint inhibitors, immune-related adverse events
- Immune thrombocytopenia, refractory
- Inflammatory bowel disease, Crohn's disease, via Extracorporeal Photopheresis
- Lambert-Eaton myasthenic syndrome
- Malaria
- Multiple sclerosis, chronic
- Myasthenia Gravis, long term treatment
- Myeloma cast nephropathy
- Nephrogenic systemic fibrosis
- Neuromyelitis optica spectrum disorders, maintenance
- Paraneoplastic autoimmune retinopathies
- Paraneoplastic neurologic syndromes
- Pemphigus vulgaris
- Phytanic acid storage disease
- Post transfusion purpura
- Psoriasis
- Red blood cell alloimmunization, pregnancy complications
- Sepsis with multiorgan failure
- Sickle cell disease (unless noted above as proven)
- Steroid-responsive encephalopathy associated with autoimmune thyroiditis
- Stiff-person syndrome
- Sudden sensorineural hearing loss
- Sydenham's chorea, severe
- Systemic lupus erythematosus, severe complications
- Systemic sclerosis
- Thrombocytosis
- Thrombotic microangiopathy
  - Coagulation mediated (THBD, DGKE and PLG mutations)
  - Complement mediated (Factor H autoantibody and complement factor gene mutations)

- Drug associated (Ticlopidine, Clopidogrel, Gemcitabine, Quinine)
- Infection associated (STEC-HUS, severe; pHUS)
- Pregnancy associated, severe; extremely preterm preeclampsia, severe
- Transplantation associated
- Thyroid storm
- Toxic epidermal necrolysis
- Transplantation, Heart
  - Rejection prophylaxis via extracorporeal Photopheresis
  - Antibody mediated rejection
- Transplantation, hematopoietic stem cell ABO incompatible:
  - Minor ABOi HPC(A)
  - Pure red cell aplasia
- Transplantation, hematopoietic stem cell, HLA desensitization
- Transplantation, Intestine
- Transplantation, Liver
  - Desensitization, ABO incompatible, deceased donor
  - Antibody mediated rejection
  - Immune suppression withdrawal
  - Desensitization, ABO Incompatible, via extracorporeal Photopheresis
- Transplantation, Lung,
  - Antibody mediated rejection
  - Desensitization
- Vaccine-induced immune thrombotic thrombocytopenia
- Vasculitis, ANCA-associated, eosinophilic granulomatosis with polyangiitis
- Vasculitis, IgA:
  - Crescentic rapidly progressive glomerulonephritis
  - Severe extra-renal manifestations
- Vasculitis
  - Hepatitis B polyarteritis nodosa
  - Kawasaki disease
  - Multisystem inflammatory syndrome in children

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

## Definitions

**Photopheresis:** A procedure where blood is removed from the body, treated with ultraviolet light and medications that are activated by the ultraviolet light, then reinfused into the body (National Cancer Institute, 2021).

**Plasma Exchange:** A procedure that involves the use of a machine to separate and remove the plasma from the blood cells and then replace the plasma with a solution prior to reinfusion into the patient. Also called Plasmapheresis (National Cancer Institute, 2021).

**Therapeutic Apheresis:** A procedure in which blood is collected, part of the blood (such as platelets or white blood cells) are removed, and the remaining components of the blood are reinfused into the body. It is a general term which includes all apheresis- based procedures; also called pheresis (National Cancer Institute, 2021, Schwartz, et al., 2016, Connelly-Smith, et al. 2023).

## 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 and Guidelines 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

*CPT® is a registered trademark of the American Medical Association*

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

## Description of Services

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 one week.

**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.

**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.

**Double Filtration Plasmapheresis (DFPP):** A two-step procedure that removes pathogenic substances from plasma where membrane plasma separation is followed by plasma filtration. The procedure is used for elimination of autoantibodies, immune complexes or lipoproteins.

**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.

**Low-density lipoprotein (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.

**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).

**Red Blood Cell (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.

**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.

## Clinical 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.

Wade et al. (2022) performed a retrospective chart review of pediatric patients with SCD receiving chronic red cell exchange (RCE) over 3 years to determine the frequency of adverse events (AEs) and identify procedural and patient AE risk factors. AE incidence, AE rate, incident rate ratios (IRRs), and relative risks (RR) were calculated based on various procedural and patient characteristics by univariable (UV) and multivariable (MV) analyses. In 38 patients receiving 760 procedures, there were 150 (19.7%) AEs, of which 36 (4.7%) were symptomatic AEs. The rate of AEs was 20.2 per 100 person-months [95% CI 17.2, 23.6], and the rate of symptomatic AEs was 4.8 per 100 person-months [95% CI 3.49, 6.70]. AE incidences were hypocalcemia (117; 15.4%), dizziness (22; 3.0%), hypotension (15; 2.0%), and nausea (14; 1.8%). Patients with a baseline Hct  $\geq$  30% experienced more total AEs and symptomatic AEs. Pre-procedure initial systolic BP < 50th percentile and patients with severe CNS vasculopathy and non SCA phenotype (i.e., HbSC or S $\beta$ + thalassemia) were associated with an increase in total AEs. IHD depletion was not associated with an increased incidence of AEs or symptomatic AEs. The authors concluded that patients with SCD and HCT  $\geq$  30%, systolic BP < 50th percentile, severe CNS vasculopathy and possibly non-SCA genotype may be at higher risk for RCE-related AEs. The effect of isovolemic hemodilution (IHD) on AE risk is likely minimal. Individualized AE risk assessment should be performed in all patients with SCD undergoing chronic automated RCE.

A systematic review and meta-analysis by Mukherjee et al. (2022) was performed to evaluate the efficacy and safety profile of automated red cell exchange (aRBX) procedure over manual red cell exchange transfusion (MET) in patients with SCD. A



standard meta-analysis protocol was developed, and after performing a comprehensive literature search in PubMed/MEDLINE, Cochrane and International Clinical Trial Registry Platform (ICTRP), reviewers assessed eligibility and extracted data from nine relevant studies. A random effects model was used to estimate the pooled effect size calculated from the mean difference in hemoglobin S (HbS) percentage, serum ferritin level and risk ratio for the AEs. Quality assessment was done using the risk-of-bias assessment tool, and a summary of observations was prepared using standard Cochrane methodology with GradePro GDT. The random-model analysis revealed a mean difference of 4.10 (95% CI: -3.29-11.49; Z = 1.09; p = 0.28) for HbS percentage, mean difference of 435.29 (95% CI: -73.74-944.32; Z = 1.68; p = 0.09) for serum ferritin and pooled risk ratio of 1.35 (95% CI: 0.63-2.87; Z = 0.77; p = 0.44) for ADs. The authors concluded that this meta-analysis did not reveal any benefit of aRBX in reducing HbS percentage and attenuating the serum ferritin level when compared with MET. There was also no significant increased risk of AEs detected in association with aRBX. The Fasano et al. (2016) publication previously cited in this policy was included in this systematic review study.

Hequet et al. (2021) completed a prospective case series to evaluate the clinical safety of the red blood cell (RBC) exchange (RCE)/RBC-primed procedure in 12 children with sickle cell anemia (SCA) and low-body weight (< 20 kg) under either a chronic RCE program or emergency treatment over 65 sessions. The authors monitored grade 2 AEs such as a decrease in blood pressure, increase in heart rate, fainting sensation, or transfusion reactions and identified the critical times during the sessions in which AEs could occur. Post-apheresis hematocrit (Hct) and a fraction of cell remaining (FCR) values were compared to the expected values. They also compared the impact of automatic RCE (n = 7) vs. RCE/RBC-primed (n = 8) on blood viscosity and RBC rheology. A low incidence of complications was observed in the 65 RCE sessions with only seven episodes of transient grade 2 AEs. Post-apheresis Hct and FCR reached expected values with the RCE/RBC-primed method. Both the automatic and priming procedures improved RBC deformability and decreased the sickling tendency during deoxygenation. Blood rheological features improved in both RCE/RBC-primed and automatic RCE without priming conditions. The authors concluded that RCE/RBC-primed procedure provides blood rheological benefits, and is safe and efficient to treat, notably in young children with SCA in prophylactic programs or curatively when a SCA complication occurs.

Cochrane has published systematic reviews for the use of transfusion therapies, including simple or exchange transfusions, for the treatment of complications of SCD including chronic chest complications (Estcourt et al., 2019) and intrahepatic cholestasis (Martí-Carvajal and Martí-Amarista, 2020). In both of these systematic reviews, the authors could not find any published randomized controlled trials to evaluate the use of transfusion therapies in these instances. The authors recommend randomized controlled trials looking at the safety and efficacy of transfusion therapies compared to current standard therapies for these complications of SCD.

Wahl et al. (2012) compared alloimmunization rates between patients receiving simple or exchange chronic transfusions with erythrocytapheresis (ECP). Data were retrospectively collected for 45 patients with SCD (n = 23 simple, n = 22 ECP) who received blood transfusion of 10 to 15 ml of red blood cells (RBCs)/kg with each transfusion every three to four weeks 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 six new alloantibodies during the study period; therefore, the overall alloimmunization rate was 0.055 alloantibodies per 100U. 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.

