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 5, 2018
Next Review Date: June 2019

Related policies:
CP# 04.02.08  Plasmapheresis and plasma exchange

About this policy: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ 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 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’ 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’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the use of low-density lipoprotein apheresis using either heparin-induced extracorporeal low-density lipoprotein precipitation or dextra sulfate adsorption to be clinically proven and, therefore, medically necessary for treatment of severe familial hypercholesterolemia 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 criteria (National Institute for Health and Care Excellence, 2017; American College of Cardiology, 2016; Schwartz, 2016; U.S. Food and Drug Administration, 2016; Howell, 2015; National Heart, Lung, and Blood Institute, 2011):

- Functional homozygous form with low-density lipoprotein cholesterol ≥ 500 mg/dL.
- Functional heterozygous form with low-density lipoprotein cholesterol ≥ 300 mg/dL and no known cardiovascular disease.
- Functional heterozygous form with low-density lipoprotein 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 documented by stress test.
- Primary focal segmental glomerulosclerosis recurring after kidney transplantation (Muso, 2014).

AmeriHealth Caritas considers the use of high-density lipoprotein apheresis to be investigational and, therefore, not medically necessary.

**Limitations:**

All other uses of low-density lipoprotein apheresis are not medically necessary (Gerhard-Herman, 2017; Schwartz, 2016; Click, 2015; Stone, 2014; Hayes, 2011).

The frequency of low-density lipoprotein apheresis considered medically necessary varies, but typically averages about once every two weeks to obtain an intrapheresis low-density lipoprotein cholesterol (low-density lipoprotein-C) level ≤ 120 mg/dL. It may be medically necessary to treat individuals with homozygous familial hypercholesterolemia more frequently.

Contraindications include, but are not limited to (Hayes, 2011):
- Anticoagulation disorders.
- Severe cardiac insufficiency, acute myocardial infarction, or severe cardiac arrhythmia.
- Acute apoplexy.
- Severe uncontrollable hypertension or hypotension.
- Hypersensitivity to dextran, heparin, or ethylene oxide.

**Alternative covered services:**

- Lifestyle management.
- Surgery for persons with severe familial hypercholesterolemia — Ileal bypass and liver transplantation.
- For treatment of focal segmental glomerulosclerosis — 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) removes 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 depending on the blood component being removed. The techniques may involve centrifugation, semipermeable membranes, photoactivation, or adsorption to remove blood components, and reinfusion of the treated cell product back to the patient.

**Lipoprotein apheresis:**

Lipoproteins enable fats and cholesterol to move within the water-based solution of the bloodstream (Feingold, 2017). Lipoprotein apheresis involves the selective extracorporeal removal of low-density lipoproteins, lipoprotein(a) particles, very low-density lipoproteins, or high-density lipoproteins from either whole blood or plasma using a series of membrane filtering devices. It is used for disorders with marked hyperlipidemia.

Selective removal of the low-density lipoproteins can occur through several processes. The U.S. Food and Drug Administration (2018) has approved two systems for lipoprotein apheresis in the United States. Both are regulated as Class III devices indicated for removal of low-density lipoproteins from the plasma of high-risk patients for whom a lipid-lowering diet and maximum drug therapy have been ineffective or not tolerated:

- **Dextran-sulfate adsorption,** which selectively binds apolipoprotein B-containing lipoproteins (low-density lipoprotein, lipoprotein(a) particles, and very low-density lipoproteins). Marketed as the Liposorber® LA-15 system (Kaneka Pharma America Corp., New York, New York).
- **Heparin-induced extracorporeal low-density lipoprotein precipitation,** which selectively precipitates out apolipoprotein B-containing lipoproteins from plasma at a given pH level in the presence of heparin. Marketed as HELP® (B. Braun Avitum AG, Melsungen, Germany).

Approval for Liposorber was extended as a Humanitarian Use Device for treatment of pediatric patients with primary focal segmental glomerulosclerosis either before renal transplantation or after renal transplantation when there is recurrence of the disease (U.S. Food and Drug Administration, 2013).

