Lipoprotein apheresis

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Next review date: 11/2025

Policy contains: Familial hypercholesterolemia; HELP; Liposorber; low-density lipoprotein apheresis; primary focal segmental glomerulosclerosis.

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Coverage policy

Low-density lipoprotein apheresis, using heparin-induced extracorporeal precipitation or dextra sulfate adsorption, may be medically necessary for severe familial hypercholesterolemia when there is an inadequate response to, or intolerance of, maximum drug therapy (a six-month trial of ≥ two hypolipidemic agent classes) and one of the following criteria(National Institute for Health and Care Excellence, 2019; Connelly-Smith, 2023; U.S. Food and Drug Administration, 2013, 2018):

- 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; Raina, 2019a).

High-density lipoprotein apheresis is investigational/not clinically proven and, therefore, not medically necessary.

Limitations

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

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 members with homozygous familial hypercholesterolemia more frequently.

Alternative covered services

- Lifestyle management.
- Intensive lipid-lowering drug treatment.
- Surgery for members with severe familial hypercholesterolemia — Ileal bypass and liver transplantation.
- For treatment of focal segmental glomerulosclerosis — corticosteroids, cyclophosphamide, or cyclosporine in members refractory to prednisone therapy, plasmapheresis, and renal transplantation.

Background

Familial hypercholesterolemia is a congenital metabolic disorder resulting in severe elevations of blood cholesterol levels (Youngblom, 2022). Left untreated, it can lead to early development of atherosclerosis and coronary heart disease. 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. 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 (Goldberg, 2011; Youngblom, 2022).

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.

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 (Feingold, 2023). 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 (2023) has approved two systems for lipoprotein apheresis. 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) (U.S. Food and Drug Administration, 2013).

- 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). Approval was extended again in 2018 for treatment of adult patients with nephrotic syndrome caused by primary focal segmental glomerulosclerosis.

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.

Findings

Clinical Guidelines

Several evidence-based guidelines recommend low-density lipoprotein apheresis for patients with severe familial hypercholesterolemia inadequately controlled with drug therapy. The American Society for Apheresis recommends low-density lipoprotein apheresis for severe familial hypercholesterolemia (Connelly-Smith, 2023). The National Lipid Association Expert Panel on Familial Hypercholesterolemia issued patient selection criteria for low-density lipoprotein apheresis based on low-density lipoprotein cholesterol levels, risk factors, and comorbidities (Goldberg, 2011). They recommend low-density lipoprotein apheresis for patients with homozygous familial hypercholesterolemia and low-density lipoprotein cholesterol ≥ 300 mg/dL (or non-high-density lipoprotein cholesterol ≥ 330 mg/dL), and for patients with heterozygous familial hypercholesterolemia and low-density lipoprotein cholesterol ≥ 300 mg/dL (or non-high-density lipoprotein cholesterol ≥ 330 mg/dL) with 0-1 risk factors, low-density lipoprotein cholesterol ≥ 200 mg/dL (or non-high-density lipoprotein cholesterol ≥ 230 mg/dL) with ≥ 2 risk factors or high lipoprotein(a) ≥ 50 mg/dL, or low-density lipoprotein cholesterol ≥ 160 mg/dL (or non-high-density lipoprotein cholesterol ≥ 190 mg/dL) with very high-risk characteristics such as established coronary heart disease, other cardiovascular disease, or diabetes.

Similar guidance has been issued by the National Institute for Health and Care Excellence (2019) and the British Committee for Standards in Haematology (Howell, 2015). The American Heart Association recommends low-density lipoprotein apheresis (with a four-drug combination) for patients with adherent drug treatment whose cholesterol level remains above the target goal after three months (Gidding, 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 (2012) 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 Writing Committee for the American College of Cardiology (2016) 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.

