Apheresis (for Louisiana Only)

Policy Number: CS004LA.K~~J~~
Effective Date: ~~April 1, 2020~~ TBD

➲ Instructions for Use

Table of Contents **Page**

Application

This Medical Policy only applies to the state of Louisiana.

Coverage Rationale

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

- Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome), primary treatment
- Acute liver failure (requiring High Volume **Therapeutic** Plasma Exchange **(TPE-HV))**~~;~~
- ~~ANCA-associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis; and Microscopic Polyangiitis)~~
  - ~~Dialysis dependent~~
  - ~~Diffuse alveolar hemorrhage (DAH)~~
- Anti-glomerular basement membrane disease (Goodpasture's syndrome)
  - ~~Dialysis dependent~~
  - ~~DAH~~
- ~~Cardiac transplantation, second line therapy~~
  - ~~Recurrent rejection~~
  - ~~Desensitization~~
  - **Dialysis independent**
  - **Diffuse alveolar hemorrhage (DAH)**
- Chronic inflammatory demyelinating polyneuropathy **(CIDP)**
- Cryoglobulinemia, second line therapy
- Cutaneous T-cell lymphoma **(CTCL)**~~;~~ mycosis fungoides; **Sézary** ~~Sezary~~ syndrome, erythrodermic

- **Dilated cardiomyopathy, idiopathic, New York Heart Association Class II-IV, via Immunoadsorption**
- Familial hypercholesterolemia
  - Homozygous
  - Heterozygous, second line therapy
- Focal segmental glomerulosclerosis, recurrent in transplanted kidney, second line therapy
- Graft-versus-host disease
  - Acute
  - Chronic, second line therapy
- ~~Heart transplantation in children less than 40 months of age, ABO incompatible, second line therapy~~
- Hereditary hemochromatosis
- ~~Hyperlipoproteinemia~~
- Hypertriglyceridemic pancreatitis, severe
- Hyperviscosity in hypergammaglobulinemia
- ~~Idiopathic dilated cardiomyopathy, NYHA class II-IV, via IA~~
- Inflammatory bowel disease, **ulcerative colitis/Crohn's Disease via Adsorptive Cytapheresis** ~~via adsorptive cytapheresis~~
- ~~Liver transplantation, ABO incompatible~~
  - ~~Desensitized ABOi~~
  - ~~Living donor~~
- ~~Lung transplantation, bronchiolitis obliterans syndrome~~
- ~~Major hematopoietic stem cell transplant, ABO incompatible, second line therapy~~
  - ~~HPC(M)~~
  - ~~HPC(A)~~
- **Lipoprotein(a) hyperlipoproteinemia,**
- Multiple sclerosis, second line therapy
  - Acute **central nervous system (**CNS**)** inflammatory, demyelinating
  - Relapsing form with steroid resistant exacerbations
- Myasthenia gravis, acute
- Myeloma cast nephropathy, second line therapy
- Neuromyelitis optica spectrum disorders (**NMOSD/**Devic's syndrome), acute or relapse, second line therapy
- *N*-methyl D-aspartate receptor antibody encephalitis
- Paraproteinemic **demyelinating neuropathies** ~~polyneuropathies~~ via Therapeutic Plasma Exchange (TPE)
  - Anti-**myelin-associated glycoprotein (**MAG**)**
  - Multifocal motor **neuropathy**
  - IgG/IgA
  - IgM
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) exacerbation~~)~~
- Peripheral vascular diseases
- Polycythemia vera; erythrocytosis
- Progressive multifocal leukoencephalopathy **(PML)** associated with natalizumab
- Pruritus due to hepatobiliary diseases
- ~~Renal transplantation, ABO compatible~~
  - ~~Antibody mediated rejection~~

- ~~Desensitization, living donor~~
- ~~Renal transplantation, ABO incompatible, second line therapy~~
  - ~~Antibody mediated rejection~~
- Rheumatoid arthritis, refractory, second line therapy
- Sickle cell disease
  - Acute stroke or **multiorgan** ~~multi-organ~~ failure
  - Acute chest syndrome **(ACS),** ~~,~~ severe, second line therapy
  - Stroke prevention
  - **Individuals requiring chronic transfusion (receiving transfusions once every 5 weeks or more frequently)**
  - ~~Prevention of transfusional iron overload~~
- ~~Thrombotic microangiopathy, complement mediated~~
  - ~~*MCP mutations*~~ **thrombotic**
- ~~Thrombotic microangiopathy, Shiga toxin mediated~~
  - ~~Absence of severe neurological symptoms~~
- ~~Thrombotic~~ thrombocytopenic purpura **(TTP)**
- **Transplantation, cardiac, second line therapy**
  - **Cellular/recurrent rejection,**
  - **Desensitization**
  - **In children less than 40 months of age, ABO incompatible**
- **Transplantation, hematopoietic stem cell, ABO incompatible (ABOi), second line therapy**
  - **Haemopoietic progenitor cells collected from marrow HPC(M)**
  - **Haemopoietic progenitor cells collected by apheresis HPC(A)**
- **Transplantation, Liver, desensitization, ABOi living donor**
- **Transplantation, Lung, bronchiolitis obliterans syndrome**
- **Transplantation, Renal, ABO compatible**
  - **Antibody mediated rejection**
  - **Desensitization, living donor**
- **Transplantation, Renal, ABO incompatible, second line therapy**
  - **Antibody mediated rejection**
- **Vasculitis, Antineutrophil cytoplasmic antibodies (ANCA) -associated**
  - **Dialysis dependent**
  - **DAH**
- Vasculitis
  - Behcet's disease (**Adsorptive Cytapheresis),** ~~adsorptive cytapheresis)~~
  - Idiopathic **polyarteritis nodosa (**PAN**)** (TPE)
- Voltage gated potassium channel **(VGKC) antibody** ~~antibodies~~-related **diseases** ~~conditions~~
- Wilson's disease, fulminant