In a single center retrospective case series, Venkateswaran et al. (2011) performed chart reviews on 93 patients to evaluate the incidence of allo- and auto-immunization to red cell antibodies in patients with SCD who were started on chronic red cell transfusion (RCT). Each patient received RCTs every three to four weeks for a minimum of six months with a total of 4,472 packed red blood cell units being administered. The authors reported that nine patients (9%) had red cell antibodies prior to the initiation of chronic RCT and 23 patients (24%) developed one or more red cell antibodies during chronic RCT. The authors concluded that limited red cell antigen matching is effective for reducing the incidence of allo- and auto-immunization in chronically transfused children with SCD and that RCE does not appear to increase the risk of allo- or auto-immunization, despite exposure to more red cell units.

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 SCA 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 post procedure 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 post procedure 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.

Hulbert et al. (2006) conducted a retrospective cohort study of 137 children with 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.

## Desensitization for Kidney 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.

Chen et al. (2022) conducted a retrospective study to investigate and analyze the clearance effects of desensitization therapy on HLA antibodies to provide a reference for the formulation of clinical desensitization therapy regimens. Twenty-seven individual recipients of kidney transplant who received preoperative/postoperative desensitization therapy based on Protein A immunoadsorption (PA-IA) therapy in combination with drug therapy were enrolled. The pre-treatment mean fluorescence intensity (MFI) of 1324 human leukocyte antigen (HLA) antibody specificities (MFI > 2000) and the post-treatment MFI of the corresponding antibody specificities (after one, four, seven, and 10 sessions) were recorded to analyze the changes in antibody level reduction for the different antibody classes and MFI ranges. After 10 sessions of PA-IA therapy, the MFI of class I antibodies decreased from 8298.56 to 3196.15 (reduction of 66.80%), while the MFI of class II antibodies decreased from 13,521.09 to 2773.29 (reduction of 71.14%). The pre-treatment level of class II antibodies was significantly higher than that of class I antibodies ( $p < 0.001$ ), whereas the post-treatment levels of class I and II antibodies were comparable ( $p > 0.05$ ). The clearance effects of PA-IA therapy were greater for strongly positive (MFI > 10,000) class II antibodies than for strongly positive class I antibodies, showing a reduction of 62.59% (25.17% to 91.04%) and 45.13% (32.70% to 73.94%), respectively ( $p = 0.015$ ). The removal efficacy of PA-IA for HLA antibodies was confirmed. The removal efficacy of class II antibodies on PA-IA was not inferior to that of class I. Under an adequate number of treatment sessions, the clearance effect of PA-IA therapy for strongly positive class II antibodies may be greater than that for strongly positive class I antibodies. Following a thorough analysis of the differences in antibody clearance among different classes, initial MFI subgroups, and different treatment phases, findings confirmed the clearance effects of PA-IA on HLA antibodies. The authors concluded that the findings imply that desensitization therapy based on PA-IA is clinically effective in ensuring the successful completion of kidney transplantation and the stable recovery of postoperative renal allograft function. The conclusions of these previous studies are subject to limitations due to their small HLA antibody-specific sample size, an insufficient number of groups, or the inadequate number of treatments. Future prospective and control trials are required to validate the above conclusions.

In a single-center retrospective study, Campise et al (2019) evaluated their experience with prophylactic and therapeutic plasmapheresis in a cohort of 21 individual recipients of deceased-donor kidney transplant with primary focal segmental glomerulosclerosis (FSGS). The authors analyzed ten patients who received post-transplant prophylactic plasmapheresis only with eleven who received both pre- and post-transplant prophylactic plasmapheresis. They also compared these groups to a historical control group of transplant recipients with FSGS who did not receive plasmapheresis prophylaxis. The authors observed that response to treatment was only seen in patients who received a more intensive prophylactic plasmapheresis



regimen and that half of the recipients with FSGS recurrence did not respond to plasmapheresis and developed graft failure, a quarter of the recipients showed complete response and the remaining 25% became plasmapheresis dependent. While therapeutic plasmapheresis is still a valid treatment option for first-line treatment of relapsing FSGS, the authors concluded that there is no benefit from prophylactic plasmapheresis in deceased-donor kidney transplant recipients with FSGS and recommended that prospective randomized trials comparing alternative preemptive strategies be done. They acknowledged the limitations of this study including the retrospective design, the small, homogeneous sample size, and the differences in follow-up between the treatment groups.

Montgomery et al. (2011a) used a protocol that included plasmapheresis and the administration of low-dose IVIG to desensitize 211 patients sensitized to HLA who underwent live-donor renal transplantation (treatment group). The rates of death were compared between the group undergoing desensitization treatment and two 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 one year, 85.7% at three years, 80.6% at five years, and 80.6% at eight 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 eight 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.

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.

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 Immunoabsorption (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.

## Pediatric ABO-Incompatible Heart Transplantation

Issitt et al. (2021) completed a retrospective case series of patients transplanted using intraoperative anti-A/B immunoadsorption (ABO-IA) to compare outcomes with those undergoing plasma exchange facilitated ABO-incompatible heart transplantation (ABO-PE). Data were retrospectively analyzed on all ABO-incompatible heart transplants undertaken at a single center between January 1, 2000, and June 1, 2020. Data included all routine laboratory tests, demographics and pre-operative characteristics, intraoperative details and post-operative outcomes. Primary outcome measures were volume of blood product transfusions, maximum post-transplant isohemagglutinin titers, occurrence of rejection, and graft survival. Secondary outcome measures were length of intensive care and hospital stay. Demographic and survival data were also obtained for ABO-compatible transplants during the same time period for comparison. Thirty-seven patients ages 7 months to 8 years old underwent ABO-incompatible heart transplantation, with 27 (73%) using ABO-PE and 10 (27%) using ABO-IA. ABO-IA patients were significantly older than ABO-PE patients ( $p < 0.001$ ) and the total volume of blood products transfused during the hospital admission was significantly lower (164 [126-212] ml/kg vs 323 [268-379] ml/kg,  $p < 0.001$ ). No significant differences were noted between methods in either pre- or post-transplant maximum isohemagglutinin titers, incidence of rejection, length of intensive care or total hospital stay. Survival comparison showed no significant difference between antibody reduction methods, or indeed ABO-compatible transplants ( $p = 0.6$ ). The authors concluded that this technique appears to allow a significantly older population than typical to undergo ABO-incompatible heart transplantation, as well as significantly reducing blood product utilization. Furthermore, intraoperative anti-A/B immunoadsorption does not demonstrate increased early post-transplant isohemagglutinin accumulation or rates of rejection compared to ABO-PE. Early survival is equivalent between ABO-IA, ABO-PE and ABO-compatible heart transplantation.

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 3,209 mL. Isohemagglutinin titers that were as high as 1:32 preoperatively were reduced to a range of 0–1:16 post transplantation. 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.

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 seven patients, donor-specific isohemagglutinin titers were elevated at the time of transplantation but were significantly reduced using intraoperative plasma exchange. Only two of the seven required treatment for AMR (which occurred early post-transplantation, 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 seven 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.

## Pediatric Autoimmune Neuropsychiatric Disorders Including Pediatric Acute-Onset Neuropsychiatric Disorders Associated with Streptococcus (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

Prus et al. (2022) conducted a retrospective chart review on all patients treated with therapeutic plasma exchange (TPE) for pediatric autoimmune neuropsychiatric disorders associated with streptococcal (PANDAS) infections and pediatric acute-onset neuropsychiatric syndrome (PANS) indications via a single outpatient apheresis service located in a medium-sized urban medical center. In total, 16 patients were identified (aged 14–41 years, median 19.5 years). Eight patients had recorded concurrent psychiatric comorbidities, including obsessive-compulsive disorder (OCD) ( $n = 6$ ), anxiety ( $n = 3$ ), autism, bipolar disorder, depression, and schizophrenia ( $n = 1$ ). Five of these patients had at least two different diagnoses. Twelve patient records revealed previous medication-based psychiatric treatments prior to TPE referral. Eleven of those patients remained on

psychiatric medications at the time of TPE. Prior to TPE, most patients had received other PANDAS/PANS-oriented treatments. Seven patients had completed at least one course of antibiotics, usually with azithromycin though two patients used amoxicillin clavulanic acid. Two patients reported use of steroids. For TPE treatment, one course was defined as five or seven single plasma volume TPE with 5% albumin replacement and citrate anticoagulant, utilizing a Spectra Optia. Fourteen (5 male, 9 female) received 7 days of treatment, while the remaining two female patients received 5 days of TPE treatment, all scheduled every other day (excluding weekends). Four female patients were treated with multiple courses of TPE, receiving 1, 2, 3, or 8 additional courses. The longest duration of treatment was over nine courses, performed for symptomatic indications. Ages of those receiving multiple courses were 16, 18, 18, and 22 years. No adverse reactions or complications of apheresis treatment were identified. Seven patients had recorded post-TPE PANDAS/PANS responses, denoting improved (n = 4) or not improved (n = 3). Improvement after TPE was noted 1–10 days after treatment in four females aged 16–18. Three of these responders received subsequent TPE courses for PANDAS/PANS exacerbations. The authors concluded that improvement was noted in over half of the patients with available follow-up information. However, limitations of the study include the retrospective nature, lack of comparison group, and incomplete data availability, including post-treatment ASO and Cunningham Panel results. Well designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

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.

## 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 five weeks. The clinical response was evaluated at the completion of the series and again four 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 LCAP 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 four 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 four 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 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 sixth 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 post marketing 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, placebo RCT 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 seven and eight 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 five 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.

