FEP Medical Policy Manual

FEP 8.02.04 Lipid Apheresis

Effective Policy Date: October 1, 2019

Original Policy Date: December 2011

Related Policies:

None

Lipid Apheresis

Description

This use of low-density lipoprotein (LDL) apheresis has been proposed to treat various types of familial hypercholesterolemia (FH) and other significant hyperlipidemia and to reduce atherosclerosis in cardiovascular disease. Lipid apheresis discriminately removes LDL particles from plasma while leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

OBJECTIVE

The objective of this evidence review is to determine whether the use of low-density lipoprotein apheresis in patients with hyperlipidemia of varying etiology improves the net health outcome.

POLICY STATEMENT

Low-density lipoprotein (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 have failed diet therapy and maximum tolerated combination drug therapy* (see Policy Guidelines section) AND who meet the following U.S. Food and Drug Administration-approved indications (all LDL levels represent the best achievable LDL level after a program of diet and drug therapy):

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1. Functional hypercholesterolemic heterozygotes with LDL ≥300 mg/dL

2. Functional hypercholesterolemic heterozygotes with LDL ≥200 mg/dL AND documented coronary artery disease.

LDL apheresis is considered investigational for other uses, including nonfamilial hypercholesterolemia, nephrotic syndrome, sudden sensorineural hearing loss, severe diabetic foot ulcerations, peripheral artery disease, preeclampsia, and non-arteritic acute anterior ischemic optic neuropathy.

Therapeutic apheresis with selective high-density lipoprotein delipidation and plasma reinfusion is considered investigational for all indications, including but not limited to acute coronary syndrome.

a For definitions of maximum tolerated drug therapy and documented coronary artery disease, see the Policy Guidelines section.

POLICY GUIDELINES

A scientific statement from American Heart Association (Gidding et al [2015]) for the treatment of heterozygous familial hypercholesterolemia (FH) has indicated that adults should be treated with available pharmacotherapy with an initial goal of reducing low-density lipoprotein cholesterol (LDL-C) by at least 50%, usually with a statin. This treatment can be followed by achieving an LDL-C of less than 100 mg/dL (absent coronary artery disease [CAD] or other major risk factors) or 70 mg/dL (presence of CAD or other major risk factors). The following approach for pharmacotherapy is suggested:

- High-intensity statin therapy to target >50% LDL-C reduction, such as rosuvastatin or atorvastatin.
- If the patient is adherent and LDL-C is above the target goal after 3 months, consider adding ezetimibe.
- If the patient is adherent and LDL-C is above the target goal after 3 months, consider adding a PCSK9 inhibitor or colesevelam (or other bile acid sequestrant or niacin).
- If the patient is adherent and LDL-C is above the target goal after 3 months, proceed to complex therapy combination such as a 4-drug combination plus LDL apheresis.

Documented CAD 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 nonexercise stress test.

LDL apheresis represents a chronic, lifelong therapy.

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

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Two LDL apheresis systems have been approved by the U.S. Food and Drug Administration (FDA) for marketing. In 1996, the Liposorber LA-15 System (Kaneka Pharma), dextran sulfate device, 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 (familial hypercholesterolemia (FH)) for whom diet has been ineffective or not tolerated."

In 1997, the HELP System (B. Braun), a heparin-induced extracorporeal LDL precipitation, was approved by the FDA through the premarket approval process for the same indication. FDA product code: MMY.

In 2013, the Liposorber LA-15 System was approved for additional indications through the humanitarian device exemption process for the treatment of pediatric patients (FDA expanded indication to include adults in March 2018) with primary focal segmental glomerulosclerosis when the following conditions apply:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitor treatments, are unsuccessful or not well-tolerated, and the patient has a GFR [glomerular filtration rate] ≥60 mL/min/1.73 m² or
FEP 8.02.04 Lipid Apheresis

• The patient is post renal transplantation.

No devices have been approved by the FDA specifically for HDL delipidation. The Lipid Sciences Plasma Delipidation System-2 (Lipid Sciences) was tested in clinical studies, but the company ceased business operations in 2012.

**RATIONALE**

**Summary of Evidence**

**Familial Hypercholesterolemia**

For individuals with homozygous FH and unable to achieve target LDL-C with maximally tolerated pharmacotherapy who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies and a systematic review. The relevant outcomes are overall survival (OS), disease-specific survival, change in disease status, morbidity events, and treatment-related morbidity. Studies have reported reductions in LDL-C levels after apheresis, with means ranging from 57% to 75%. Currently, the direct evidence does not demonstrate that reductions in LDL-C levels seen with LDL apheresis will reduce adverse cardiovascular events. RCTs comparing drug therapy alone, apheresis alone, no intervention, usual care, or apheresis plus drug therapy are not feasible, and unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a treatment of last resort when maximally tolerated pharmacotherapy has failed to achieve target LDL-C levels. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with heterozygous FH and unable to achieve target LDL-C with maximally tolerated pharmacotherapy who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies as well as a systematic review. The relevant outcomes are OS, disease-specific survival, change in disease status, morbidity events, and treatment-related morbidity. Studies have reported reductions in LDL-C levels after apheresis with means ranging from 58% to 63%. Currently, there is no direct evidence that reductions in LDL-C levels seen with LDL apheresis will reduce adverse cardiovascular events. RCTs comparing drug therapy alone, apheresis alone, no intervention, usual care, or apheresis plus drug therapy are not feasible, and unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a treatment of last resort when maximally tolerated pharmacotherapy has failed to achieve target LDL-C levels. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Nonfamilial Hypercholesterolemia**