Due to insufficient evidence of efficacy, Therapeutic Apheresis ~~therapeutic apheresis~~ **including Plasma Exchange,** ~~plasmapheresis~~**Plasmapheresis,**~~plasma exchange, plasmapheresis,~~ **or Photopheresis**~~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 inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome), after IVIG~~
- **Acute liver failure (requiring TPE)**
- Age related macular degeneration**, dry**
- Amyloidosis, systemic
- Amyotrophic lateral sclerosis

- ANCA-associated rapidly progressive glomerulonephritis, dialysis independent (Granulomatosis with polyangiitis; and Microscopic Polyangiitis)
- Anti-glomerular basement membrane disease, dialysis dependent, without DAH (Goodpasture's syndrome)
- Aplastic anemia; pure red cell aplasia
- Atopic (neuro-) dermatitis (atopic eczema), recalcitrant
- Autoimmune hemolytic anemia**; severe** ~~:~~ warm autoimmune hemolytic anemia **(WAIHA); severe** ~~,~~ cold agglutinin disease
- Babesiosis**, severe**
- Burn shock resuscitation
- Cardiac neonatal lupus
- ~~Cardiac transplantation~~
  - ~~Antibody mediated rejection~~
  - ~~Rejection prophylaxis~~
- Catastrophic antiphospholipid syndrome**/Hemolytic uremic syndrome**
- Chronic focal encephalitis (Rasmussen's encephalitis)
- Coagulation factor inhibitors
- Complex regional pain syndrome
- Cutaneous T-cell lymphoma; mycosis fungoides; Sézary syndrome, non-erythrodermic
- ~~Dermatomyositis/polymyositis~~
- **Dilated cardiomyopathy, idiopathic, New York Heart Association Class II-IV, via TPE**
- Erythropoietic porphyria, liver disease
- Focal segmental glomerulosclerosis, **recurrent** ~~native~~ kidney **transplant or** ~~,~~ steroid resistant **in native kidney via LA or TPE**
- ~~Hashimoto's encephalopathy~~**Hemolysis, Elevated Liver enzymes and Low Platelets (**
- HELLP**)** syndrome
- ~~Hematopoietic stem cell transplantation,~~
  - ~~HLA desensitized~~
  - ~~Major/minor ABO incompatibility with pure RBC aplasia~~
  - ~~Minor HPC(A)~~
- ~~Hemolytic uremic syndrome~~
- Hemophagocytic lymphohistiocytosis **(HLH)/Hemophagocytic syndrome/Macrophage activating syndrome**
- ~~Henoch-Schonlein purpura~~
- Heparin induced thrombocytopenia and thrombosis **(HIT/HITT)**
- Hyperleukocytosis
- Hypertriglyceridemic pancreatitis, prevention **of relapse**
- Immune thrombocytopenia
- IgA nephropathy (Berger's Disease)
- Inflammatory bowel disease, **Crohn's Disease,** via Extracorporeal Photopheresis
- Lambert-Eaton myasthenic syndrome
- ~~Liver transplantation~~
  - ~~ABO incompatible~~
  - ~~Antibody mediated rejection~~
- ~~Lung transplantation~~
  - ~~Antibody mediated rejection~~
  - ~~Desensitization~~
- Malaria

- Multiple sclerosis, chronic ~~(unless noted above as proven)~~
- **Myasthenia Gravis, long term treatment**
- **Myeloma cast nephropathy**
- Nephrogenic systemic fibrosis
- Neuromyelitis optica spectrum disorders **(NMOSD),** ~~,~~ maintenance
- Overdose, **envenomation** ~~venoms~~, and poisoning
- Paraneoplastic neurologic syndromes
- Paraproteinemic **demyelinating polyneuropathies** ~~polyneuropathy~~, multiple **myeloma (2C** ~~indications (unless noted above as proven~~)
- **PANDAS;** ~~Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (~~Sydenham's chorea, severe ~~)~~
- Pemphigus vulgaris
- Phytanic acid storage disease (Refsum's disease)
- Post transfusion purpura **(PTP))**
- Psoriasis
- Red cell alloimmunization, prevention and treatment
- ~~Renal transplantation, ABO compatible, desensitized, deceased donor~~
- Scleroderma (systemic sclerosis)
- Sepsis with multiorgan failure
- Sickle cell disease (unless noted above as proven)
- **Steroid-responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto's encephalopathy)**
- Stiff-person syndrome
- Sudden sensorineural hearing loss
- Systemic lupus erythematosus, severe **complications**
- Thrombocytosis
- Thrombotic microangiopathy ~~(unless noted above as proven)~~
  - **Coagulation mediated (THBD, DGKE and PLG mutations)**
  - **Complement mediated (Factor H autoantibody and complement factor gene mutations)**
  - **Drug associated**
  - **Infection associated (STEC-HUS, severe; pHUS)**
  - **Transplantation associated**
- Thyroid storm
- Toxic epidermal necrolysis **(TEN)**
- **Transplantation, cardiac**
  - **Rejection prophylaxis**
  - **Antibody mediated rejection**
- **Transplantation, hematopoietic stem cell ABOi:**
  - **HLA desensitized**
  - **Minor ABOi HPC(A)**
  - **Major/minor ABOi w/ pure RBC aplasia**
- **Transplantation, hematopoietic stem cell, HLA desensitization**
- **Transplantation, Liver**
  - **ABO incompatible**
  - **Antibody mediated rejection**
- **Transplantation, Lung**
  - **Antibody mediated rejection**
  - **Desensitization**
- **Transplantation, Renal, ABO compatible, desensitization, deceased donor**