## Focal Segmental Glomerulosclerosis (FSGS)

A 2020 ECRI health technology assessment focuses on the effectiveness of LDL apheresis for treating steroid-resistant nephrotic syndrome associated with focal segmental glomerulosclerosis (FSGS.) The conclusion of four small studies reported that LDL apheresis treatment may delay progression to end-stage renal disease and complications associated with chronic kidney disease. Additional studies and long-term follow up would be useful to confirm findings. All studies identified were conducted in Japan and results may not be generalizable to other countries and healthcare systems.

## Heart Disease

Luirink, et al. (2020) performed an observational multicenter case series on data from an international registry on the execution and outcomes of lipoprotein apheresis (LA) in children with homozygous familial hypercholesterolemia (hoFH). Their analysis included 50 children aged 0-19 years who were treated at 15 sites in nine countries and who were on medication and LA for hoFH. The median age at diagnosis was 5.0 (3.0 – 8.0) years, and in 46 (92%) patients, the diagnosis of hoFH or compound heterozygous FH (heFH) was genetically confirmed. The median untreated low-density lipoprotein cholesterol (LDL-C) level was 19.2 (16.2 – 22.1) mmol/L and the total cholesterol was 22.0 (18.4-24.4) mmol/L for the study participants. On medication, the median LDL-C level was 14.4 (10.8 – 16.7) mmol/L showing a median reduction of LDL-C on medication of 19.3% (11.6 – 37.6). The children were started on apheresis on average at 2.8 (1.0-4.7) years after their diagnosis. The frequency of treatment ranged from two times per week to once every three weeks with most patients (n = 21; 43%) being treated weekly or once every two weeks (n = 18; 37%) with most patients (n = 35; 71%) having been treated for more than two years. Their analysis showed that the medial LDL-C in patients on LA for longer than 3 months dropped to 4.6 (3.8 – 7.2) mmol/L with the LDL-C being lower on average the more frequently patients were treated with LA. They reported that 7 (17%) patients reached mean LDL-C levels < 3.5 mmol/L, all of which were treated either once a week (n = 4) or twice a week (n = 3). The authors concluded that the results show that LA may lead to a significant and relevant reduction of LDL-C in children with hoFH and that twice a week LA was significantly more effective in lowering mean LDL-C. They noted that the study had several limitations including the potential for variability in the data being entered and that the results might not be representative of the entire population of children with hoFH since the registry was not open to all sites treating all children with hoFH around the world. The authors recommend further studies with long-term follow-up data of the effect of LA on CVD or surrogate markers for CVD.

Khan et al. (2017) conducted a single-blinded RCT to determine the clinical impact of lipoprotein apheresis in 20 patients with refractory angina and raised lipoprotein(a) > 500 mg/L. Participants received three months of blinded weekly lipoprotein apheresis or sham, followed by crossover. The primary endpoint was change in quantitative myocardial perfusion reserve (MPR). Secondary endpoints included measures of atheroma burden, exercise capacity, symptoms, and quality of life. MPR increased following apheresis compared with sham, yielding a net treatment increase of 0.63. All secondary endpoints showed improvements as well. The researchers concluded that lipoprotein apheresis may represent an effective novel treatment for patients with refractory angina and raised lipoprotein(a). They state that a larger study in these patients incorporating the impact of apheresis on major cardiovascular AEs would help to validate the findings.

Low levels of high-density lipoprotein (HDL) are associated with increased risk of cardiovascular disease. Researchers theorize 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 seven 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.



A prospective, multi-center, international, two-arm matched-pair cohort study known as MultiSELECT is in progress, evaluating the clinical benefit of lipoprotein apheresis on cardiovascular outcomes. For more information, refer to [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and review Identifier NCT02791802. (Accessed July 11, 2023).

## Light Chain Nephropathy

In a multicenter retrospective study from ten plasmapheresis centers in Turkey, Kalpakci et al (2021) observed that Therapeutic Plasma Exchange (TPE) reduced all biochemical markers related to cast nephropathy (CN) in patients with multiple myeloma (MM) when TPE was performed for up to seven days until improvement was seen in patient's symptoms and laboratory findings. A mean: 3.3 (median: 3) sessions of TPE were performed in newly diagnosed MM, mean: 4 (median: 4.5) sessions of TPE were performed in relapsed refractory disease, and 22 patients received concomitant chemotherapy containing bortezomib. According to the authors, the overall response rate was 83.6% (n = 51) with statistically significant differences observed in serum levels of all clinically relevant biomarkers before and after treatment. The authors stated that TPE also contributed to the clinical improvement in 40 of 50 patients with multiple myeloma and CN. The incidence of side effects associated with TPE was reported by the authors to affect four patients (6.6%), with no severe side effects that required termination of the procedure. These results were noted one week after TPE was added to standard medical treatment. The authors noted that the main limitations of their study were the small sample size and the absence of a comparative control group.

Premuzic et al. (2018) examined whether plasmapheresis in combination with chemotherapy could significantly remove free light chains (FLCs) in patients with multiple myeloma (MM) and acute kidney injury (AKI), ultimately improving renal recovery and patient survival in a single center study. During the study period, 29 patients with MM and AKI were treated with two different therapy modalities (plasmapheresis with chemotherapy or bortezomib). At the end of treatment, a significant decrease of FLCs was present in the group treated with plasmapheresis compared to the bortezomib group. While overall survival was similar between groups, there was a significantly higher decrease of FLCs and longer survival in patients treated with  $\geq$  three plasmapheresis sessions than in patients treated with two sessions. The authors concluded that plasmapheresis therapy still remains a useful and effective method in the treatment of AKI in MM patients. Plasmapheresis significantly reduces FLCs compared to bortezomib, especially with higher number of plasma exchange sessions, but it must be combined with other chemotherapy agents in order to prolong renal recovery and therefore patient survival.

Yu et al. (2015) conducted a meta-analysis to quantitatively evaluate the clinical efficacy of chemotherapy with or without plasmapheresis in the treatment of patients with MM and renal failure. Three RCTs were selected and analyzed. A total of 63 patients received chemotherapy only and 84 patients were given both chemotherapy and plasmapheresis. No difference was observed in six-month survival rate between plasmapheresis and control group (75% vs. 66.7%). The six-month dialysis-dependent ratio was significantly lower in patients treated with both chemotherapy and plasmapheresis than chemotherapy alone (15.6% vs. 37.2%). The authors concluded that plasmapheresis used as an adjunct to chemotherapy had a benefit in the management of dialysis-dependent MM patients with renal failure.

A systematic review covering 56 articles regarding survival benefits, recovery, and improvement in renal function after extracorporeal removal of sFLCs did not suggest a benefit of plasmapheresis independent of chemotherapy for patients with MM and acute renal injury (Gupta et al., 2010).

## Inflammatory Bowel Disease

Sakai et al. (2023) conducted a retrospective analysis to determine whether leukocytapheresis/granulocytapheresis (L/G-CAP) compared with anti-tumor necrosis factor- $\alpha$  monoclonal antibody biological preparations (BP) agents for refractory ulcerative colitis (UC) offered sustained beneficial effects over 2-year period. The patients who had moderately to severely active UC (Rachmilewitz clinical activity index (CAI)  $\geq$  5) and were treated with a series (10 sessions) of L/G-CAP (n = 19) or BP (n = 7) as an add-on therapy to conventional medications were followed. At baseline, L/G-CAP and BP groups manifested similar disease activity (CAI, L/G-CAP; 7.0 [6.0-10.0], BP; 10.0 [6.0-10.0], p = .207). The L/G-CAP and BP treatment suppressed the activity, with CAI 1 or less attained on day 180. When the L/G-CAP group was dichotomized into L/G-CAP-high and L/G-CAP-low group based on CAI values ( $\geq$  3 or  $<$  3) on day 365, CAI was gradually elevated in L/G-CAP-high group but remained suppressed in L/G-CAP-low group without additional apheresis for 2 years. Anemia was corrected more rapidly, and hemoglobin levels were higher in BP group. The authors concluded that L/G-CAP is as effective as BP in a substantial number of patients over 2 years. Thus, L/G-CAP can effectively manage the disease activity with no additional implementation for 2 years although further therapeutic modalities might be required in a certain population with high CAI observed on day 365. study was conducted in 2

individual facilities for relatively a short duration, and the study population was small. Current treatment protocols for UC with anti-TNF- $\alpha$  monoclonal antibody agents stick in principle to the continued use of these products even though the remission is maintained. In contrast, the L/G-CAP therapy is conducted at the start of the study and no additional session of L/G-CAP is performed unless required, which strategy might tend to elevate the disease activity in a certain population. Further investigation is needed before clinical usefulness of this procedure is proven.

