Clinical Policy Title: Lipoprotein apheresis

Clinical Policy Number: 04.03.07

Effective Date: October 1, 2016
Initial Review Date: June 15, 2016
Most Recent Review Date: June 15, 2016
Next Review Date: June 2017

Related policies:

CP# 04.02.08 Plasmapheresis and plasma exchange

ABOUT THIS POLICY: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania's clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Pennsylvania considers the use of low-density lipoprotein (LDL) apheresis using either heparin-induced extracorporeal LDL precipitation (HELP) or dextra sulfate adsorption to be clinically proven and, therefore, medically necessary for treatment of:

- Severe familial hypercholesterolemia (FH) with an inadequate response to, or intolerance of, maximum drug therapy (defined as a six-month trial of ≥ two separate classes of hypolipidemic agents) and one of the following LDL criteria:
  - Functional homozygous FH with LDL cholesterol ≥ 500 mg/dL.
  - Functional heterozygous FH with LDL cholesterol ≥ 300 mg/dL and no known cardiovascular disease.
  - Functional heterozygous FH with LDL cholesterol ≥ 200 mg/dL and cardiovascular disease documented as either:
    - History of myocardial infarction, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, or alternative revascularization procedure.
    - Angina with coronary heart disease (CHD) documented by stress test.
- Primary focal segmental glomerulosclerosis (FSGS) recurring after kidney transplantation.
AmeriHealth Caritas Pennsylvania considers the use of high-density lipoprotein (HDL) apheresis to be investigational and, therefore, not medically necessary.

Limitations:

- All other uses of LDL apheresis are not medically necessary.
- The frequency of LDL apheresis considered medically necessary varies, but typically averages about once every two weeks to obtain an intrapheresis LDL cholesterol (LDL-C) level ≤ 120 mg/dL. It may be medically necessary to treat individuals with homozygous FH more frequently.
- Contraindications include, but are not limited to:
  - Anticoagulation disorders.
  - Severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia.
  - Acute apoplexy.
  - Severe uncontrollable hypertension or hypotension.
  - Hypersensitivity to dextran, heparin or ethylene oxide.

NOTE: The following codes are not included in the Medicaid medical fee schedule in Pennsylvania

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

Alternative covered services:

- Lifestyle management.
- Surgery for persons with severe FH — ileal bypass and liver transplantation.
- For treatment of FSGS — Corticosteroids, cyclophosphamide or cyclosporine in patients refractory to prednisone therapy, plasmapheresis, and renal transplantation.

Background

Apheresis is the extracorporeal process of removing one or more blood constituents from whole blood and returning the remainder to the circulation. Therapeutic apheresis (also called blood component therapy) involves removal of the abnormal pathogenic component, which, theoretically, should improve the disease course. Depending on clinical use, apheresis may be performed as a one-time-only treatment or several times per week for several weeks. For some it may be a lifelong commitment.

Several apheresis techniques are available and differ in their underlying mechanisms of action (i.e., adsorption, precipitation or selective filtration), depending on the blood component being removed. They are:

- Plasmapheresis using centrifugation or semipermeable membranes.
- Cytoreductive apheresis (e.g., erythrocytapheresis, leukapheresis and plateletppheresis) using centrifugation.
- Extracorporeal photopheresis involving leukapheresis centrifugation, photoactivation, and reinfusion of treated cell product back to the patient.
- Extracorporeal immunoadsorption with plasma reinfusion, also referred to as protein immunoadsorption therapy or by the trade name Prosorba® Column (Cypress Biosciences, San Diego, CA), using a highly purified protein complex bonded to a silica matrix.
Extracorporeal selective adsorption or selective filtration of lipoproteins with plasma reinfusion (lipoprotein apheresis).

**Lipoprotein apheresis:**

Lipoprotein apheresis involves the selective extracorporeal removal of LDLs, lipoprotein(a) particles (Lp[a]), very low-density lipoproteins (VLDLs, such as triglycerides) or HDLs from either whole blood or plasma using a series of membrane filtering devices. The patient initially undergoes an apheresis procedure to isolate the plasma. Selective removal of the LDLs can occur through immunoadsorption, HELP, dextran sulfate adsorption or double-filtration plasma pheresis of lipoprotein (also called rheopheresis). Lipid apheresis is used for disorders with marked hyperlipidemia.