- Vasculitis**, ANCA-associated (AAV** ~~(unless noted above as proven~~)
  - **MPA/GPA/RLV: RPGN, Cr <5.7**
  - **EGPA**
- **Vasculitis, IgA (Henoch-Schönlein purpura)**
- **Vasculitis (unless noted above as proven)**

Note: Refer to the **Description of Services** ~~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, Padmanabhan, et al., 2019).

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 federal, state, or contractual requirements 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 immunoadsorption, selective adsorption or selective filtration and plasma reinfusion
36522	Photopheresis, extracorporeal

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

Codes labeled with an asterisk(*) are not on the Louisiana Medicaid Fee Schedule and therefore may not be covered by the state of Louisiana Medicaid Program.

Description of Services

~~Therapeutic apheresis is a procedure in which the blood of a patient is passed through an extracorporeal medical device which separates components of blood to treat a disease. It is a general term which includes all apheresis- based procedures. (Schwartz, et al., 2016; Padmanabhan et al., 2019).)~~

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

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

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

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

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

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

Filtration Selective Removal: A procedure which uses a filter to remove components from the blood based on size. Depending on the pore size of the filters used, different components can be removed. Filtration-based instruments can be used to perform plasma exchange or LDL apheresis. They can also be used to perform donor plasmapheresis where plasma is collected for transfusion or further manufacture.

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

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

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

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

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

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

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, a2-macroglobulin, low-density lipoprotein cholesterol, and IgM to reduce plasma viscosity and red cell aggregation. This is done to improve blood flow and tissue oxygenation. LDL apheresis devices and selective filtration devices using two filters, one to separate plasma from cells and a second to separate the high-molecular-weight components, are used for these procedures.

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

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

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

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Clinical Evidence

~~The American Society for Apheresis (ASFA) (Padmanabhan et al., 2019) has reviewed therapeutic apheresis outcomes and published practice guidelines. The guidelines included analysis based on the quality of the evidence as well as the strength of recommendation derived from the evidence. ASFA categorizes disorders as noted below:~~

- ~~Category I: Disorders for which apheresis is accepted as first line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.~~
- ~~Category II: Disorders for which apheresis is accepted as second line therapy, either as a standalone treatment or in conjunction with other modes of treatment.~~
- ~~Category III: Optimum role of apheresis therapy is not established. Decision making should be individualized.~~
- ~~Category IV: Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.~~

~~ASFA recognized that categories alone are difficult to translate into clinical practice. Thus, they adopted a system to assign recommendation grades for therapeutic apheresis to enhance the clinical value of ASFA categories. The grading recommendation are adopted from Guyatt et al. 2008, Szczepiorkowski et al. 2010, Schwartz et al., 2016, and Padmanabhan et al., 2019:~~

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

Sickle Cell Disease

~~Wade et al. (2022) performed a retrospective review of pediatric sickle cell disease (SCD) patients 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 ≥ 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 Sß+ 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 SCD patients with HCT ≥ 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 SCD patients 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 sickle cell disease (SCD) patients. 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 adverse events. 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 adverse events. 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 adverse events detected in association with aRBX.~~

~~Hequet et al. (2021) completed a prospective analysis to evaluate the clinical safety of the red blood cell (RBC) exchange (RCE)/RBC-primed procedure in 12 sickle cell anemia (SCA) low-weight children under either a chronic RCE program or emergency treatment over 65 sessions. The authors monitored grade 2 adverse events (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 adverse events (AEs) could occur. Post-apheresis hematocrit (Hct) and a fraction of cell remaining (FCR) values were compared to the expected values. We 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.~~

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 review of pediatric sickle cell disease (SCD) patients 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

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Cochrane has published systematic reviews for the use of transfusion therapies, including simple or exchange transfusions, for the treatment of complications of sickle cell disease 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 sickle cell disease.