Iizuka et al. (2022) conducted a systematic review aimed to summarize the current literature on the use of cytopheresis (CAP) in patients with ulcerative colitis (UC) showing a poor response or secondary loss of response (LOR) to biologics and its advantages and limitations. In addition, the efficacy of CAP in patients with UC showing insufficient response to thiopurines or immunomodulators (IM) was analyzed. Eight studies evaluated the efficacy of CAP in patients with UC with inadequate responses to thiopurines or IM. There were no differences in the rate of remission and steroid-free remission between patients exposed or not exposed to thiopurines or IM. Three studies evaluated the efficacy of CAP in patients with UC showing an insufficient response to biologic therapies. Mean remission rates of biologics exposed or unexposed patients were 29.4 % and 44.2%, respectively. Fourteen studies evaluated the efficacy of CAP in combination with biologics in patients with inflammatory bowel disease showing a poor response or LOR to biologics. The rates of remission/response and steroid-free remission in patients with UC ranged 32%-69% (mean: 48.0%, median: 42.9%) and 9%-75% (mean: 40.7%, median: 38%), respectively. CAP had the same effectiveness for remission induction with or without prior failure on thiopurines or IM but showed little benefit in patients with UC refractory to biologics. Although heterogeneity existed in the efficacy of the combination therapy with CAP and biologics, these combination therapies induced clinical remission/response and steroid-free remission in more than 40% of patients with UC refractory to biologics on average. The authors concluded given the safety profile of CAP, this combination therapy can be an alternative therapeutic strategy for UC refractory to biologics. Extensive prospective studies are needed to understand the efficacy of combination therapy with CAP and biologics.

A retrospective observational study was completed by Fukuchi et al. (2022) to examine the long-term maintenance rate after inducing UC remission by intensive granulocyte/monocyte adsorptive apheresis (GMA) without use of corticosteroids (CS) and GMA re-treatment efficacy in the same patients upon relapse with ulcerative colitis. Patients who achieved clinical remission and mucosal healing (MH) by first-time intensive GMA (first GMA) without CS were enrolled. The cumulative non-relapse survival rate up to week 156 was calculated. Patients with relapse during the maintenance period underwent second-time intensive GMA without CS. Clinical remission and MH rates following second GMA were compared to those following first GMA in the same patients. Of the 84 patients enrolled, 78 were followed until week 156 and 34 demonstrated relapse. The cumulative non-relapse survival rate by week 156 was 56.4%. The authors concluded for the goal of MH in UC patients, intensive GMA prior to use of CS and biologics can be a suitable choice. Such cases generally have a favorable clinical prognosis, including a sufficient rate of clinical remission maintenance, as well as superior re-induction rate of clinical and endoscopic remission by GMA re-treatment even when disease relapse occurs. The findings are, however, limited by lack of a comparison group.

In a systematic review and meta-analysis on the role of granulocyte and monocyte apheresis (GMA) in the induction and maintenance of clinical remission in ulcerative colitis (UC), Kiss, et al. (2021) analyzed 11 studies that included a total of 589 patients. The studies consisted of 11 RCTs, including the Domènech (2018) and the Eberhardson (2017) studies previously included in this policy, with one study with minimization. Eight of the studies reported on patients with active UC and three contained data on patients with UC who were in clinical remission. In the studies on patients with active UC, 350 patients received GMA and 248 were in control groups. With regard to the three studies reporting on patients with UC who were in clinical remission, there were 71 participants, of which, 36 received GMA and 35 were in the control groups. In the meta-analysis, GMA was shown to induce and maintain clinical remission more effectively than conventional therapy alone, primarily sham or steroids. Risk of bias was assessed as high risk for three of the studies due to the unblinded design of the studies, four studies were assessed as high risk due to the lack of a description of the blinding process and two others were assessed as high risk of bias for other biases. The authors noted that their results were limited by the relatively low number of patients and the heterogeneous reporting of AEs. The study was also limited by the heterogeneity of the study designs such as the treatments rendered, the length of the studies, and the number of participants. The authors concluded that GMA appears to be more effective as an adjunctive treatment in inducing and maintaining remission in patients with UC than conventional therapy alone (low certainty). It is however unclear how this therapy would compare to more recent medications, such as biologics. The authors recommend further RCTs to justify the role of GMA for inducing remission in patients with UC.

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 LCAP. 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 LCAP ( $\geq$  four sessions within the first two weeks) was used in  $> 70\%$  of the patients. AEs were seen in 10.3%, which were severe in only five patients. Any concomitant medications did not increase the incidence of AEs. The authors concluded that that LCAP, 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.

## Idiopathic Dilated Cardiomyopathy (DCM)

In a meta-analysis on 12 studies with 395 patients with dilated cardiomyopathy (DCM), Bian, et al. (2021) reported that immunoadsorption (IA) treatment resulted in significantly improved left ventricular ejection fraction, reduced the left ventricular end diastolic diameter, and reduced severity of symptoms according to the New York Heart Association (NYHA) functional classification but that IA did not have any effect on values for safety parameters. There were 201 patients that received IA therapy and 194 that received optimal medical treatments other than IA. The 12 included studies were all comparative and 4 were randomized studies. The studies included 5 that assessed IA therapy, 4 that assessed IA/immunoglobulin G polytherapy, 3 that assessed IVIG and 2 studies that included a placebo treatment in the control group. Limitations noted by the authors included the number of studies and participants, the heterogeneity among studies including different treatments and different treatment durations. The authors concluded that IA treatment can improve clinical outcome in DCM patients and recommended further studies to validate the relative safety of IA treatment with multi-center, double blind studies.

## Idiopathic Inflammatory Myopathies

There is insufficient quality evidence to support the use of apheresis for idiopathic inflammatory myopathies.

Kruse et al. (2022) conducted a retrospective case series study and literature review of patients presenting with necrotizing autoimmune myopathy (NAM) and undergoing treatment with therapeutic plasma exchange (TPE) performed. Clinical data including patient demographics, symptoms, physical exam findings, muscle biopsy, lower extremity imaging, prior therapy, and duration from diagnosis to TPE initiation were collected retrospectively for adult patients with NAM treated with TPE after failing to respond to immunomodulatory therapy. Laboratory data including change in CK levels and myositis-specific antibody titers from baseline were measured in some patients. Six patients (median age at diagnosis 52.5 years, interquartile range [IQR] 35.8-64.5 years, four male/two female) underwent a median of 7.5 (IQR: 5-10) TPE procedures with 5% albumin as replacement. All patients exhibited a statistical reduction in CK level from pre-TPE baseline (range: 43.0%-58.7% reduction). Responses in this cohort were best in patients with antibodies targeting HMGCR and SRP, which are most strongly associated with NAM. These results compare favorably to a literature review of NAM patients ( $n = 19$ ) treated with TPE, who also exhibited positive clinical and laboratory responses across varying treatment lengths. The authors concluded that TPE can play a role in the management of NAM, particularly in patients with HMGCR or SRP antibodies who are refractory to pharmacologic immunosuppression. Limitations include this being a single-center, retrospective analysis with few patients, and short trials of TPE for NAM treatment. Heterogeneity with regard to underlying antibody, as well as prior and concurrent treatments makes attribution of clinical benefit to TPE uncertain. Furthermore, response to myopathy treatments is largely subjective having been based on patients' reporting of clinical benefit whereby CK was the only available biomarker used to assess response. Further research with randomized controlled trials is needed to validate these findings.

Ning et al. (2019) conducted a retrospective study to investigate therapeutic plasma exchange (TPE) treatment outcomes in 18 patients with acute polymyositis/dermatomyositis interstitial lung disease (PM/DM-ILD) who were resistant to conventional therapies. Five patients were diagnosed with dermatomyositis (DM) (27.8%), 11 with clinically amyopathic dermatomyositis (CADM) (61.1%), and two with polymyositis (PM) (11.1%). Among 18 patients, 11 (61.1%) achieved satisfactory improvement after four or more rounds of TPE, whereas seven died due to respiratory failure. Risk factors to predict unresponsiveness to TPE in these patients was also analyzed. Notably, the prevalence of subcutaneous/mediastinal emphysema was significantly higher in the non-responsive group (6/7, 85.7%) than in the responsive group (2/11, 18.2%;  $p = 0.013$ ); moreover, patients with this complication were mainly in the CADM subgroup (6/8, 75%). Subcutaneous/mediastinal emphysema and increased serum ferritin levels were shown to be poor prognostic factors, predictive of unresponsiveness to TPE, in PM/DM patients. No autoantibodies were found to be associated with TPE outcome; the clinical significance of other myositis-specific autoantibodies, especially anti-melanoma differentiation-associated gene 5 (MDA5) antibody, is not known. The authors concluded results indicate that TPE might be an alternative treatment for acute PM/DM-ILD patients resistant to conventional therapies, except for those with subcutaneous/mediastinal emphysema and high serum ferritin levels. Further,

subcutaneous/mediastinal emphysema and serum ferritin levels might serve as poor prognostic factors of responsiveness to TPE. More controlled trials and long-term observations are required in the future.

## Immune Thrombocytopenia (ITP)

There is insufficient quality evidence to support the use of apheresis for immune thrombocytopenia (ITP).

Basturk, et al. (2021) conducted a multicenter retrospective analysis on the efficacy of TPE in ITP. The study included 17 adult patients (8 male, 9 female) with chronic refractory ITP who failed to respond to standard treatment, had platelet counts  $< 30 \times 10^9 / L$  and underwent TPE in 5 healthcare centers. The authors reported that partial response was achieved in 7 patients (41%), while complete response was achieved in 9 patients (52%). One patient who failed to respond died due to bleeding at the end of 2 sessions. All patients had received corticosteroids for an average of 4 weeks before TPE and were administered Intravenous immunoglobulin (IVIg) before TPE. Three patients had also been received both rituximab and eltrombopag before TPE, and 4 patients had undergone splenectomy before TPE. There were also three patients who underwent splenectomy after TPE. The platelet count reached  $> 30 \times 10^9/L$  in a mean of 2.07 sessions using plasma, and in mean of 4.6 sessions using albumin. The authors concluded that TPE may be an alternative treatment option in patients with chronic refractory ITP and recommended prospective, randomized controlled studies to evaluate the effectiveness of TPE for preventing bleeding in patients with ITP. The findings are limited by lack of a comparison group.

