Low-Density Lipid Apheresis

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Next Review: 4/2015

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for low-density lipid apheresis when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
LDL apheresis may be considered medically necessary in patients with homozygous familial hypercholesterolemia as an alternative to plasmapheresis.

LDL apheresis may be considered medically necessary in patients with heterozygous familial hypercholesterolemia who:
1. have failed a 6-month trial of diet therapy and maximum tolerated combination drug therapy, AND
2. meet the following FDA-approved indications: (All LDL levels represent the best achievable LDL level after a program of diet and drug therapy.)
   a. Functional hypercholesterolemic heterozygotes with LDL ≥ 300 mg/dL, or
   b. Functional hypercholesterolemic heterozygotes with LDL ≥ 200 mg/dL AND documented coronary artery disease

When Policy Topic is not covered
LDL apheresis is considered investigational for all other uses, including use in preeclampsia.

Considerations
Maximum tolerated drug therapy is defined as a trial of drugs from at least 2 separate classes of hypolipidemic agents such as bile acid sequestrants, HMG-CoA reductase inhibitors, fibrac acid derivatives, or niacin/nicotinic acids.

Documented coronary artery disease includes a history of myocardial infarction, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty or alternative revascularization procedure, or progressive angina documented by exercise or non-exercise stress test.

Since LDL apheresis represents a chronic, lifelong therapy, Plans may consider requiring precertification or prior approval to ensure that the patient meets the patient selection criteria.

Frequency of LDL apheresis varies, but typically averages about once every 2 weeks to obtain an interapheresis level of LDL cholesterol at less than 120 mg/dL. Patients with homozygous FH may be treated more frequently. Patients are simultaneously treated with diet and drug therapy.

In 2003, CPT established a code 36516; Therapeutic apheresis; with extracorporeal selective adsorption or selective filtration and plasma reinfusion. Although code 36516 is not specific to LDL apheresis, this code does generally encompass LDL apheresis. There is no specific CPT or HCPCS code for the disposable supplies associated with LDL apheresis. For example, dextran sulfate systems (e.g., Liposorber LA-15 System) require the use of a disposable column consisting of dextran sulfate ligands on cellulose beads.
There is a HCPCS code specific to the HELP procedure: S2120; Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation.

**Description of Procedure or Service**

Low-density lipoprotein (LDL) apheresis describes a variety of technologies used to remove LDL from the plasma. It is a specific form of plasmapheresis that discriminately removes the LDL particles from the plasma while leaving other factors intact, allowing the filtrated plasma to be returned to the patient. LDL apheresis has been investigated as a technique to treat patients with familial hypercholesterolemia (FH).

**Background**

Familial Hypercholesterolemia (FH) is a dominantly inherited disorder involving a mutation of the gene that encodes for the specific cell surface receptor responsible for low-density lipoprotein (LDL) uptake by the cells. The heterozygous form affects about 1 in 500 people. The number of LDL receptors is halved in this condition, resulting in serum low-density lipoprotein cholesterol (LDL-C) levels that are approximately 2 to 3 times levels that are considered acceptable (i.e., greater than 300 mg/dL). Affected male patients typically develop coronary heart disease in their thirties and forties, while women develop coronary heart disease in their fifties. Depending on the patient, heterozygous FH may or may not respond adequately to lipid-lowering drugs.

Homzygous hypercholesterolemia is rare, only occurring in 1 in 1 million subjects. Serum levels of LDL-C may be elevated 6-fold (greater than 500 mg/dL), due to the total lack of functioning LDL receptors. Homozygotes may develop severe aortic stenosis and coronary heart disease by age 20 years. These patients typically do not adequately respond to drug or diet modification therapy. In the past, patients with homozygous FH may have been treated with plasma exchange, but the advent of LDL apheresis provides a more targeted approach by permitting selective removal of LDL from the plasma.