~~In a single center, retrospective cohort study comparing the effect of simple transfusion (ST), partial manual exchange (PME) and red cell exchange (RCE) on liver iron concentration (LIC), Fasano et al. (2016) reviewed the medical records of 28 patients with sickle cell anemia who were on a chronic transfusion therapy regimen that included transfusions administered every 3 to 5 weeks with the goal of maintaining a pretransfusion HbS of <30%. Patients were included if they were on this chronic transfusion regimen for at least 12 months, on a stable dose of at least 25 mg/kg/day deferasirox and had at least 6 months of monthly laboratory data available. Patients were placed on either PME or RCE for continued or worsening iron overload on ST or if they had an inability to maintain HbS within the target range on ST. Six of the patients crossed over from one method of transfusion to another to include 36 transfusion modality intervals (20 ST, 6 PME, and 10 RCE). The authors found no significant difference in alloimmunization rate between ST/PME and RCE groups. They found that chronic RCE in combination with iron chelation is effective at reducing both serum ferritin and LIC over time and that RCE does not result in an increased rate of RBC alloimmunization.~~

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

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

~~Turner et al. (2009) evaluated the efficacy of exchange transfusion (XC) versus simple transfusion (ST) for treatment of 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 postprocedure length of stay (XC 5.6 days vs. ST 5.9 days) or total length of stay (XC 8.4 days vs. ST 8.0 days). A total of 10.3 +/- 3.0 units were transfused for XC compared to 2.4 +/- 1.2 units for ST. Based on postprocedure length of stay or total length of stay, the authors could~~

~~not detect a difference in the efficacy of XC compared to ST in populations despite red blood cell product usage fourfold higher in the XC group. According to the authors, there is a need for an adequately powered, randomized trial to examine the true risk-benefit ratio of XC in ACS.~~

Wahl et al. (2012) compared alloimmunization rates between patients receiving simple or exchange chronic transfusions with erythrocytapheresis (ECP). Data were retrospectively collected for 45 SCD patients (N=23 simple, N=22 ECP) **who received blood transfusion of 10 to 15 ml of red blood cells (RBCs)/kg with each transfusion every 3 to 4 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 6 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 sickle cell disease (SCD) who were started on chronic red cell transfusion (RCT). Each patient received RCTs every 3-4 weeks for a minimum of 6 months with a total of 4,472 packed red blood cell units being administered. The authors reported that 9 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.

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

- ~~In children with SCA, screen annually with TCD according to methods employed in the STOP studies, beginning at age 2 and continuing until at least age 16.~~
- ~~In children with conditional (170-199 cm/sec) or elevated (>200 cm/sec) TCD results, refer to a specialist with expertise in chronic transfusion therapy aimed at preventing stroke.~~
- ~~In all persons with SCD, perform urgent exchange transfusion with consultation from hematology, critical care, and/or apheresis specialists when there is rapid progression of ACS as manifested by oxygen saturation below 90 percent despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates, and/or decline in hemoglobin concentration despite simple transfusion.~~
- ~~In consultation with a sickle cell expert, perform exchange transfusion in people with SCD who develop acute stroke confirmed by neuroimaging.~~
- ~~Initiate prompt evaluation, including neurologic consultation and neuroimaging studies, in people with SCD who have mild, subtle, or recent history of signs or symptoms consistent with transient ischemic attack.~~
- ~~In children and adults who have had a stroke, initiate a program of monthly simple or exchange transfusions.~~

- ~~In adults and children with SCA, transfuse RBCs to bring the hemoglobin level to 10 g/dL prior to undergoing a surgical procedure involving general anesthesia.~~
- ~~In adults and children with HbSC or HbSB⁺-thalassemia, consult a sickle cell expert to determine if full or partial exchange transfusion is indicated before a surgical procedure involving general anesthesia.~~
- ~~Administer iron chelation therapy, in consultation with a hematologist, to patients with SCD and with documented transfusion acquired iron overload.~~

~~Professional Societies~~

~~American Society for Apheresis (ASFA)~~

~~Regarding sickle cell disease, ASFA states:~~

- ~~Red blood cell (RBC) exchange is an option for patients with acute 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, (Padmanabhan et al., 2019).~~

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Desensitization for Renal Transplants

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

In a single-center retrospective study, Campise et al (2019) evaluated their experience with prophylactic and therapeutic plasmapheresis in a cohort of 21 deceased-donor kidney transplant recipients with primary focal segmental glomerulosclerosis (FSGS). The analyzed ten patients who received post-transplant prophylactic plasmapheresis only with eleven who received both pre- and post-transplant prophylactic plasmapheresis. The 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 view, the small, homogeneous sample size, and the differences in follow-up between the treatment groups.

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

~~Meng et al. (2009) determined the percentage of panel reactivity and specificity of anti-HLA immunoglobulin (IgG) antibodies in 73 presensitized renal allograft recipients who underwent cadaveric renal transplantation compared with 81 unsensitized recipients who received cadaveric renal transplantation (control group). Sensitized patients had higher rates of graft rejection and graft loss. A total of 20 out of the 73 patients received pre-transplantation plasmapheresis (PP) and/or immunoadsorption (IA) and of these, 10~~

~~achieved negative panel reactive antibodies (PRAs). Graft rejection rate was 18% in unsensitized group, 41% in non-PP and/or IA sensitized group, and 20% in PP and/or IA sensitized group. Graft loss rate was 5% in unsensitized group, 21% in non-PP and/or IA sensitized group, and 15% in PP and/or IA sensitized group (20% positive PRA at transplant and 10% negative PRA at transplant). The authors concluded that pre-transplant PRA preparations might improve the access of presensitized patients to renal donors.~~

Montgomery et al. (2011b) used mathematical simulations verified by actual data from several national kidney-paired donation (KPD) programs to evaluate which donor/recipient phenotypes are likely to benefit from each transplant modality. They found that pairs that are easy to match are likely to receive compatible kidneys in a KPD. Those who are hard to match may be better served by desensitization with high-dose IVIG or plasmapheresis and low-dose IVIG. The phenotype which is both hard to match and hard to desensitize due to board and strong HLA reactivity are most likely to be transplanted by a hybrid modality utilizing desensitization after identifying a more immunologically favorable donor in a KPD. The authors state that recent outcomes from desensitization in which starting donor-specific antibody strength is low have been very good. For broadly sensitized patients with a high-strength cross-match, searching for a better donor in a KPD pool can facilitate a safer and more successful desensitization treatment course.