## Kawasaki Disease Vasculitis

There is insufficient quality evidence to support the use of apheresis for Kawasaki disease vasculitis.

Yamada et al. (2021) conducted a systematic review and meta-analysis to assess whether plasma exchange (PE) is associated with prognosis in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) patients. A systematic search of PubMed, MEDLINE, Embase, and CENTRAL databases from inception to 17 June 2020 was conducted. Four RCTs comparing PE vs. no PE (n = 827) and 1 RCT comparing PE vs. pulse steroid treatment (n = 137) were included. All participants were MPA or GPA patients (no EGPA patients). PE was not associated with main primary outcomes compared with no PE (mortality RR 0.93 [95% confidence interval {CI} 0.70-1.24], I2 = 0%; CR RR 1.02 [95% CI 0.91-1.15], I2 = 0%; and AE RR 1.10 [95% CI 0.73-1.68], I2 = 37%) or pulse steroid (mortality RR 0.99 [95% CI 0.71-1.37]; CR [the Birmingham Vasculitis Activity score] mean difference - 0.53 [95% CI - 1.40-0.34]; and AE RR 1.05 [95% CI 0.74-1.48]). Focusing on the early treatment phases, PE was associated with a reduction in end-stage renal disease incidence compared with both no PE (PE 1/43 vs. no PE 10/41; RR 0.14 [0.03-0.77] at 3 months) and pulse steroid (PE 11/70 vs. pulse steroid 23/67; RR 0.46 [0.24-0.86] at 3 months). The authors concluded that In AAV patients, performing PE was not associated with the risk of mortality, CR, and AE. No RCT exists evaluating the efficacy of PE for EGPA; hence, this is required in the future. The results may affect the development of guidelines for AAV and may indicate the direction of future clinical research on AAV. Further investigation is needed before clinical usefulness of this procedure is proven.

Mori et al. (2004) conducted a retrospective study to assess whether plasma exchange is a safe and effective prophylaxis against coronary artery lesions (CALs) in children with Kawasaki disease (KD) intractable to intravenous gamma-globulin (IVGG) therapy. Eighty-nine children with KD at high risk of CALs were selected on the basis of increases in fractional changes in inflammatory markers such as white blood cell count, neutrophil count, and C-reactive protein between the baseline and 1–2 days after IVGG treatment. Of 105 children who received a second course of IVGG therapy because the initial course was ineffective, plasma exchange (PE) was performed in 46 children who had not responded to the second IVGG treatment. The outcome was compared with the results when a third course of IVGG therapy was given to the other 59 children. No complications occurred with the plasma exchange therapy. CALs developed in only 8 of the 46 children (17.3%) who underwent plasma exchange, but they occurred in 24 of the 59 (40.7%) who had received a third course of IVGG therapy (p < 0.0012). The authors concluded that PE was a safe and effective prophylactic measure against CALs in children with KD intractable to IVGG therapy. PE should be performed at an early stage, as soon as fractional increases in inflammatory markers are found after IVGG therapy. This study is limited by its retrospective observations. In addition, the IVGG regimen used was different from that which was currently standard in other countries, and it varied from patient to patient. Further research with randomized controlled trials is needed to validate these findings.

## Pemphigus Vulgaris

There is insufficient quality evidence to support the use of apheresis for pemphigus vulgaris.

Martin et al. (2011) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of interventions for pemphigus vulgaris and pemphigus foliaceus. Randomized controlled trials (RCTs) including participants with the diagnosis of pemphigus vulgaris or pemphigus foliaceus confirmed with clinical, histopathological, and immunofluorescence criteria were included. All interventions were considered. Primary outcomes studied were remission and mortality. Secondary outcomes included disease control, relapse, pemphigus severity score, time to disease control, cumulative glucocorticoid dose, serum antibody titers, AEs, and quality of life. Eleven studies with a total of 404 participants were identified. Interventions assessed included prednisolone dose regimen, pulsed dexamethasone, azathioprine, cyclophosphamide, cyclosporine, dapsone, mycophenolate, plasma exchange, topical epidermal growth factor, and traditional Chinese medicine. Plasma exchange was evaluated in one study of 40 participants. The effect of plasma exchange was inconclusive on all reported outcomes. The authors found some interventions to be superior for certain outcomes, although they were unable to conclude which treatments are superior overall. The authors concluded there is inadequate evidence available at present to ascertain the optimal therapy for pemphigus vulgaris and pemphigus foliaceus. Many interventions for pemphigus have not been evaluated in controlled trials. All studies were insufficiently powered to establish definitive results. Further research with randomized controlled trials is needed to validate these findings.

## Post Transfusion Purpura (PTP)

There is insufficient quality evidence to support the use of apheresis for post transfusion purpura.

Porretti et al. (1992) conducted a single patient case report investigating intravenous immunoglobulins and therapeutic plasma exchange (TPE) in a 74-year-old multiparous Caucasian female who developed severe thrombocytopenia following red blood cell transfusion who developed post-transfusion purpura (PTP). Six ineffective platelet transfusions (a total of 42 random donor concentrates) were given from day 0 to day + 6, high-dose steroids from day + 1, progressively tapered until day + 30, and a total of 150 g of intravenous immunoglobulins from day + 2 to day + 6. As platelet count had not increased significantly by day + 8, four plasma exchange procedures, each consisting of 2,000 ml of plasma exchanged with 5% albumin solution, were performed on days + 8, + 10, + 14 and + 18. Platelet count was 5, 50, 100 and 234 x 10<sup>9</sup>/l on days + 8, + 14, + 26 and + 32 (discharge), respectively. The patient's acute phase serum contained increased levels of platelet alloantibodies with anti-HPA-1a (PIA1, Zwa) specificity and a titer of 3,200. IgG1, IgG2 and IgG3 subclasses of platelet-reactive antibodies in the patient's serum were elevated, whereas IgG4, IgM and IgA were within the reference values. Levels of IgG1, IgG2 and IgG3 of antiplatelet antibodies showed a marked and parallel reduction during treatment, however, were still above the reference values at the end of treatment and 1 year later, when the patient platelet count was normal. The authors concluded that although a failure of intravenous immunoglobulins cannot be proven in this case, plasma exchange seems to have contributed more than intravenous immunoglobulins to clinical remission. The full understanding of the pathogenesis of PTP caused by platelet antibodies with different specificities requires further study. In particular, further investigation is warranted to clarify the relative role of different immunoglobulin sub classes and the mechanisms and timing of the catabolism of platelet antigens of donor origin in determining the clearance of autologous platelets. Well designed, adequately powered, prospective, controlled clinical trials of TPE are needed to further describe safety and clinical outcomes (or efficacy).

## Sepsis with Multiorgan Failure

There is insufficient quality evidence to support the use of apheresis for sepsis with multiorgan failure.

Keith et al. (2020) conducted a retrospective, observational chart review evaluating outcomes of patients with catecholamine-resistant septic shock and multiple organ failure in intensive care units at a tertiary care. This study aimed to evaluate the efficacy of adjunct therapeutic plasma exchange (TPE) for septic shock with multiple organ failure compared to standard therapy alone. Adult patients with catecholamine-resistant septic shock ( $\geq 2$  vasopressors) and evidence of multiple organ failure were included. Patients who received adjunct TPE were identified and compared to patients who received standard care alone. A propensity score using age, gender, chronic co-morbidities (HTN, DM, CKD, COPD), APACHE II score, SOFA score, lactate level, and number of vasopressors was used to match patients, resulting in 40 patients in each arm. The mean baseline APACHE II and SOFA scores were 32.5 and 14.3 in TPE patients versus 32.7 and 13.8 in control patients, respectively. The 28-day mortality rate was 40% in the TPE group versus 65% in the standard care group ( $p = 0.043$ ). Improvements in baseline SOFA scores at 48 h were greater in the TPE group compared to standard care alone ( $p = 0.001$ ), and patients receiving adjunct TPE had a more favorable fluid balance at 48 h ( $p = 0.01$ ). Patients receiving adjunct TPE had longer ICU and hospital lengths of stay ( $p = 0.003$  and  $p = 0.006$ , respectively). The authors concluded adult patients with septic shock and multiple organ failure demonstrated improved 28-day survival with adjunct TPE compared to standard care alone. Hemodynamics, organ dysfunction, and fluid balance all improved with adjunct TPE, while lengths of stay were increased in survivors. The study

design does not allow for a generalized statement of support for TPE in all cases of sepsis with multiple organ failure but offers valuable information for a prospective, randomized clinical trial. Further investigation is needed before clinical usefulness of this procedure is proven.

## Stiff-Person Syndrome

There is insufficient quality evidence to support the use of apheresis for stiff-person syndrome.