The patient initially undergoes an apheresis procedure to isolate the plasma. The LDLs are then selectively removed from the plasma by either immunoadsorption, heparin-induced extracorporeal LDL precipitation (referred to as HELP), or dextran sulfate adsorption. In immunoadsorption, polyclonal antihuman apo B antibodies from sheep selectively bind and remove LDL. (Apo B is the protein moiety of LDL.) In HELP, LDL and other particles containing apo B are precipitated by heparin at an acidic pH. Dextran sulfate adsorption removes LDL by binding the positively charged apo B to dextran sulfate particles bound to cellulose. LDL apheresis must be distinguished from plasma exchange (also referred to as plasmapheresis). In plasma exchange the plasma is collected during a pheresis procedure, then discarded and replaced with crystalloids. In contrast, LDL apheresis is a selective procedure in which only pathogenic LDLs are removed. The plasma is then returned to the patient.

**Regulatory Status**

Two lipid apheresis systems have received approval from the U.S. Food and Drug Administration (FDA) for marketing. In February 1996, dextran sulfate device “Liposorber LA-15® System” (Kaneka Pharma, New York City, NY) was approved by the FDA through the premarket approval process for use to “acutely remove LDL-C from the plasma of high risk patient populations for whom diet has been ineffective or not tolerated.”

In September 2007, heparin-induced extracorporeal LDL precipitation “HELP® System” (B. Braun, Melsungen, Germany) was approved by the FDA through the premarket approval process for use in the above indication.

**Rationale**

This policy was created in July 1999 and updated periodically with a literature review of the MEDLINE database. The most recent update covers the period of June 2012 through June 2013.
**LDL apheresis for familial hypercholesterolemia (FH)**

This assessment is based on a 1999 TEC Assessment (1) that offered the following observations and conclusions:

- Three randomized controlled trials [RCTs] report that lipid apheresis is associated with clinically and statistically significantly greater reduction in low-density lipoprotein (LDL) cholesterol than that achieved by medication alone for patients with refractory hypercholesterolemia.
- Nonrandomized studies included patients who had failed diet and drug therapy. The efficacy of LDL lowering was of similar magnitude compared to that observed in the randomized studies.
- There is currently insufficient direct evidence to demonstrate that the reductions in LDL cholesterol seen with LDL apheresis will result in reduced adverse cardiovascular events. However, given the established causal relationship of LDL cholesterol and cardiac events, such an effect is likely, particularly given the fact that LDL apheresis acutely lowers the LDL cholesterol by 50–70% or more.

In August 2008, the National Institute for Health and Clinical Excellence (NICE [UK]) produced a systematic review of literature on FH, including LDL apheresis in its management. (2) Although small RCTs were identified, they were not randomized to the treatment question of LDL apheresis versus other treatment but rather had apheresis in each arm. Therefore studies with lower level evidence informed the authors’ conclusions. They did conclude that in homoygous individuals, apheresis is relatively safe and reduces LDL but were unable to draw definitive conclusions regarding newer statin agents in conjunction, or in lieu of, apheresis. They could not form recommendations on frequency of treatments. For heterozygous individuals, the authors concluded that there was insufficient evidence to define entry criteria for apheresis treatment and recommended this intervention only in exceptional cases.

**LDL apheresis for other indications**

Bianchin and colleagues reported on the use of HELP-apheresis in the treatment of sudden sensorineural hearing loss (SSNHL, which is an acute, mostly unilateral, inner ear disorder of unknown etiology), in a prospective, randomized controlled study. (3) One hundred thirty-two patients with an acute, one-sided SSNHL and a value of LDL cholesterol (LDL-C) greater than 120 mg/dL and/or fibrinogen greater than 320 mg/dL were randomly assigned to standard treatment, or standard treatment plus 1 session of HELP-apheresis. Standard treatment consisted of an infusion of 500 mL of glycerol, once a day for 10 days and intramuscular dexamethasone, 8 mg once a day for 10 days. Patient age range was 35-80 years (average 60.4 years) for the first group and 31-83 years (average 52.8 years) for the second group. In the HELP-apheresis plus standard therapy group, hearing recovery was observed in 75% of patients 24 hours after treatment and in 76.4% 10 days after treatment. In the standard therapy group, the percentage of patients with hearing recovery was 41.7% after 24 hours and 45% after 10 days. The authors concluded that in patients with alterations in cholesterol and/or fibrinogen, HELP-apheresis treatment was an option in the treatment of SSHL.