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

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

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Pediatric ABO-Incompatible Heart Transplantation

~~Dipchand 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 (≤ 14 months old, 1996-2006) showed no important differences in pretransplantation characteristics. In 7 patients, donor-specific isohemagglutinin titers were elevated at the time of transplantation but were significantly reduced using intraoperative plasma exchange. Only 2 of the 7 required treatment for AMR (which occurred early posttransplantation, was easily managed and did not recur in follow-up). Occurrence of graft vasculopathy (11%), malignancy (11%) and freedom from severe renal dysfunction were identical in both groups. Survival was identical (74% at 7 years post-transplantation). The researchers concluded that ABO blood group incompatible heart transplantation has excellent outcomes that are indistinguishable from those of the ABO-compatible population and there is no clinical justification for withholding this lifesaving strategy from all infants listed for heart transplantation. Further studies into observed differing responses in the development of donor-specific isohemagglutinins and the implications for graft accommodation are warranted.~~

Issitt et al. (2021) completed a retrospective analysis and first case series of patients transplanted with 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 isohaemagglutinin 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 isohaemagglutinin 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 isohaemagglutinin 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 3209 mL. Isohemagglutinin titers that were as high as 1:32 preoperatively were reduced to a range of 0-1:16 **post transplantation.**~~posttransplantation.~~ One patient expired from causes unrelated to organ rejection. The authors concluded that through the use of a combination of adult reservoir/pediatric oxygenator and extracorporeal circuit, ABO-incompatible plasma exchange transfusions can be undertaken safely using a simplified "3 times" method, reducing the circulating levels of isohemagglutinins while providing minimal circuit size. This allows ABO-incompatible heart transplantation in a broader patient population than reported previously.

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

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

~~Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and Sydenham's Chorea (SC) are pediatric post-infectious autoimmune neuropsychiatric disorders. Both share an array of neuropsychiatric symptoms and both may~~

~~have a shared etiopathogenesis. Because of the possible role of antineuronal antibodies in the pathogenesis, antibody removal by therapeutic plasma exchange (TPE) may be effective. However, the mechanism for the benefit of TPE is not clear, as there is a lack of relationship between therapeutic response and the rate of antibody removal (Szczepiorkowski, et al., 2010).~~

Eighteen patients were entered into a randomized controlled trial (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).

Rheumatoid Arthritis

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

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

Furst et al. (2000) conducted a double-blind, placebo RCT to determine the efficacy of the Prosorba Immunoadsorption Column in patients with refractory RA. Ninety-nine patients

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

Cardiovascular Disease

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.

Luirink, et al. (2020) performed an an observational multicenter cohort study 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/, 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 surrogage 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 3 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** ~~posit~~ that plasma selective delipidation converts alpha-HDL to pre-beta-like HDL, the most effective form of HDL for lipid removal from arterial plaques. However, there is a paucity of clinical evidence regarding HDL delipidation for various cardiac disease indications, including acute coronary syndrome (ACS). A search of the peer-reviewed medical literature identified one placebo-controlled RCT (N=28) (Waksman et al., 2010). This study sought to determine whether serial autologous infusions of selective HDL delipidated plasma are feasible and well tolerated in patients with ACS. Patients undergoing cardiac catheterization were randomized to either 7 weekly HDL selective delipidated or control plasma apheresis/ reinfusions. Patients underwent intravascular ultrasound (IVUS) evaluation of the target vessel. ~~,~~ All reinfusion sessions were tolerated well by all patients. The levels of prebeta-like HDL and alphaHDL in the delipidated plasma converted from 5.6% to 79.1% and 92.8% to 20.9%, respectively. The IVUS data demonstrated a numeric and non-significant trend toward regression in the total atheroma volume in the delipidated group compared with an increase of total atheroma volume in the control group. Study results demonstrated that serial autologous infusions of selective HDL delipidated plasma is clinically feasible and well tolerated. Study limitations included small study population and lack of appropriate blinding methods. The study may not have been sufficiently powered to detect differences between treatment and controls. Additional well-designed studies are necessary to determine the ability of HDL delipidation and plasma **reinfusion** ~~reinfsuion~~ 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, go to **www.clinicaltrials.gov and review Identifier NCT02791802.** ~~www.clinicaltrials.gov.~~ (Accessed ~~October 4, 2021~~ **August 9, 2022** ~~July 18, 2019~~)

Light Chain Nephropathy

In a multicenter retrospective study from 10 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 means 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 multiple myeloma patients with CN. The incidence of side effects associated with TPE was reported by the authors to affect 4 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. examined whether plasmapheresis in combination with chemotherapy could significantly remove free light chains (FLCs) in multiple myeloma (MM) patients with 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 ≥ 3 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 (2018).