Albahra, et al. (2019) retrospectively analyzed the clinical data and outcomes of 10 patients (9 female) with the clinical diagnosis of anti-GAD65 positive stiff person syndrome (SPS) in which TPE was used to improve symptoms refractory to conventional treatments including immunosuppression therapies, anti-anxiety medications, muscle relaxants, anticonvulsants, and pain relievers. Five patients (50%) had diabetes (one of which had type 1 diabetes), and two patients (20%) had a history of cancer. TPE was administered via peripheral access in seven patients (total of 350 procedures) or via central double lumen dialysis type catheter in three patients (total of 28 procedures) as a complementary therapy in patients with worsening symptoms of SPS. TPE became a chronic treatment for six of the study participants following their initial course. The authors reported that four patients developed a relapse of symptoms when the interval between procedures was increased and that one of these four patients had worsening of symptoms following complete cessation of TPE. The authors also reported that another 4 patients underwent only an acute hospitalized course of treatment with TPE with one achieving complete resolution of symptoms, one with a partial response and two who did not experience any improvement. Limitations include the single-center, retrospective design of the study, the small sample size, the heterogeneity of previous conventional treatments received, and the lack of a control arm. The authors concluded that TPE may be beneficial for the management of patients with anti-GAD65 positive SPS for both acute exacerbations and for long-term maintenance, either as an adjunct therapy or in lieu of treatment with disease modifying agents.

## Sydenham's Chorea

There is insufficient quality evidence to support the use of apheresis for Sydenham's chorea.

Eighteen patients were entered into a randomized controlled trial (RCT) designed to determine if IVIG 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).

## Toxic Epidermal Necrolysis (TEN)

There is insufficient quality evidence to support the use of apheresis for toxic epidermal necrolysis.

In a prospective, single center, observational study conducted by Han, et al. (2017), the effectiveness of plasmapheresis therapy was evaluated in 28 pediatric and adult patients with toxic epidermal necrolysis (TEN) or TEN with overlapping Stevens-Johnson syndrome (SJS). The study participants were divided into either the plasmapheresis group (n = 13) or the non-plasmapheresis group (n = 15) on the basis of whether plasma exchange was performed after admission. The plasmapheresis group was further divided into two subgroups with 6 participants in the pure plasmapheresis group, whose members were treated with plasmapheresis alone, and 7 participants in the co-plasmapheresis group, whose members were treated with plasmapheresis in combination with glucocorticoids and/or IVIg. The authors reported that there were no statistical differences with respect to the children/adult ratio, male/female ratio and stripping area after admission between the plasmapheresis group and the non-plasmapheresis group. The authors also reported no statistical difference in the severity of illness score on the 1<sup>st</sup> and 4<sup>th</sup> day after admission between the two groups; however, the scores of the plasmapheresis group were lower than those of the non-plasmapheresis group on the 7<sup>th</sup>, 10<sup>th</sup> and 20<sup>th</sup> day of admission. The authors noted that the rate of recovery was higher in the plasmapheresis group and they concluded that plasmapheresis as a first line therapy might present a significant advantage compared to glucocorticoids and/or IVIg in reducing mortality of TEN patients as well as in shortening the duration of stay in the intensive care unit. The authors also concluded that plasmapheresis combined with IVIg and/or glucocorticoids might not be advantageous compared to the effect of plasmapheresis alone.

Zimmerman, et al. (2017) conducted a meta-analysis of 96 studies with 3248 patients diagnosed Stevens-Johnson syndrome (SJS) and/or toxic epidermal necrolysis (TEN) who were treated with supportive care or systemic immunomodulating therapies (SITs) including glucocorticosteroids, intravenous immunoglobulins, cyclosporine, plasmapheresis, thalidomide, cyclophosphamide, hemoperfusion, tumor necrosis factor inhibitors, and granulocyte colony-stimulating factor. Only one of the 96 studies was a randomized clinical trial, with 68 retrospective cohort studies, 9 prospective cohort studies and 17 other observational studies with unclear study designs. There were 40 studies that reported findings obtained from case series and 56 studies that include two or more different therapy arms; however, most patients with SJS/TEN were treated without SITs (62 [34.1%]), with glucocorticosteroids (45 [24.7%]), or with intravenous immunoglobulins (IVIg) (37 [20.3%]). The authors noted that few patients were treated with another SIT, including cyclosporine, plasmapheresis, cyclophosphamide, or thalidomide, or with a combination therapy with more than 1 SIT. The authors also found that, among the 56 publications that describe more than 1 therapy group and were suitable for meta-analysis at the study level, less than half provided enough information to be used to estimate therapy effects. Glucocorticosteroids were associated with a survival benefit for patients in all 3 analyses but were statistically significant in only (aggregated data: OR, 0.5; 95% CI, 0.3-1.01; IPD, unstratified: OR, 0.7; 95% CI, 0.5-0.97; IPD, stratified: OR, 0.8; 95% CI, 0.4-1.3). Despite the low patient size, cyclosporine was associated with a promising significant result in the only feasible analysis of IPD (unstratified model) (OR, 0.1; 95% CI, 0.0-0.4). No beneficial findings were observed for other therapies.

## Clinical Practice Guidelines

### *American Academy of Pediatrics (AAP)*

The American Academy of Pediatrics and the PANDAS Physicians Network (PPN) treatment guidelines (Pupillo, 2017) for rheumatic fever with Sydenham chorea state that antibiotics may be recommended despite a negative strep throat culture. Prophylactic levels of antibiotics should be considered for children with severe symptoms of PANDAS, those recovering from immunotherapy or those with multiple GAS-associated neuropsychiatric exacerbations. In addition, cognitive behavioral therapy can benefit those with mild impairments. If symptoms persist, nonsteroidal anti-inflammatory drugs, corticosteroids, intravenous immunoglobulin (IVIg) or therapeutic plasma exchange may be necessary. IVIg and therapeutic plasma exchange, however, can be expensive and treatment remains controversial.

### *American Academy of Neurology (AAN)*

AAN treatment guidelines (Cortese et al., 2011) for PANDAS/PANS state 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 (Class III evidence, Level U). There is insufficient evidence to support or refute the use of plasmapheresis in the treatment of acute OCD and tic symptoms in the setting of PANDAS (Level U).

The AAN published a practice parameter on the use of immunotherapy for the treatment of Guillain-Barré Syndrome (GBS) that recommends treatment with therapeutic plasma exchange (TPE) or intravenous immunoglobulin (IVIg) to hasten recovery from GBS. The Academy noted that combining the two treatments is not beneficial and that steroid treatments given alone are not beneficial. The Practice Parameter states that TPE is recommended for adult patients with GBS who are non-ambulatory and are treated within 4 weeks of the onset of neuropathic symptoms and that TPE should also be considered for ambulatory patients seen within 2 weeks of the onset of neuropathic symptoms (Hughes et al., 2003; reaffirmed 2022).

### *American College of Rheumatology (ACR)*

In their 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis, the ACR focused their guidance on the pharmacologic management of rheumatoid arthritis. Although they initially intended to include nonpharmacologic treatment approaches in this guideline, the ACR stated that the use of vaccines and nonpharmacologic treatment approaches will be included in future ACR treatment guideline publications.

### *American Heart Association*

In their statement on current diagnostic and treatment strategies for specific dilated cardiomyopathies, the AHA did not mention immunoadsorption or therapeutic plasma exchange as treatment modalities for any cardiomyopathic condition (Bozkurt, 2016).



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

The ASFA (Connelly-Smith, et al. 2023) 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. Institutional Review Board (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 recommendations are adopted from Guyatt et al., 2008, Szczepiorkowski et al., 2010, Schwartz et al., 2016, Padmanabhan et al., 2019, and Connelly-Smith et al, 2023:

- 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.

Regarding sickle cell disease, ASFA states:

- Red blood cell (RBC) exchange is an option for patients with acute stroke, severe acute chest syndrome (ACS), or other complications including but not limited to multiorgan failure.
- RBC exchange is also recommended as a prophylaxis for primary or secondary stroke.
- Studies have shown automated RBC exchange results in a more efficient removal/replacement of HbS RBCs than manual exchange or simple transfusions.
- Long-term RBC exchange has the advantage of preventing or markedly reducing transfusional iron accumulation (Connelly-Smith et al, 2023).

## ***American Society of Hematology (ASH)***

The ASH published a clinical guideline for the prevention, diagnosis, and treatment of cerebrovascular disease in children and adults with sickle cell disease that includes the following as strong recommendations (DeBaun et al. 2020):

- For children with HbSS or HbS $\beta$ 0 thalassemia (ages 2-16 years), the panel recommends:
  - Annual Transcranial Doppler (TCD) screening (strong recommendation).
  - Regular blood transfusions for at least a year (vs. no transfusion) with the goal of keeping maximum HbS levels below 30% and maintaining hemoglobin levels .9.0 g/dL to reduce the risk of stroke for children with abnormal TCD velocities who live in a high-income setting where regular blood transfusion therapy, typically every three to four weeks, is feasible (strong recommendation).
  - Blood transfusion goals for secondary stroke prevention of increasing the hemoglobin above 9 g/dL at all times and maintaining the HbS level at, 30% of total hemoglobin until the time of the next transfusion if the child has a history of prior ischemic stroke.
- For children or adults with SCD and acute neurological deficits, including transient ischemic attack (TIA), the ASH guideline panel recommends prompt blood transfusion given immediately upon recognition of symptoms within two hours of acute neurological symptom presentation. The type of transfusion (simple, modified exchange, or apheresis) is dependent on individual patient factors and local transfusion resources.