Selective high-density lipoprotein apheresis involves selective removal of cholesterol from high-density lipoprotein, converting the major alpha high-density lipoprotein to pre-beta-like high-density lipoprotein, which is then re-infused to the patient. The pre-beta-like high-density lipoprotein is a form of high-density lipoprotein that enhances cholesterol transport to the liver and is thought to reduce atherosclerosis development and burden. No extracorporeal apheresis device for high-density lipoprotein apheresis has been approved for clinical use.

**Familial hypercholesterolemia:**

Familial hypercholesterolemia is a congenital metabolic disorder resulting in severe elevations of blood cholesterol levels (Youngblom, 2014). 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 familial hypercholesterolemia typically range from 350 to 550 mg/dL and in homozygous familial hypercholesterolemia range from 650 to 1,000 mg/dL. Familial hypercholesterolemia can lead to early development of atherosclerosis and coronary heart disease if left untreated. Long-term intensive cholesterol-lowering drug therapy significantly reduces or removes the excess lifetime risk of coronary heart disease, lowering the level of risk to that of the general population. Some remain intolerant of or refractory to cholesterol-lowering therapy and require adjunct therapy (Youngbloom, 2014; Goldberg, 2011).

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on April 13, 2018. 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 two systematic reviews (Hayes, 2011; Click, 2015), five evidence-based guidelines (Howell, 2015; Stone, 2014; Schwartz, 2013; National Heart, Lung, and Blood Institute, 2011; National Institute for Health and Care Excellence, 2008), and no cost-effectiveness studies of lipoprotein apheresis. The majority of the evidence consists of small randomized controlled trials and observational studies of low-density lipoprotein apheresis for treating selected patients with familial hypercholesterolemia. The evidence is insufficient to support low-density lipoprotein apheresis for any other indication, including
treatment for hypertriglyceridemia-related acute pancreatitis or for pre-treatment of primary focal segmental glomerulosclerosis. We found no evidence of selective high-density lipoprotein 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 focal segmental glomerulosclerosis (Muso, 2014). Based on a handful of small, retrospective case series (58 total patients), low-density lipoprotein apheresis is safe and effective for inducing remission of refractory nephrotic syndrome in approximately 50 percent of patients. The main probable benefit of treatment of focal segmental glomerulosclerosis without renal transplantation is delayed progression to end-stage renal disease while exposing 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 end-stage renal disease.

Limited evidence from small randomized controlled trials suggests that Liposorber and heparin-induced extracorporeal low-density lipoprotein precipitation apheresis methods, when combined with standard treatment, are safe and effective for reducing serum levels of total cholesterol, low-density lipoprotein cholesterol, and lipoproteins in patients with familial hypercholesterolemia 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, so 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 low-density lipoprotein apheresis include vascular access often requiring an arteriovenous fistula, the time associated with each treatment session (two to four hours), the frequency of treatment, and availability of treatment centers.

Definitive patient selection criteria cannot be established from published research. U.S. Food and Drug Administration approval of low-density lipoprotein apheresis is based on the following criteria:

- Homozygous familial hypercholesterolemia with low-density lipoprotein-C > 500 mg/dL.
- Heterozygous familial hypercholesterolemia with low-density lipoprotein-C ≥ 300 mg/dL.
- Heterozygous familial hypercholesterolemia with low-density lipoprotein-C ≥ 200 mg/dL and documented coronary artery disease.

The National Lipid Association Expert Panel on Familial Hypercholesterolemia issued slightly broader patient selection criteria for low-density lipoprotein apheresis (Goldberg, 2011):
• Patients who are not at a low-density lipoprotein 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, low-density lipoprotein apheresis is indicated according to these guidelines:
  - Functional homozygous familial hypercholesterolemia patients with low-density lipoprotein cholesterol $\geq 300$ mg/dL (or non-high-density lipoprotein cholesterol $\geq 330$ mg/dL).
  - Functional heterozygous familial hypercholesterolemia patients with low-density lipoprotein cholesterol $\geq 300$ mg/dL (or non-high-density lipoprotein cholesterol $\geq 330$ mg/dL) and zero to one risk factors.
  - Functional heterozygous familial hypercholesterolemia patients with low-density lipoprotein cholesterol $\geq 200$ mg/dL (or non-high-density lipoprotein cholesterol $\geq 230$ mg/dL) and high risk characteristics such as $\geq$ two risk factors or high lipoprotein (a) $\geq 50$ mg/dL using an isoform insensitive assay.
  - Functional heterozygous familial hypercholesterolemia with low-density lipoprotein cholesterol $\geq 160$ mg/dL (or non-high-density lipoprotein cholesterol $\geq 190$ mg/dL) and very high risk characteristics (established coronary heart disease, other cardiovascular disease, or diabetes).