One study reported a case series of 11 patients with non-arteritic acute anterior ischemic optic neuropathy who were treated with 3 courses of LDL apheresis in conjunction with standard therapy of prednisone, salicylate, and pentoxyphylline. (4) All patients reported improvements in visual function, but the contribution of the LDL apheresis cannot be evaluated in this small uncontrolled trial.

There are several reports of LDL apheresis use for other indications, including the treatment of small cohorts with peripheral arterial disease (5) and preeclampsia (6). While these studies lack the methodologic rigor required to add medically necessary indications to the policy statement, they suggest potential investigational uses for LDL-apheresis. In 1 case series from Japan, 31 patients with peripheral artery disease (84% Fontaine’s symptom classification II) and an average LDL of 197 mg/dL underwent mean 9.6 LDL-apheresis treatments. (5) Improvement of at least 10% for symptomatic parameters (coldness, 89%; numbness, 64%; and rest pain, 100%) was observed with no symptom worsening. Using the same 10% criterion, ankle brachial pressure index improved in 60% of limbs.
observed (worsened in 2%), and mean tolerated walking distance improved in 16 of 23 (70%) patients. No change was observed in any of the arterial occlusive lesions observed. A European study reported on LDL-apheresis use in preeclampsia. (6) Of the 13 patients with preeclampsia, 9 underwent between 1 and 7 heparin-mediated extracorporeal LDL precipitation (HELP) apheresis treatments and were reported to have experienced a mean 18 days (range 3–49) longer gestation. Mortality was 1 in 9 in neonates of apheresis-treated mothers and 1 in 4 in neonates of mothers not treated with apheresis. The high risk of mortality in preeclampsia and the improved perinatal outcomes that accompany longer gestation are important reasons for further study of LDL apheresis.

A series of 17 patients with severe diabetic foot ulcerations were treated with LDL apheresis on the hypothesis that drastically lowered fibrinogen, and possibly lowered plasma viscosity, would improve perfusion to the ischemic tissue and facilitate wound healing. (7) Patients underwent between 1 and 7 treatments and were followed up for 2–73 months. LDL apheresis may have improved wound healing and reduced the risk of lower leg amputations; however, there was no control group or formal quantitative assessments of the lesions.

Ongoing Clinical Trials

A search of online site ClinicalTrials.gov identified one randomized trial in which LDL apheresis will be compared to traditional treatment for diabetic foot ulcers in 132 patients (NCT01518205). Other nonrandomized studies were identified that will examine LDL apheresis for the treatment of non-exudative (dry) age-related macular degeneration in 20 patients (NCT01840683) and to evaluate the safety and efficacy of the DALI (Direct Adsorption of Lipoproteins) system and the MONET (Membrane Filtration Optimized Novel Extracorporeal Treatment) system in cohorts totaling 100 patients (NCT01753232).

Summary

Low-density lipoprotein (LDL) apheresis describes a variety of technologies used to remove LDL from the plasma. It is a specific form of plasmapheresis that discriminately removes the LDL particles from the plasma while leaving other factors intact, allowing the filtrated plasma to be returned to the patient. LDL apheresis has been investigated as a technique to treat patients with familial hypercholesterolemia (FH).

Homozygous familial hypercholesterolemia is a rare disorder. Sufficiently-powered randomized controlled trials evaluating the net benefit of low-density lipoprotein apheresis to these patients are unlikely to be forthcoming. Based on strong recommendations from low-quality evidence, apheresis is a reasonable alternative to plasmapheresis in homozygotes who, despite maximal medical therapy, continue to maintain significantly elevated low-density lipid profiles or have evidence of progressive lipid-associated complications.

Heterozygous familial hypercholesterolemia is less rare and evidence is less compelling to recommend apheresis. However, due to known variability of severity of lipid disorders with this condition, apheresis is a reasonable strategy in these patients to reduce low-density lipid (LDL) levels to reduce atherosclerotic risk when, despite maximal medical therapy over 6 months, LDL remains above 300 mg/dL in asymptomatic individuals, or above 200 mg/dL in patients with known coronary artery disease. At this time, the data are insufficient to determine the impact of LDL apheresis on health outcomes for other investigational uses (e.g., preeclampsia, treatment of diabetic foot ulcers).