The ASH guideline also includes the following conditional recommendations:

- For children who have compound heterozygous SCD other than HbSC and have evidence of hemolysis in the same range as those with HbSS, the ASH guideline panel suggests:
  - TCD screening.



- Regular blood transfusions for at least a year (vs. no transfusion) with the goal of keeping maximum HbS levels below 30% to reduce the risk of stroke if the child has an abnormal TCD velocity, and lives in a high-income setting where regular blood transfusion therapy is feasible.
- For children with SCD (ages 2-16 years) and abnormal TCD results who have been receiving transfusion therapy for at least one year and are interested in stopping transfusion, according to the clinical trial risk stratification with an MRI and magnetic resonance angiography (MRA) of the brain, the ASH guideline panel suggests that hydroxyurea treatment at the maximum tolerated dose can be considered to substitute for regular blood transfusions.
- For children (ages 2-16 years) with HbSS, HbSβ0 thalassemia, or compound heterozygous SCD who have abnormal TCD screening and live in low-middle-income settings where regular blood transfusion therapy and chelation therapy are not available or affordable, the ASH guideline panel suggests hydroxyurea therapy with at least 20 mg/kg per day at a fixed dose or the maximum tolerated dose.
- For children or adults with SCD and acute neurological deficits including TIA, the ASH guideline panel suggests exchange transfusion vs. simple transfusion. When exchange transfusion is not available within two hours of presentation for medical care and hemoglobin is #8.5 g/dL, simple transfusion can be performed to avoid delays in treatment while a manual exchange transfusion or an automated apheresis is planned.
- For adults and children with SCD, moyamoya syndrome, and a history of stroke or TIA, the ASH guideline panel suggests evaluation for revascularization surgery in addition to regular blood transfusion.
- For all patients, the administration of tissue plasminogen activator (tPA) should not delay prompt simple or exchange blood transfusion therapy for adults with SCD presenting with symptoms of acute ischemic stroke who are being evaluated for IV tPA (age ≥ 18 years, no hemorrhage on computed tomography [CT] scan, within 4.5 hours of onset of symptoms/signs and without contraindications for thrombolysis).

The ASH also published guidelines for transfusion support for patients with SCD which includes the following suggestions regarding transfusion and transfusion modalities in patients with SCD who require chronic therapy (Chou et al., 2020):

- The use of automated red cell exchange (RCE) over simple transfusion or manual RCE:
  - In patients with SCD (all genotypes) receiving chronic transfusions.
  - In patients with SCD and severe acute chest syndrome.
  - In patients with SCD and moderate acute chest syndrome.
- Either RCE with isovolemic hemodilution (IHD-RCE) or conventional RCE in patients with SCD (all genotypes) receiving chronic transfusions.
- Either prophylactic transfusion at regular intervals or standard care (transfusion when clinically indicated for a complication or hemoglobin lower than baseline) for pregnant patients with SCD (all genotypes).
- Preoperative transfusion over no preoperative transfusion in patients with SCD undergoing surgeries requiring general anesthesia and lasting more than one hour.
- Iron overload screening by MRI (MRI; R2, T2\*, or R2\*) for liver iron content every one to two years compared with serial monitoring of ferritin levels alone in patients with SCD (all genotypes) receiving chronic transfusion therapy.
- Not adding routine iron overload screening by T2\* MRI for cardiac iron content compared with serial monitoring of ferritin levels alone in patients with SCD (all genotypes) receiving chronic transfusion therapy.

### **European Atherosclerosis Society (EAS)**

Kronenberg et al. (2022) provided a consensus statement by the European Atherosclerosis Society (EAS) (2022) on lipoprotein(a) [Lp(a)] to provide updated evidence and clinical guidance for the role of Lp(a) in atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis. The EAS state findings do not support Lp(a) as a risk factor for venous thrombotic events and impaired fibrinolysis. Very low Lp(a) levels may be associated with increased risk of diabetes mellitus meriting further study. Lp(a) has pro-inflammatory and pro-atherosclerotic properties, which may partly relate to the oxidized phospholipids carried by Lp(a). This panel recommends testing Lp(a) concentration at least once in adults; cascade testing has potential value in familial hypercholesterolemia, or with family or personal history of (very) high Lp(a) or premature ASCVD. Without specific Lp(a)-lowering therapies, early intensive risk factor management is recommended, targeted according to global cardiovascular risk and Lp(a) level. Lipoprotein apheresis is an option for very high Lp(a) with progressive cardiovascular disease despite optimal management of risk factors. The authors concluded this statement reinforces evidence for Lp(a) as a causal risk factor for cardiovascular outcomes. Trials of specific Lp(a)-lowering treatments are needed to confirm clinical benefit for cardiovascular disease and aortic valve stenosis.

## **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 white blood cell count in acute promyelocytic leukemia (APL) because of the difference in leukemia biology. However, in life threatening cases with leukostasis that is not responsive to other modalities, leukapheresis can be considered with caution (2023).

The NCCN Clinical Practice Guideline for Multiple Myeloma indicates that plasmapheresis should be used as an adjunctive therapy for symptomatic hyperviscosity. The Guideline also notes that mechanical removal of free light chains (FLCs) with high cutoff dialysis filters or plasmapheresis may have a limited role as a category 2B recommendation (2023).

## **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, July 2023).

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

In the clinical pathway for managing familial hypercholesterolemia (FH), NICE (2021) made the following recommendations regarding clinical indications for low density lipoprotein (LDL) apheresis:

- Lipid-modifying drug therapy be considered before LDL apheresis in patients under 16 years of age;
- LDL apheresis should be considered for adults and children/young people with homozygous FH depending on factors such as the person's response to lipid-modifying drug therapy and the presence of coronary artery disease;
- LDL apheresis should be considered for people with heterozygous FH in exceptional circumstances, such as when there is progressive, symptomatic heart disease that does not respond to maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy.

NICE clinical guidelines on the management of multiple sclerosis in adults do not address any type of therapeutic apheresis (2022).

NICE clinical guideline on the diagnosis and management of multiple myeloma recommends that facilities treating people with myeloma provide regional access through their network to therapeutic apheresis (2018).

NICE also recommended that Extracorporeal Photopheresis should not be used outside the context of research for Crohn's disease for both adults and children (2009).

## **U.S. Food and Drug Administration (FDA)**

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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/pmn.cfm>. (Accessed July 11, 2023)

The FDA has granted premarket approval (PMA) for one Extracorporeal Photopheresis (ECP) device, the Therakos CELLEX Photopheresis Kit (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 is approved by FDA for the same indication. Additional information is available at the following website:

[https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?start\\_search=1&applicant=&tradename=&productcode=&pmanumber=P860003&supplementnumber=&advisorycommittee=&docketnumber=&supplementtype=&expeditedreview=&](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?start_search=1&applicant=&tradename=&productcode=&pmanumber=P860003&supplementnumber=&advisorycommittee=&docketnumber=&supplementtype=&expeditedreview=&)

UVADEX was granted Orphan Drug Status “for use in conjunction with the UVAR™ XTS™ or THERAKOS™ CELLEX™ Photopheresis Kit 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: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/020969s006lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020969s006lbl.pdf). (Accessed July 11, 2023)

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## Policy History/Revision Information

Date	Summary of Changes
03/01/2024	<p><b>Coverage Rationale</b></p> <ul style="list-style-type: none"> <li>● Revised list of conditions/diagnoses for which Therapeutic Apheresis is <b>proven and medically necessary</b>:               <ul style="list-style-type: none"> <li>○ Added:                   <ul style="list-style-type: none"> <li>▪ Chronic acquired demyelinating polyneuropathies; IgG/IgA/IgM related and anti-myelin-associated glycoprotein</li> <li>▪ Familial hypercholesterolemia, all patients via therapeutic Plasma Exchange (TPE)</li> <li>▪ Transplantation, heart, second line therapy, rejection prophylaxis via therapeutic Plasma Exchange</li> <li>▪ Transplantation, kidney, ABO incompatible, second line therapy, desensitization, living donor</li> <li>▪ Transplantation, lung, chronic lung allograft dysfunction</li> </ul> </li> <li>○ Removed:                   <ul style="list-style-type: none"> <li>▪ Paraproteinemic demyelinating neuropathies via TPE; anti-myelin-associated glycoprotein, multifocal motor neuropathy, IgG/IgA, and IgM</li> <li>▪ Vasculitis, Behcet’s disease (Adsorptive Cytapheresis) and idiopathic polyarteritis nodosa (PAN) (TPE)</li> </ul> </li> </ul> </li> </ul>