The U.S. Food and Drug Administration (FDA) has approved two systems for lipoprotein apheresis in the U.S. Both are regulated as Class III devices indicated for removal of LDLs from the plasma of high-risk patients for whom a lipid-lowering diet and maximum drug therapy have been ineffective or not tolerated (FDA, 2016):

- Dextran-sulfate adsorption, which selectively binds apolipoprotein B (ApoB)-containing lipoproteins (LDL, Lp[a] and VLDL). Marketed as the Liposorber® LA-15 system (Kaneka Pharma America Corp., New York, NY).
- HELP, which selectively precipitates out ApoB-containing lipoproteins from plasma at a given pH level in the presence of heparin. Marketed as HELP® (B. Braun Avitum AG, Melsungen, Germany).

FDA extended approval of the Liposorber as a Humanitarian Use Device (HUD) for treatment of pediatric patients with primary FSGS either before renal transplantation or after renal transplantation when there is recurrence of FSGS (FDA, 2013). An HUD is eligible for marketing approval under the Humanitarian Device Exemption (HDE) marketing pathway.

Selective HDL apheresis involves selective removal of cholesterol from HDL, converting the major alpha HDL to pre-beta-like HDL, which is then re-infused to the patient. The pre-beta-like HDL is a form of HDL that enhances cholesterol transport to the liver and is thought to reduce atherosclerosis development and burden. FDA has not approved any extracorporeal apheresis device for HDL apheresis.

**Familial hypercholesterolemia (FH):**

FH is a congenital metabolic disorder resulting in severe elevations of blood cholesterol levels. The heterozygous form occurs in approximately one in 300 to 500 people in many populations, and may be higher in certain populations in the United States; the rare homozygous form occurs in approximately one in one-million individuals (Goldberg, 2011). Total cholesterol concentrations in patients with heterozygous FH typically range from 350 to 550 mg/dL and in homozygous FH range from 650 to 1,000 mg/dL. FH is present from childhood, leading to early development of atherosclerosis and CHD if left untreated. Long-term intensive cholesterol-lowering drug therapy of patients with FH significantly reduces or removes the excess lifetime risk of CHD, lowering the level of risk to that of the general population. Some persons with FH remain intolerant of or refractory to cholesterol-lowering therapy and require adjunct therapy (Goldberg, 2011; Youngbloom, 2014; Bouhairie, 2015).

**Searches**

AmeriHealth Caritas Pennsylvania searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
We conducted searches on May 5 — 6, 2016. Search terms were: “blood component removal” [MeSH], "plasmapheresis/therapeutic use” [MeSH], and free text terms "therapeutic apheresis," "selective adsorption," and “lipoprotein apheresis.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

We identified three systematic reviews, three evidence-based guidelines and no cost-effectiveness studies of lipoprotein apheresis. The majority of the evidence consists of small randomized controlled trials (RCTs) and observational studies of LDL apheresis for treating selected patients with FH. The evidence is insufficient to support LDL apheresis for any other indication, including treatment for hypertriglyceridemia (HTG)-related acute pancreatitis (AP) and for pre-treatment of PSGS. We found no evidence of selective HDL therapeutic apheresis with plasma reinfusion; therefore, this procedure will not be considered further in this policy.

We included one narrative review of Liposorber apheresis as treatment for hyperlipidemia in patients with refractory nephrotic syndrome caused by primary FSGS (Muso, 2014). Based on a handful of small, retrospective case series (58 total patients), LDL apheresis is safe and effective for inducing remission of refractory nephrotoxic syndrome in approximately 50 percent of patients. The main probable benefit of treatment of FSGS without renal transplantation is delayed progression to end-stage renal disease (ESRD) while exposing the patients to a lower risk profile than extensive immunosuppression. After transplantation Liposorber apheresis induces remission of nephrotic syndrome in patients at high risk for progression of renal disease to ESRD.

Limited evidence from small RCTs suggests that Liposorber and HELP apheresis methods, when combined with standard treatment, are safe and effective for reducing serum levels of total cholesterol, LDL cholesterol and lipoproteins in patients with FH who do not respond to diet and intensive drug treatment. A few observational studies found that apheresis treatment improved coronary blood flow and halted or reversed the progression of stenoses. Long-term follow up was lacking, and it is not known whether the treatment effects were maintained. It remains to be seen what effect the recent emergence of several novel and powerful lipid-lowering drugs will have on its future clinical role.