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

• Low-density lipoprotein apheresis may be considered during pregnancy if there is significant atherosclerotic disease or if the patient has homozygous familial hypercholesterolemia.

The National Institute for Health and Care Excellence (2008) and the British Committee for Standards in Haematology (Howell, 2015) have issued similar guidance. 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 (2011) stated children with homozygous familial hypercholesterolemia and extremely elevated low-density lipoprotein-C levels (> 500 mg/dL) have undergone effective low-density lipoprotein-lowering therapy with biweekly low-density lipoprotein 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. The American Society for Apheresis recommends low-density lipoprotein apheresis for severe familial hypercholesterolemia and therapeutic plasma exchange for focal segmental glomerulosclerosis that recurs after kidney transplantation (Schwartz, 2013).
Policy updates:

In 2017, we identified two updated guidelines for this policy. The American Society for Apheresis released an update of indications for therapeutic apheresis (Schwartz, 2016). The guideline includes one new clinical indication for low-density lipoprotein apheresis that was not in the 2013 version — steroid-resistant focal segmental glomerulosclerosis in the native kidney. They issued a weak recommendation based on very low-quality evidence from one case series and a case report (15 total patients) with mixed results.

The Writing Committee for the American College of Cardiology (2016) provided an Expert Consensus Decision Pathway for the use of non-statin therapies for low-density lipoprotein-cholesterol lowering in managing atherosclerotic cardiovascular disease. They suggested that low-density lipoprotein apheresis be reserved for patients with homozygous familial hypercholesterolemia, severe heterozygous familial hypercholesterolemia that is inadequately responsive to pharmacotherapy, or either homozygous familial hypercholesterolemia or severe heterozygous familial hypercholesterolemia and concomitant atherosclerotic cardiovascular disease during pregnancy. These findings are consistent with the current policy. Therefore, no policy changes are warranted.

In 2018, two observational studies conducted in Germany reported on the effects of lipoprotein apheresis for treatment of lipoprotein(a)-hyperlipoproteinemia—one enrolled 180 patients with progressive cardiovascular disease and followed them over a 5-year period (Roeseler, 2016), and the second enrolled 10 patients with peripheral arterial disease after a revascularization procedure and followed them over a 2-year period (Poller, 2017). Both patient populations received maximal medical therapy, and the majority of patients received weekly lipoprotein apheresis. Results suggest lipoprotein apheresis had a lasting effect on preventing cardiovascular events and on improving peripheral circulation, pain level, walking distance, and the need for repeat peripheral revascularizations.