~~As an adjunct to chemotherapy, several new extracorporeal techniques have raised interest as a further means to reduce serum FLC (sFLC) concentrations in the treatment of myeloma cast nephropathy. Whether addition of extracorporeal therapies to renoprotective therapy can result in better renal recovery is still a matter of debate and there are currently no guidelines in this field (Fabbrini et al., 2016).~~

Yu et al. (2015) conducted a meta-analysis to quantitatively evaluate the clinical efficacy of chemotherapy with or without plasmapheresis in the treatment of MM patients with 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 6-month survival rate between plasmapheresis and control group (75% vs. 66.7%). The 6-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. ~~In a review on current approaches to diagnosing and managing acute renal failure in individuals with multiple myeloma (MM), Leung and Behrens state that rapid reduction of sFLC, the cause of cast nephropathy, is required to reverse renal injury. If extracorporeal removal is used, it should be directed by sFLC levels, although its efficacy remains to be determined (2012).~~

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 MM patients with acute renal injury (Gupta et al., 2010).

~~National Comprehensive Cancer Network (NCCN)~~

~~NCCN MM Panel members consider the use of plasmapheresis for improvement of renal function as category 2B (2019).~~

~~Severe Cryoglobulinemia~~

~~In a 2018 review on the use of emergency apheresis in the management of plasma cell disorders, Kalayoglu Besisik stated that in hepatitis C virus-related mixed cryoglobulinemias, plasmapheresis is indicated if rapidly evolving life-threatening disease with immunosuppressive agent exists. In non-infectious mixed cryoglobulinemia~~

~~plasmapheresis is indicated when the disease manifestations are severe, as a second line option.~~

~~Rockx and Clark conducted a review of the medical literature over a 20-year span for evidence supporting or refuting the reported use of plasmapheresis for cryoglobulinemia. The 11 articles reviewed included a total of 156 patients. While plasma exchange is an accepted treatment for cryoglobulinemia, there were no large multicenter RCTs of plasma exchange versus placebo or versus immunosuppressive therapy. None had a clear report of the apheresis procedures or clearly defined quantitative outcomes. The quality and variability of the evidence precluded a meta-analysis or systematic analysis however, the authors found that these studies weakly supported the use of plasma exchange largely on a mechanistic basis. Further studies of greater rigor will provide better evidence to support or refute the use of plasma exchange in treating this condition (2010).~~

~~Inflammatory Bowel Disease~~

~~A large scale, prospective, observational study was performed by Yokoyama et al. (2014) which enrolled patients from 116 medical facilities in Japan with active ulcerative colitis (UC) treated with 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 (≥4 sessions within the first 2 weeks) was used in >70% of the patients. AEs were seen in 10.3%, which were severe in only 5 patients. Any concomitant medications did not increase the incidence of adverse events. The authors concluded that that 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.~~

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

Inflammatory Bowel Disease

A retrospective observational study was completed by Fukuchi et al. (2022) to examine the long-term maintenance rate after inducing 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 (second 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%. Clinical remission and MH rates after

second GMA did not differ from those after first GMA in the same patients (week 6: clinical remission, 100% vs 88.4%, p = 0.134; MH, 100% vs 84.8%, p = 0.074). 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.

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 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. 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 heterogenous reporting of adverse events. 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). The authors recommend further RCTs to justify the role of GMA for inducing remission in patients with UC. ~~With this being the first trial of its kind in humans, further studies with larger participant groups are needed.~~

~~Domènech and colleagues conducted a multi-center, open randomized trial to evaluate the efficacy and safety of adding granulocyte/monocyte apheresis (GMA) to oral prednisone in patients with steroid-dependent UC. The study compared GMA plus oral prednisone (40 mg/day) with prednisone alone administered in 7 weekly sessions to 123 patients with active, steroid-dependent UC. The GMA group consisted of 63 participants, and 62 received prednisone alone. A 9-week tapering schedule of prednisone was pre-established in both study groups. The primary endpoint was steroid-free remission at week 24, with no re-introduction of corticosteroids. Remission at week 24 was achieved in 13% in the GMA group and 7% in the control group. Time to relapse was significantly longer and steroid-related AEs were significantly lower in the GMA group. The authors concluded that while the addition of GMA to a conventional course of oral prednisone delayed clinical relapse, it did not increase the proportion of steroid-free remissions in patients with active steroid-dependent UC (2018).~~

~~Eberhardson et al.~~~~National Institute of Neurological Disorders and Stroke (NINDS)~~

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

~~National Institute for Health and Clinical Excellence (NICE)~~

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

~~National Comprehensive Cancer Network (NCCN)~~

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Clinical Practice Guidelines

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 Society for Apheresis (ASFA)

The ASFA (Padmanabhan et al., 2019) has reviewed therapeutic apheresis outcomes and published practice guidelines. The guidelines included analysis based on the quality of the evidence as well as the strength of recommendation derived from the evidence. ASFA categorizes disorders as noted below:

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

- Category IV: Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

ASFA recognized that categories alone are difficult to translate into clinical practice. Thus, they adopted a system to assign recommendation grades for therapeutic apheresis to enhance the clinical value of ASFA categories. The grading recommendations are adopted from Guyatt et al., 2008, Szczepiorkowski et al., 2010, Schwartz et al., 2016, and Padmanabhan et al., 2019:

- 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 (Padmanabhan et al., 2019).