Apheresis procedures are safe when performed in a clinical setting by experienced personnel. Adverse effects are not serious or life-threatening and usually are related to technique, anticoagulation, substitution solutions and underlying pathology. The most frequent complications were hypotension, paresthesia, chills, and vasovagal reactions. Post-treatment bleeding can occur secondary to heparin used during the
procedure. Challenges associated with LDL apheresis include vascular access often requiring an arteriovenous fistula, the time associated with each treatment session (2-4 hours), the frequency of treatment and availability of treatment centers.

Definitive patient selection criteria cannot be established from published research. FDA approval of LDL apheresis is based on the following criteria:

- Homozygous FH with LDL-C > 500 mg/dL.
- Heterozygous FH with LDL-C ≥ 300 mg/dL.
- Heterozygous FH with LDL-C ≥ 200 mg/dL and documented CAD.

The National Lipid Association Expert Panel on Familial Hypercholesterolemia issued slightly broader patient selection criteria for LDL apheresis (Goldberg, 2011):

- Patients who are not at LDL cholesterol treatment goal or who have ongoing symptomatic disease.
- In patients who, after six months, do not have an adequate response to maximum tolerated drug therapy, LDL apheresis is indicated according to these guidelines:
  - Functional homozygous FH patients with LDL cholesterol ≥ 300 mg/dL (or non-HDL cholesterol ≥ 330 mg/dL).
  - Functional heterozygous FH patients with LDL cholesterol ≥ 300 mg/dL (or non-HDL cholesterol ≥ 330 mg/dL) and zero to one risk factors.
  - Functional heterozygous FH patients with LDL cholesterol ≥ 200 mg/dL (or non-HDL cholesterol ≥ 230 mg/dL) and high risk characteristics such as ≥ two risk factors or high lipoprotein (a) ≥ 50 mg/dL using an isoform insensitive assay.
  - Functional heterozygous FH with LDL cholesterol ≥ 160 mg/dL (or non-HDL cholesterol ≥ 190 mg/dL) and very high risk characteristics (established CHD, other cardiovascular disease, or diabetes).

- High CHD risk is defined as: clinically evident CHD or other atherosclerotic cardiovascular disease; diabetes; a family history of very early CHD (in men, 45 years of age, and women, 55 years of age); current smoking; two or more CHD risk factors; or high Lp(a) ≥ 50 mg/dL using an isoform insensitive assay.

- LDL apheresis may be considered during pregnancy if there is significant atherosclerotic disease or if the patient has homozygous FH.

The National Institute for Health and Care Excellence (NICE) and the British Committee for Standards in Haematology have issued similar guidance (NICE, 2008; Howell, 2015). The American College of Cardiology/American Heart Association Task Force on Practice Guidelines made no recommendation for or against use of apheresis for treating blood cholesterol in persons with an insufficient response to statin therapy (Stone, 2014). The National Heart, Lung, and Blood Institute (NHLBI) stated children with homozygous FH and extremely elevated LDL-C levels (> 500 mg/dL) have undergone effective LDL-lowering therapy with biweekly LDL apheresis under the care of lipid specialists in academic medical centers based on results from observational studies, but they made no explicit recommendation for or against apheresis (NHLBI, 2011). The American Society for Apheresis recommends LDL apheresis for severe FH and therapeutic plasma exchange for FSGS that recurs after kidney transplantation (Schwartz, 2013).