Lipoprotein apheresis for treatment of lipoprotein(a)-hyperlipoproteinemia in persons with progressive cardiovascular disease is not uniformly accepted in current U.S. practice (Gerhard-Herman, 2017; Schwartz, 2016). One updated guideline on familial hypercholesterolemia from the National Institute for Health and Care Excellence (2017) is consistent with their previous version with respect to use of lipoprotein apheresis. There are no changes to the policy.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerhard-Herman (2017)</td>
<td>Key points:</td>
</tr>
<tr>
<td>2016 American Heart Association/American College of Cardiology Guideline on the Management of Patients</td>
<td>- No mention of lipoprotein apheresis as a treatment option.</td>
</tr>
<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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<tr>
<td>-------------------------------------------------------------------------</td>
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<tr>
<td>With Lower Extremity Peripheral Artery Disease</td>
<td></td>
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<tr>
<td>National Institute for Health and Care Excellence (2017, update of 2008)</td>
<td><strong>Key points:</strong></td>
</tr>
</tbody>
</table>
| Familial hypercholesterolemia                                            | - In children and young people with homozygous familial hypercholesterolemia, consider lipid-modifying drug therapy before lipoprotein apheresis.  
- Consider offering LDL apheresis for the treatment of:  
  - Homozygous familial hypercholesterolemia.  
  - Heterozygous familial hypercholesterolemia. |
| Click (2015)                                                             | **Key points:**                                                                                   |
| Hypertriglyceridemia-related acute pancreatitis                          | - Systematic review of 74 uncontrolled studies (301 unique patients).  
- Overall quality: low. High risk of bias due to small, uncontrolled studies and variable reporting of criteria to define acute pancreatitis.  
- 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.  
- Apheresis resulted in an average reduction of serum triglycerides by 85.4% (P < 0.001).  
- Effect of apheresis in reducing acute pancreatitis severity is inconclusive due to low-quality evidence. |
| Howell (2015) for the British Committee for Standards in Haematology     | **Key points:**                                                                                   |
| Evidence-based guideline for apheresis procedures                        | - Lipoprotein apheresis is required for patients with homozygous familial hypercholesterolemia or for compound heterozygotes, when serum cholesterol remains > 9mmol/L or decreases by < 50% despite treatment with high dose statin, plus ezetimibe or bile acid sequestrants or nicotinic acid-containing compounds (1A-high-quality evidence).  
- Lipoprotein apheresis should be considered for patients with heterozygous familial hypercholesterolemia or other forms of severe hypercholesterolemia and with progressive coronary heart disease whose low-density lipoprotein cholesterol remains > 5mmol/L or decreases by < 40% on maximally tolerable doses of combined drug therapy (1B-moderate-quality evidence).  
- Lipoprotein apheresis should be considered for patients with a raised lipoprotein (a) level and progressive coronary heart disease despite treatment with maximally tolerable combined drug therapy (1B-moderate-quality evidence).  
- Lipoprotein apheresis procedure is performed weekly or biweekly in specialized units providing a regional or supra-regional service (1C-low-quality evidence).  
- Treatment target reduction for low-density lipoprotein cholesterol for all patients on any lipoprotein apheresis treatment is an interval mean of < 2.6mmol/L or 60% – 75% reduction target. Lipoprotein(a) reduction aim is an interval mean of < 500mg/L (1B-moderate-quality evidence).  
- Patients receiving lipoprotein apheresis who become pregnant can safely continue their treatment during their pregnancy (1B-moderate-quality evidence). |
<p>| Hayes (2007; updated 2011)                                               | <strong>Key points:</strong>                                                                                   |
| Extracorporeal apheresis for conditions affecting the circulatory system and blood | - Systematic review of 12 studies of low-density lipoprotein apheresis and heparin-induced extracorporeal low-density lipoprotein precipitation apheresis (730 total patients) for hypercholesterolemia and cardiac disease, and three controlled studies of |</p>
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<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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|          | rheology or heparin-induced extracorporeal low-density lipoprotein precipitation apheresis (96 total patients) for ischemic stroke.  
- Overall quality: low. Small sample sizes except for three controlled studies with > 100 patients, lack of long-term follow-up, and variation in treatment parameters and patient populations.  
- Hypercholesterolemia and cardiac disease: Both low-density lipoprotein and heparin-induced extracorporeal low-density lipoprotein precipitation apheresis reduced serum levels of total cholesterol, low-density lipoprotein 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.  
- Ischemic stroke (three controlled studies [96 total patients]): no significant improvement in neurological outcomes with either rheology or heparin-induced extracorporeal low-density lipoprotein precipitation compared with standard therapy. |

References

Professional society guidelines/other:


**Peer-reviewed references:**


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


**National coverage articles:**

A54542 Therapeutic Apheresis for Familial Hypercholesterolemia.

A54543 Therapeutic Apheresis for Familial Hypercholesterolemia.

A54544 Therapeutic Apheresis for Familial Hypercholesterolemia.

A54545 Therapeutic Apheresis for Familial Hypercholesterolemia.

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

No LCDs identified as of the writing of this policy.

**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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<th>Description</th>
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<td>S2120</td>
<td>Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation</td>
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