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 HbSβ0 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 3-4 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 2 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 1 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 2 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 1 hour.**
- **Iron overload screening by MRI (MRI; R2, T2*, or R2*) for liver iron content every 1 to 2 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**

National Comprehensive Cancer Network (NCCN)

Guidelines on acute myeloid leukemia indicate that leukapheresis is not recommended in the routine management of patients with a high WBC in acute promyelocytic leukemia (APL**) 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 (~~2021~~**2022**~~2019~~).

The NCCN Clinical Practice Guideline for Multiple Myeloma indicates that ~~there is an update in progress for the Discussion section of the guideline; however, the Response Criteria and Supportive Care section updates have been completed~~**plasmapheresis should be used as an adjunctive therapy for symptomatic hyperviscosity. The Guideline also notes** ~~. The Response Criteria section includes plasmapheresis as adjunctive therapy for symptomatic hyperviscosity and the Supportive Care section~~**that** ~~for~~ **supportive management of renal disease in multiple myeloma includes plasmapheresis for the mechanical removal of Free Light Chains (FLCs) with a goal of removal of 50% as a category 2B recommendation (**~~2021~~2022).

National Heart, Lung, and Blood Institute (NHLBI)

The NHLBI published a clinical guideline for the management of SCD that includes the following recommendations relative to therapeutic apheresis (2014):

- **In children with Sickle Cell Anemia (SCA), screen annually with Transcranial Doppler (TCD) screening according to methods employed in the Stroke Prevention Trial in Sickle Cell Anemia (STOP) studies, beginning at age 2 and continuing until at least age 16.**
- **In children with conditional (170–199 cm/sec) or elevated (>200 cm/sec) TCD results, refer to a specialist with expertise in chronic transfusion therapy aimed at preventing stroke.**
- **In children and adults with SCD with confirmed acute hepatic syndrome (AHS) or severe acute intrahepatic cholestasis (AIC), perform simple or exchange transfusion**
- **In all persons with SCD, perform urgent exchange transfusion—with consultation from hematology, critical care, and/or apheresis specialists—when there is rapid progression of ACS as manifested by oxygen saturation below 90 percent despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates, and/or decline in hemoglobin concentration despite simple transfusion.**
- **In consultation with a sickle cell expert, perform exchange transfusion in people with SCD who develop acute stroke confirmed by neuroimaging.**
- **Initiate prompt evaluation, including neurologic consultation and neuroimaging studies, in people with SCD who have mild, subtle, or recent history of signs or symptoms consistent with transient ischemic attack.**
- **In children and adults who have had a stroke, initiate a program of monthly simple or exchange transfusions.**

- **In people with SCD and multi-symptom organ failure (MSOF), immediately initiate either simple or exchange transfusion in consultation with a sickle cell expert or hematologist.**
- **In adults and children with SCA, transfuse red blood cells (RBCs) to bring the hemoglobin level to 10 g/dL prior to undergoing a surgical procedure involving general anesthesia.**
- **In adults and children with Hemoglobin SC disease (HbSC) or Hemoglobin SB+ (beta) thalassemia (HbSB+-thalassemia), consult a sickle cell expert to determine if full or partial exchange transfusion is indicated before a surgical procedure involving general anesthesia.**
- **Administer iron chelation therapy, in consultation with a hematologist, to patients with SCD and with documented transfusion-acquired iron overload.**

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, ~~August 2020~~July 2022).

National Institute for Health and Clinical 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~~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 MS in adults do not address any type of therapeutic apheresis (~~2014; updated November 11, 2019).~~2022).

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).

~~Multiple clinical trials studying therapeutic apheresis and inflammatory bowel disease have been completed but results have not yet been published. For more information, go to www.clinicaltrials.gov. (Accessed October 11, 2021July 18, 2019)~~

~~*Professional Societies*~~

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

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

~~American Academy of Neurology (AAN)~~

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

~~Additional Search Terms~~

~~Photoimmune therapy, photoimmunotherapy~~

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 ~~October 11, 2021~~ **August 9, 2022** ~~July 18, 2019~~)

The FDA has granted premarket approval (PMA) to one **Extracorporeal Photopheresis** ~~extracorporeal photopheresis~~ (ECP) device, the UVAR Photopheresis System (Therakos, Inc., Exton, PA, USA). This system is currently only approved for the palliative treatment of skin manifestations resulting from cutaneous T-cell lymphoma (CTCL), which are unresponsive to other treatments. Therakos now markets a second generation of the system under the name UVAR XTS. The UVAR XTS system utilizes the photoactive drug, UVADEX (8-methoxsalen), also manufactured by Therakos and 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=&ivdproducts=off&combinationproducts=off&decisiondatefrom=&decisiondateto=&noticedatefrom=&noticedateto=&PAGENUM=50. (Accessed** ~~October 11, 2021~~**August 9, 2022**~~https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?start_search=1&applicant=&tradename=&productcode=&pmanumber=P860003&supplementnumber=&advisorycommittee=&docketnumber=&supplementtype=&expeditedreview=&ivdproducts=off&combinationproducts=off&decisiondatefrom=&decisiondateto=&noticedatefrom=&noticedateto=&PAGENUM=50. (Accessed July 18, 2019~~)