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Click (2015)</td>
<td>Key points:</td>
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<tr>
<td>HTG-related acute</td>
<td>- Systematic review of 74 uncontrolled studies (301 unique patients).</td>
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<tr>
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<td>Content, Methods, Recommendations</td>
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<td>------------------------------------------------------------------------</td>
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<tr>
<td>pancreatitis (AP)</td>
<td>• Overall quality: Low. High risk of bias due to small, uncontrolled studies and variable reporting of criteria to define AP.</td>
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<td>• Most patients were young (mean age 37.9 +/- 10.4 years) and male (71.5%). About two-thirds received apheresis within 48 hours and most required only one or two sessions.</td>
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<td>• Apheresis resulted in an average reduction of serum triglycerides by 85.4% ($P &lt; 0.001$).</td>
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<tr>
<td>Howell (2015) for the British Committee for Standards in Haematology</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>Evidence-based guideline for apheresis procedures</td>
<td>• Lipoprotein apheresis is required for patients with homozygous FH or for compound heterozygotes, when serum cholesterol remains &gt; 9mmol/L or decreases by &lt; 50% despite treatment with high dose statin, plus ezetimibe or bile acid sequestrants or nicotinic acid-containing compounds (1A-high quality evidence).</td>
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<td>• Lipoprotein apheresis should be considered for patients with homozygous FH or other forms of severe hypercholesterolemia and with progressive CHD whose LDL cholesterol remains &gt; 5mmol/L or decreases by &lt; 40% on maximally tolerable doses of combined drug therapy (1B-moderate quality evidence).</td>
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<td>• Lipoprotein apheresis should be considered for patients with a raised lipoprotein (a) level and progressive CHD despite treatment with maximally tolerable combined drug therapy (1B-moderate quality evidence).</td>
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<td>• Lipoprotein apheresis procedure is performed weekly or bi-weekly in specialized units providing a regional or supra-regional service (1C-low quality evidence).</td>
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<td>• Treatment target reduction for LDL cholesterol for all patients on any lipoprotein apheresis treatment is an interval mean of &lt; 2.8mmol/L or 60% – 75% reduction target. Lp(a) reduction aim is an interval mean of &lt;500mg/L (1B-moderate quality evidence).</td>
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<td>Hayes (2007; updated 2011)</td>
<td><strong>Key points:</strong></td>
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<td>Extracorporeal apheresis for conditions affecting the circulatory</td>
<td>• Systematic review of 12 studies of LDL apheresis and HELP apheresis (730 total patients) for hypercholesterolemia and cardiac disease and three controlled studies of rheology or HELP apheresis (96 total patients) for ischemic stroke.</td>
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<tr>
<td>system and blood</td>
<td>• Overall quality: Low. Small sample sizes except for three controlled studies with &gt; 100 patients, lack of long-term follow up, variation in treatment parameters and patient populations.</td>
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<td>• Hypercholesterolemia and cardiac disease: Both LDL and HELP apheresis reduced serum levels of total cholesterol, LDL cholesterol and lipoproteins in patients who were not responding sufficiently to diet and drug treatments. Indirect evidence suggests both methods may improve coronary blood flow or halt or reverse the progression of stenosis. Insufficient evidence to determine patient selection criteria, treatment parameters or durability of treatment effect.</td>
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<td>• Ischemic stroke (three controlled studies [96 total patients]): No significant improvement in neurological outcomes with either rheology or HELP compared with standard therapy.</td>
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<td>NICE (2008)</td>
<td><strong>Key points:</strong></td>
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<td>Evidence review and guidelines for FH</td>
<td>• There is limited evidence to inform specific indications for LDL apheresis in people with heterozygous FH. There is limited published evidence on the cardiovascular outcome of such patients treated with LDL apheresis.</td>
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<td>• There is little information on the outcomes of pregnancy in women with FH. A small number of conflicting studies have suggested a small increase in fetal abnormalities if the mother has taken statins during the first trimester, but there are insufficient data to provide an accurate estimate of the level of risk. There is also limited information on the risk of pregnancy (including cardiac death) in a woman with FH.</td>
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**Glossary**

**Adsorption** — The binding of molecules or particles to a surface. It differs from absorption, which is the filling of pores in a solid.

**Familial hypercholesterolemia (FH)** — A group of genetic defects resulting in the liver being incapable of metabolizing excess LDLs in the blood. Two forms are:
- Heterozygous FH patients (genetic defect inherited from one parent).
- Homozygous FH (genetic defect inherited from both parents).

**Focal segmental glomerulosclerosis (FSGS)** — A progressive and aggressive kidney disease with multiple primary or secondary causes that frequently leads to end-stage renal disease, particularly in children. Clinical features include proteinuria, reduced glomerular filtration rate and edema.

**Humanitarian Use Device (HUD)** — An FDA designation for medical devices that are intended to benefit patients in the treatment or diagnosis of a disease or condition, which affects or is manifested in fewer than 4,000 individuals in the United States per year.

**Lipoprotein** — A protein that enables fats and cholesterol to move within the water-based solution of the bloodstream. Five major groups of lipoproteins are chylomicrons, very low-density lipoproteins, low-density lipoprotein, intermediate-density lipoproteins and high-density lipoproteins.

**Rheopheresis (also called double filtration plasmapheresis)** — A blood filtration process that removes heavy proteins from the plasma.

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**Clinical trials:**

Searched clinicaltrials.gov on May 6, 2016, using terms “apheresis” or "lipid pheresis" or “lipopheresis” or "LDL pheresis" | Open Studies | United States; 102 studies were found, three were relevant.


**CMS National Coverage Determinations (NCDs):**


**CMS Local Coverage Determinations (LCDs):**


**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>Primary focal segmental glomerulosclerosis</td>
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<td>S2120</td>
<td>Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation</td>
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