Date	Summary of Changes
	<ul style="list-style-type: none"> <li>○ Replaced: <ul style="list-style-type: none"> <li>▪ “Acute inflammatory demyelinating polyneuropathy (<i>Guillain-Barré syndrome</i>), primary treatment” with “acute inflammatory demyelinating polyneuropathy, primary treatment”</li> <li>▪ “Anti-glomerular basement membrane disease (<i>Goodpasture’s syndrome</i>)” with “anti-glomerular basement membrane disease”</li> <li>▪ “Cutaneous T-cell lymphoma, mycosis fungoides, Sézary syndrome, <i>erythrodermic</i>” with “cutaneous T-cell lymphoma, <i>erythrodermic</i> mycosis fungoides, Sézary syndrome”</li> <li>▪ “Familial hypercholesterolemia, homozygous” with “familial hypercholesterolemia, homozygotes, <i>lipoprotein apheresis</i>”</li> <li>▪ “Familial hypercholesterolemia, heterozygous, second line therapy” with “familial hypercholesterolemia, heterozygotes, <i>lipoprotein apheresis</i>, second line therapy”</li> <li>▪ “Multiple sclerosis, second line therapy, acute central nervous system (CNS) inflammatory, demyelinating, and relapsing form with steroid resistant exacerbations” with “multiple sclerosis, acute attack or relapse, second line therapy”</li> <li>▪ “Neuromyelitis optica spectrum disorders (<i>Devic’s syndrome</i>), acute or relapse, second line therapy” with “neuromyelitis optica spectrum disorders, acute or relapse, second line therapy”</li> <li>▪ “Pediatric autoimmune neuropsychiatric disorders <i>associated with streptococcal infections</i> (PANDAS) exacerbation” with “pediatric autoimmune neuropsychiatric disorders, PANDAS/<i>PANS</i> exacerbation”</li> <li>▪ “Pruritus due to hepatobiliary diseases” with “pruritus due to hepatobiliary diseases, <i>treatment resistant</i>”</li> <li>▪ “Sickle cell disease, stroke <i>prevention</i>” with “sickle cell disease, stroke <i>prophylaxis</i>”</li> <li>▪ “Transplantation, <i>cardiac</i>, second line therapy, cellular/recurrent rejection” with “transplantation, <i>heart</i>, second line therapy; cellular/<i>rejection</i>, recurrent rejection”</li> <li>▪ “Transplantation, <i>renal</i>, ABO compatible, antibody mediated rejection, desensitization, living donor” with “transplantation, <i>kidney</i>, ABO compatible, antibody mediated rejection, desensitization/<i>prophylaxis</i>, living donor”</li> <li>▪ “Transplantation, <i>renal</i>, ABO incompatible, second line therapy, antibody mediated rejection” with “transplantation, <i>kidney</i>, ABO incompatible, second line therapy, antibody mediated rejection”</li> <li>▪ “Transplantation, liver, desensitization, ABO incompatible living donor” with “transplantation, liver, desensitization, ABO incompatible living donor, <i>via therapeutic Plasma Exchange</i>”</li> <li>▪ “Vasculitis, antineutrophil cytoplasmic antibodies (ANCA)-associated, <i>Dialysis dependent, DAH</i>” with “vasculitis, antineutrophil cytoplasmic antibodies (ANCA)-associated, <i>microscopic polyangiitis, granulomatosis with polyangiitis</i>”</li> </ul> </li> <li>● Revised list of conditions/diagnoses for which Therapeutic Apheresis is <b>unproven and not medically necessary</b>: <ul style="list-style-type: none"> <li>○ Added: <ul style="list-style-type: none"> <li>▪ Acute toxins, venoms, and poisons</li> <li>▪ Alzheimer’s disease (mild or moderate)</li> <li>▪ Autoimmune dysautonomia</li> <li>▪ Chronic acquired demyelinating polyneuropathies, CANOMAD/CANDA</li> <li>▪ Cryoglobulinemia</li> <li>▪ Idiopathic inflammatory myopathies, including anti-synthetase-syndrome, clinically amyopathic dermatomyositis and immune-mediated necrotizing myopathies</li> <li>▪ Immune checkpoint inhibitors, immune-related adverse events</li> <li>▪ Paraneoplastic autoimmune retinopathies</li> <li>▪ Thrombotic microangiopathy, pregnancy associated, severe, extremely preterm preeclampsia, severe</li> <li>▪ Transplantation, intestine</li> <li>▪ Transplantation, liver, immune suppression withdrawal</li> </ul> </li> </ul> </li> </ul>

Date	Summary of Changes
	<ul style="list-style-type: none"> <li>▪ Transplantation, liver, desensitization, ABO Incompatible, via extracorporeal Photopheresis</li> <li>▪ Vaccine-induced immune thrombotic thrombocytopenia</li> <li>○ Removed: <ul style="list-style-type: none"> <li>▪ Amyotrophic lateral sclerosis</li> <li>▪ Aplastic anemia; pure red cell aplasia</li> <li>▪ Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome</li> <li>▪ Overdose, envenomation, and poisoning</li> <li>▪ Paraproteinemic demyelinating polyneuropathies, multiple myeloma (2C)</li> <li>▪ Transplantation, hematopoietic stem cell ABO incompatible, HLA desensitized</li> <li>▪ Transplantation, renal, ABO compatible, desensitization, deceased donor</li> <li>▪ Vasculitis, ANCA-associated, MPA/GPA/RLV: RPGN, Cr &lt; 5.7</li> </ul> </li> <li>○ Replaced: <ul style="list-style-type: none"> <li>▪ “Acute liver failure (requiring TPE)” with “acute liver failure <i>and acute fatty liver of pregnancy</i>(requiring TPE)”</li> <li>▪ “Amyloidosis, systemic” with “amyloidosis, systemic, <i>dialysis related</i>”</li> <li>▪ “Anti-glomerular basement membrane disease, dialysis dependent, without diffuse alveolar hemorrhage (<i>Goodpasture’s syndrome</i>)” with “anti-glomerular basement membrane disease, dialysis dependent, without diffuse alveolar hemorrhage”</li> <li>▪ “Atopic (<i>neuro-</i>)dermatitis (<i>atopic eczema</i>), recalcitrant” with “atopic dermatitis, recalcitrant”</li> <li>▪ “Chronic focal encephalitis (<i>Rasmussen’s encephalitis</i>)” with “chronic focal encephalitis”</li> <li>▪ “Coagulation factor inhibitors” with “coagulation factor <i>deficiency and</i> inhibitors”</li> <li>▪ “Cutaneous T-cell lymphoma, mycosis fungoides, <i>Sézary syndrome</i>, non-erythrodermic” with “cutaneous T-cell lymphoma, mycosis fungoides, non-erythrodermic”</li> <li>▪ “Erythropoietic <i>porphyria</i>, liver disease” with “erythropoietic <i>protoporphyrin</i>, liver disease”</li> <li>▪ “Focal segmental glomerulosclerosis, <i>recurrent kidney transplant</i> or steroid resistant in native kidney via lipoprotein apheresis or TPE” with “focal segmental glomerulosclerosis, steroid resistant in native kidney via TPE or lipoprotein apheresis <i>for all types</i>”</li> <li>▪ “Hemophagocytic lymphohistiocytosis/<i>Hemophagocytic syndrome/Macrophage activating syndrome</i>” with “hemophagocytic lymphohistiocytosis”</li> <li>▪ “IgA nephropathy (<i>Berger’s Disease</i>)” with “IgA nephropathy”</li> <li>▪ “Immune thrombocytopenia” with “immune thrombocytopenia, <i>refractory</i>”</li> <li>▪ “Phytanic acid storage disease (<i>Refsum’s disease</i>)” with “phytanic acid storage disease”</li> <li>▪ “Red cell alloimmunization, <i>prevention and treatment</i>” with “red blood cell alloimmunization, <i>pregnancy complications</i>”</li> <li>▪ “<i>Scleroderma</i> (systemic sclerosis)” with “systemic sclerosis”</li> <li>▪ “Steroid-responsive encephalopathy associated with autoimmune thyroiditis (<i>Hashimoto’s encephalopathy</i>)” with “steroid-responsive encephalopathy associated with autoimmune thyroiditis”</li> <li>▪ “Thrombotic microangiopathy, drug associated” with “thrombotic microangiopathy, drug associated (<i>Ticlopidine, Clopidogrel, Gemcitabine, Quinine</i>)”</li> <li>● “Transplantation, <i>cardiac</i>, rejection prophylaxis” with “transplantation, <i>heart</i>, rejection prophylaxis <i>via extracorporeal Photopheresis</i>”</li> <li>▪ “Transplantation, <i>cardiac</i>, antibody mediated rejection” with “transplantation, <i>heart</i>, antibody mediated rejection”</li> <li>▪ “Transplantation, hematopoietic stem cell ABO incompatible <i>major/minor ABOi with pure RBC</i> aplasia” with “transplantation, hematopoietic stem cell ABO incompatible, pure <i>red cell</i> aplasia”</li> <li>▪ “Transplantation, liver, ABO incompatible” with “transplantation, liver, <i>desensitization</i>, ABO incompatible, <i>deceased donor</i>”</li> <li>▪ “Vasculitis, IgA (Henoch-Schönlein purpura)” with “Vasculitis, IgA, crescentic rapidly progressive glomerulonephritis, severe extra-renal manifestations”</li> </ul> </li> </ul>

Date	Summary of Changes
	<ul style="list-style-type: none"> <li>▪ “Vasculitis (<i>unless noted [in the policy] as proven</i>)” with “<i>vasculitis, Hepatitis B polyarteritis nodosa, Kawasaki disease, multisystem inflammatory syndrome in children</i>”</li> </ul> <p><b>Supporting Information</b></p> <ul style="list-style-type: none"> <li>• Updated <i>Description of Services, Clinical Evidence, FDA, and References</i> sections to reflect the most current information</li> <li>• Archived previous policy version CS004KY.04</li> </ul>

## Instructions for Use

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

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