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Lipoprotein apheresis

Clinical Policy ID: CCP.1238

Recent review date: 7/2021

Next review date: 11/2022

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

This policy is a Sandhills Center Clinical Coverage Policy adopted from AmeriHealth Caritas of North Carolina. These clinical policies are used to assist with making coverage determinations. Sandhills Center'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 Sandhills Center 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. Sandhills Center 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. Sandhills Center's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Sandhills Center will update its clinical policies as necessary. Sandhills Center clinical policies are not guarantees of payment.

Coverage policy

Low-density lipoprotein apheresis using either heparin-induced extracorporeal low-density lipoprotein precipitation or dextra sulfate adsorption is 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 \geq two separate classes of hypolipidemic agents) and one of the following criteria (Grundy, 2018; Howell, 2015; National Heart, Lung, and Blood Institute, 2011; Schwartz, 2016; U.S. Food and Drug Administration, 2013, 2018):

- Functional homozygous form with low-density lipoprotein cholesterol \geq 500 mg/dL.
- Functional heterozygous form with low-density lipoprotein cholesterol \geq 300 mg/dL and no known cardiovascular disease.
- Functional heterozygous form with low-density lipoprotein cholesterol \geq 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, 2019).

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 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

Familial hypercholesterolemia is a congenital metabolic disorder resulting in severe elevations of blood cholesterol levels (Youngblom, 2016). 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, 2016).

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, 2020). 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 (2021) 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) (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

We identified one systematic review (Click, 2015), five evidence-based guidelines (Howell, 2015; National Heart, Lung, and Blood Institute, 2011; National Institute for Health and Care Excellence, 2008; Schwartz, 2013 [updated in 2016]; Stone, 2014), 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 nephrotoxic syndrome in approximately 50% 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 (2013) 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 \geq 300 mg/dL.
- Heterozygous familial hypercholesterolemia with low-density lipoprotein-C \geq 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).

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, update of Schwartz, 2013). 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.

In 2019, we added one evidence-based guideline (Grundy, 2018) on the management of blood cholesterol, which recommends low-density lipoprotein apheresis for treatment of severe familial hypercholesterolemia inadequately controlled with drug therapy. We added one systematic review (Luirink, 2019) of 76 case series and case reports (n = 209 participants) that found lipoprotein apheresis was safe and substantially reduced low-density lipoprotein cholesterol and xanthomata in children with homozygous familial hypercholesterolemia. These findings are consistent with the current policy, and no policy changes are warranted. The policy ID was changed from CP# 04.03.07 to CCP.1238.

In 2020, we added an updated National Institute for Health and Care Excellence guideline (2019) on familial hypercholesterolemia, which had no changes to their recommendations for lipoprotein apheresis. We added U.S. Food and Drug Administration (2018) information that expanded approval for the Liposorber LA-15 System to adult patients with nephrotic syndrome caused by primary focal segmental glomerulosclerosis. We added two registry studies (Luirink, 2020; Pottle, 2019) and one intervention study (Raina, 2019) that confirm the safety and efficacy of lipoprotein apheresis for treating participants with familial hypercholesterolemia and drug-resistant primary focal segmental glomerulosclerosis. No policy changes are warranted.

In 2021, we updated the references and found no newly published relevant literature to add to the policy. No policy changes are warranted.

References

On April 14, 2021, 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

6/2016: initial review date and clinical policy effective date: 10/2016

6/2017: Policy references updated.

7/2017: Policy references updated.

7/2018: Policy references updated.

7/2019: Policy references updated. Policy ID changed.

7/2020: Policy references updated.

7/2021: Policy references updated.