UVADEX was granted Orphan Drug Status "for use in conjunction with the UVAR photopheresis [system] to treat diffuse systemic sclerosis" in June 1993 and "for use in conjunction with the UVAR photopheresis system to treat graft versus host disease (GVHD)" in October 1998. In addition, UVADEX was granted Orphan Drug Status "for the prevention of acute rejection of cardiac allografts" in May 1994. Additional information is available at the following website: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020969s006lbl.pdf. (Accessed ~~October 11, 2021~~ **August 9, 2022** ~~July 18, 2019~~)

~~**Additional Medical Products**~~

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

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Policy History/Revision Information

Date	Summary of Changes
TBD	**Coverage Rationale** • Revised list of conditions/diagnoses for which therapeutic apheresis is proven and medically necessary; replaced: ○ "Hyperlipoproteinemia" with "*lipoprotein(a)* hyperlipoproteinemia" ○ "Inflammatory bowel disease via adsorptive cytapheresis" with "inflammatory bowel disease, *ulcerative colitis/Crohn's Disease* via adsorptive cytapheresis" ○ "Paraproteinemic *polyneuropathies* via TPE" with "paraproteinemic *demyelinating neuropathies* via TPE" ○ "Sickle cell disease *prevention of transfusional iron overload" with* "sickle cell disease *for individuals requiring chronic transfusion (receiving transfusions once every 5 weeks or more frequently)"* ○ "Thrombotic microangiopathy, *complement mediated (MCP mutations) and Shiga toxin mediated with absence of severe neurological symptoms*" with "thrombotic microangiopathy ○ "Cardiac transplantation, second line therapy, recurrent rejection" with "transplantation, cardiac, second line therapy, *cellular*/recurrent rejection" ○ "*Major* hematopoietic stem cell transplant, ABO incompatible, second line therapy" with "transplantation, hematopoietic stem cell, ABO incompatible (ABOi), second line therapy" ○ "ANCA-associated *rapidly progressive glomerulonephritis (granulomatosis with polyangiitis and microscopic polyangiitis)"* with "*vasculitis*, antineutrophil cytoplasmic antibodies (ANCA)-associated" • Revised list of conditions/diagnoses for which therapeutic apheresis is unproven and not medically necessary: ○ Added: ▪ Acute liver failure (requiring TPE) ▪ Dilated cardiomyopathy, idiopathic, New York Heart Association Class II-IV, via TPE ▪ Myasthenia gravis, long term treatment ▪ Myeloma cast nephropathy ▪ Transplantation, hematopoietic stem cell, HLA desensitization ▪ Vasculitis, ANCA-associated (AAV): – MPA/GPA/RLV: RPGN, Cr < 5.7 – EGPA ○ Removed: ▪ Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome), after IVIG ▪ Dermatomyositis/polymyositis ○ Replaced: ▪ "Age related macular degeneration" with "age related macular degeneration, *dry*"

- "Autoimmune hemolytic anemia; warm autoimmune hemolytic anemia (WAIHA); cold agglutinin disease" with "autoimmune hemolytic anemia; *severe* warm autoimmune hemolytic anemia (WAIHA); *severe* cold agglutinin disease"
- "Babesiosis" with "babesiosis, *severe*"
- "Focal segmental glomerulosclerosis, *native* kidney, steroid resistant" with "focal segmental glomerulosclerosis, *recurrent* kidney *transplant or* steroid resistant *in native kidney via LA or TPE*"
- "Hashimoto's encephalopathy" with "*steroid-responsive encephalopathy associated with autoimmune thyroiditis* (Hashimoto's encephalopathy)"
- "Hematopoietic stem cell transplantation" with "transplantation, hematopoietic stem cell *ABOi*"
- "Hemophagocytic lymphohistiocytosis" with "hemophagocytic lymphohistiocytosis (HLH)/*hemophagocytic syndrome/macrophage activating syndrome* "
- "Henoch-Schönlein purpura" with "*vasculitis, IgA* (Henoch-Schönlein purpura)"
- "Hypertriglyceridemic pancreatitis, prevention" with "hypertriglyceridemic pancreatitis, prevention *of relapse*"
- "Inflammatory bowel disease via extracorporeal photopheresis" with "inflammatory bowel disease, *Crohn's disease*, via extracorporeal photopheresis"
- "Multiple sclerosis, chronic *(unless noted [in the policy] as proven)*" with "multiple sclerosis, chronic"
- "Overdose, *venoms*, and poisoning" with "overdose, *envenomation*, and poisoning"
- "Paraproteinemic *polyneuropathy*, multiple *indications* (unless noted [in the policy] as proven)" with "paraproteinemic *demyelinating* polyneuropathies, multiple *myeloma (2C)*"
- "Systemic lupus erythematosus, severe" with "systemic lupus erythematosus, severe *complications*"
- "Thrombotic microangiopathy *(unless noted [in the policy] as proven)*" with "thrombotic microangiopathy: coagulation mediated (THBD, DGKE and PLG mutations), complement mediated (Factor H autoantibody and complement factor gene mutations), drug associated, infection associated (STEC-HUS, severe; pHUS), transplantation associated"

Definitions

- Added definition of:
  - Photopheresis
  - Plasma Exchange
  - Therapeutic Apheresis

Applicable Codes

- Added notation to indicate CPT/HCPCS codes 0342T and S2120 are not on the State of Louisiana Fee Schedule and therefore are not covered by the State of Louisiana Medicaid Program

Supporting Information

- Updated *Description of Services*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information

	• **Archived previous policy version CS004LA.J**

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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