Practice Guidelines and Position Statements

In 2011, the National Lipid Association issued guidelines on the treatment of familial hypercholesterolemia. (8) This guidance recommends LDL apheresis for familial hypercholesterolemia in patients who do not adequately respond to maximum tolerated drug therapy after 6 months of treatment as follows with:
- Functional homozygous with LDL cholesterol ≥ 300 mg/dL (or non-HDL cholesterol ≥ 330 mg/dL);

- Functional heterozygous with LDL cholesterol ≥ 300 mg/dL (or non-HDL cholesterol ≥ 330 mg/dL) and 0-1 coronary heart disease risk factors;

- Functional heterozygous with LDL cholesterol ≥ 200 mg/dL (or non-HDL cholesterol ≥ 230 mg/dL) and high risk characteristics such as ≥ 2 risk factors or high lipoprotein (a) ≥ 50 mg/dL; or

- Functional heterozygotes with LDL cholesterol ≥ 160 mg/dL (or non-HDL cholesterol ≥ 190 mg/dL) and very high risk characteristics (established coronary heart disease, other cardiovascular disease, or diabetes).

The 2002 Third Report of the National Cholesterol Education Program (Adult Treatment Panel III or ATP III) recommends therapeutic lifestyle changes and maximal medical therapy for heterozygous familial hypercholesterolemia patients. (9) For homozygous individuals, ATP III recommends LDL apheresis and the addition of a statin for the prevention of rebound hyperlipidemia.

The American Heart Association Expert Panel on Population and Prevention Science made an additional recommendation for children diagnosed with homozygous familial hypercholesterolemia: initiate apheresis treatment as soon as feasible, consider low-dose anticoagulation. For heterozygous familial hypercholesterolemia, this group recommends considering statin treatment at 10 years of age for males and at puberty for females. (10)

The Medial Advisory Secretariat of the Ministry of Health of Ontario published an evidence-based analysis of the available literature for the period of January 1998 to May 2007. (11) Of 398 identified articles, 8 studies met the inclusion criteria of having subjects with familial hypercholesterolemia refractory to statins and diet therapy. Studies with interventions other than the HELP® system were excluded, as HELP® was the only LDL apheresis system approved at that time in Canada. Five case series, 2 case series nested within comparative studies, and 1 retrospective review, as well as a health technology assessment conducted in Alberta, and a review by the FDA were included. The authors observed large heterogeneity among the studies, which were judged to be of low quality due to study design. Overall, the mean acute (immediately following treatment) relative decrease in LDL with HELP® LDL apheresis ranged from 53% to 77%. The mean chronic (end of study) relative decrease ranged from 9% to 46%. While subjects did not reach target level of LDL in the studies, the LDL-high-density lipoprotein (HDL) and total cholesterol (TC)-HDL ratios met targeted values. The authors conclude that for homozygous familial hyperlipidemia patients, there is a strong recommendation based on low- to very low-quality evidence that the benefits of LDL apheresis outweigh risks and burdens. In contrast, the authors offer a weak recommendation based on low- to very low-quality evidence favoring apheresis for heterozygous individuals. For the small number of heterozygous individuals who are intolerant to lipid-lowering medications, or who cannot reach lipid level targets on maximal diet and medication, the authors remark that LDL apheresis is likely as beneficial and less likely to have fewer adverse effects, as plasmapheresis.

**Medicare National Coverage Decision**

National Coverage Decision 110.14 APHERESIS (therapeutic pheresis) lists the indications for which apheresis is a covered benefit in cellular and immune-complex mediated disorders. There is no determination for hypercholesterolemia or LDL apheresis. (12)

References


**Billing Coding/Physician Documentation Information**

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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>S2120</td>
<td>Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation</td>
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<td>36516</td>
<td>Therapeutic apheresis; with extracorporeal selective adsorption or selective filtration and plasma reinfusion</td>
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**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

- 4/1/05: New policy.
- 4/1/06: No policy statement changes.
- 4/1/07: No policy statement changes.
- 4/1/08: No policy statement changes.
- 4/1/09: Policy statement clarified that other uses, e.g., use in preeclampsia, are considered investigational (previously considered not medically necessary).
- 4/1/10: No policy statement changes.
- 4/1/11: No policy statement changes.
- 4/1/12: No policy statement changes.
- 4/1/13: No policy statement changes.
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