An expert consensus issued jointly by the European Rare Kidney Disease Network and the European Society of Pediatric Nephrology recommends low-density lipoprotein apheresis in children with homozygous familial hypercholesterolemia and provides guidelines for initiating treatment and managing low-density lipoprotein cholesterol levels. The consensus statement suggests starting low-density lipoprotein apheresis in children with low-density lipoprotein cholesterol levels exceeding 7.8 millimoles per liter (300 mg/dL) despite optimal lipid-lowering therapy, or in those with subclinical or clinical atherosclerotic cardiovascular disease and low-density lipoprotein cholesterol levels over 3.4 millimoles per liter (130 mg/dL). The guidelines recommend beginning treatment as early as possible in life. The quality of evidence for these recommendations is generally low due to the lack of randomized controlled trials (Reijman, 2023).

Systematic Reviews and Meta-Analyses

Several systematic reviews and meta-analyses have examined the safety and efficacy of low-density lipoprotein apheresis for familial hypercholesterolemia. Alothman (2022) conducted a systematic review and meta-analysis of seven studies (n = 194 children) with homozygous familial hypercholesterolemia. They found that low-density lipoprotein apheresis dramatically reduced cholesterol levels, but also imposed a high treatment burden on patients, with most reporting it to be tiring, painful, uncomfortable, and time-consuming, compromising educational attainment.

The review noted inadequate psychological support for these patients. Wang (2016) systematically reviewed 38 studies of patients with familial hypercholesterolemia and found that low-density lipoprotein apheresis reduced low-density lipoprotein cholesterol levels by an average of 57-75% for homozygous cases and 58-63% for heterozygous cases. Luirink (2019) conducted a systematic review of 76 case series and case reports (n = 209 participants) and found that lipoprotein apheresis was safe and substantially reduced low-density lipoprotein cholesterol and xanthomata in children with homozygous familial hypercholesterolemia.

Click (2015) conducted a systematic review and identified five small randomized controlled trials and observational studies supporting the safety and efficacy of low-density lipoprotein apheresis for reducing serum cholesterol levels in patients with familial hypercholesterolemia who do not respond to diet and intensive drug treatment. A few studies found improved coronary blood flow and halted or reversed stenosis progression, but long-term follow-up was lacking. Belanger (2022) systematically reviewed the literature and documented improvement in survival among persons with hypercholesterolemia treated with lipoprotein apheresis.

Gu (2024) conducted a systematic review of 25 seminal studies on treatments for homozygous familial hypercholesterolemia. They found that low-density lipoprotein apheresis reduced low-density lipoprotein cholesterol levels by around 40% compared to baseline based on the best available evidence from five observational studies. However, these studies were considered at high to very high risk of bias and confounding, with the largest study including only 30 patients. In contrast, high-quality evidence from randomized controlled trials demonstrated that the monoclonal antibodies evinacumab, evolocumab, and alirocumab reduced low-density lipoprotein cholesterol by 49%, 31%, and 36% respectively compared to placebo in trials totaling 184 patients. While low-density lipoprotein apheresis is effective, the authors concluded that it places a significant burden on patients and healthcare systems. They recommend that combinations of newer pharmacologic agents be considered and individualized for patients with homozygous familial hypercholesterolemia to optimize treatment outcomes

Other Evidence:

Several observational studies support the safety and efficacy of low-density lipoprotein apheresis for familial hypercholesterolemia. Two registry studies (Luirink, 2020; Pottle, 2019) and one intervention study (Raina, 2019a) confirmed the safety and efficacy of lipoprotein apheresis for treating participants with familial hypercholesterolemia. A literature review concluded that lipoprotein apheresis effectively reduced serum lipoprotein and adverse cardiovascular events in patients with familial hypercholesterolemia unresponsive to lipid-lowering medications, but more randomized trials are needed (Raina, 2019b). Two observational studies conducted in Germany found that lipoprotein apheresis had a lasting effect on preventing cardiovascular events and improving peripheral circulation, pain level, walking distance, and the need for repeat peripheral revascularizations in patients with lipoprotein(a)-hyperlipoproteinemia (Poller, 2017; Roeseler, 2016).

.In 2024, we reordered and condensed the findings section by evidence type and added a position paper (Reijman, 2023) and a new systematic review (Gu, 2023).

References

On May 17, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “blood component removal” (MeSH); “plasmapheresis/therapeutic use” (MeSH); “therapeutic apheresis,” “selective adsorption,” and “lipoprotein apheresis." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

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