For individuals with non-FH who receive LDL apheresis, the evidence includes multiple retrospective and prospective nonrandomized cohort studies. The relevant outcomes are OS, disease-specific survival, change in disease status, morbidity events, and treatment-related morbidity. These studies have reported improvements in lipid levels pre- and posttreatment. Randomized trials in patient populations that are well-characterized regarding previous treatments, lipid levels, and comorbidities are necessary to demonstrate improvements in health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Nephrotic Syndrome**

For individuals with treatment-resistant nephrotic syndrome who receive LDL apheresis, the evidence includes multiple nonrandomized prospective and retrospective cohort studies. The relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Using variable schedules of LDL apheresis with short-term follow-up, these studies have reported that LDL apheresis may improve proteinuria and lipid abnormalities in patients with steroid-resistant nephrotic syndrome. Additional studies with concurrent controls and longer term follow-up are necessary to determine whether outcomes are improved with the use of LDL apheresis in nephrotic syndrome. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Other Indications**

For individuals with sudden sensorineural hearing loss who receive LDL and fibrinogen apheresis, the evidence includes two RCTs. The relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. One RCT compared LDL apheresis with the standard treatment of prednisolone, hydroxyethyl starch, and pentoxifylline; it reported no statistically significant differences in hearing recovery between groups. The second RCT compared the combination of a single lipid apheresis procedure plus standard treatment with standard treatment alone; it reported statistically significant differences in hearing recovery with the

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addition of apheresis to standard treatment. An a priori primary endpoint, power calculations, and the statistical plan to control for type I error for multiple comparisons were not reported in the second trial. Further evaluation and replication of these findings are required given the inconsistent reporting. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with severe diabetic foot ulcerations who receive LDL apheresis, the evidence includes a single prospective case series. The relevant outcomes are symptoms, change in disease status, morbidity, and treatment-related morbidity. In the case series, patients underwent from 1 to 7 treatment procedures and were followed for 2 to 73 months. Authors reported improved wound healing and reductions in the risk of lower leg amputations but results were insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with peripheral artery disease who receive LDL apheresis, the evidence includes a single prospective case series. The relevant outcomes are change in disease status and treatment-related morbidity. Improvements in symptomatic parameters such as coldness, numbness, and resting pain were reported, but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with preeclampsia who receive LDL apheresis, the evidence includes a prospective case series. The relevant outcomes are OS, disease-specific survival, change in disease status, morbidity, and treatment-related morbidity. Improvements in gestation were reported, but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with non-arteritic acute anterior ischemic optic neuropathy who receive LDL apheresis, the evidence includes a prospective case series. The relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Improvement in visual outcomes was reported but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Acute Coronary Syndrome**

For individuals with acute coronary syndrome who receive selective HDL delipidation and plasma reinfusion, the evidence includes an RCT. The relevant outcomes are overall mortality, disease-specific survival, change in disease status, morbidity, and treatment-related morbidity. Results have shown improvements in certain biochemical measures (e.g., pre-β-like HDL and α-HDL levels). There were no significant changes in atheroma volume. Larger randomized trials, with longer follow-up and clinically relevant outcomes, are needed to determine the impact of delipidated HDL plasma on acute coronary syndrome. The evidence is insufficient to determine the effects of the technology on health outcomes.

**SUPPLEMENTAL INFORMATION**

**Practice Guidelines and Position Statements**

**National Institute for Health and Care Excellence**

The National Institute for Health and Care Excellence's (2017) guidance on familial hypercholesterolemia (FH) has stated the following:

1.3.3.1 "Healthcare professionals should consider offering LDL [low-density lipoprotein] apheresis for the treatment of adults and children/young people with homozygous FH. The timing of initiation of LDL apheresis should depend on factors such as the person's response to lipid-modifying drug therapy and presence of coronary heart disease.

1.3.3.2 In exceptional instances (such as when there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy), healthcare professionals should consider offering LDL apheresis for the treatment of people with heterozygous FH. This should take place in a specialist center on a case-by-case basis and data recorded in an appropriate registry."17.

**American Society for Apheresis**

The American Society for Apheresis (2016) issued guidelines on the use of apheresis for 7 conditions (see Table 1).18.

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Table 1. Guidelines on Use of Apheresis

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Category</th>
<th>Grade&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-density lipoprotein apheresis for homozygous familial hypercholesterolemia</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>Heterozygous familial hypercholesterolemia</td>
<td>II</td>
<td>1A</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Lipoprotein (a) hyperlipoproteinemia</td>
<td>II</td>
<td>1B</td>
</tr>
<tr>
<td>Peripheral vascular diseases</td>
<td>II</td>
<td>1B</td>
</tr>
<tr>
<td>Phytanic acid storage disease (Refsum disease)</td>
<td>II</td>
<td>2C</td>
</tr>
<tr>
<td>Sudden sensorineural hearing loss</td>
<td>III&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2A</td>
</tr>
</tbody>
</table>

<sup>a</sup> Grade 1A: strong recommendation, high-quality evidence; grade 1B: strong recommendation, moderate-quality evidence; grade 2A: weak recommendation, high-quality evidence; grade 2C: weak recommendation, low-quality evidence.

<sup>b</sup> Optimum role not established.

**American Heart Association**

A scientific statement from American Heart Association (2015) on the treatment of heterozygous FH has indicated that high-risk adults should be treated with available pharmacotherapy with an initial goal of reducing low-density lipoprotein cholesterol (LDL-C) by at least 50%, usually with a statin, and treatment should be intensified based on the response. It also stated that there are no data to inform pediatric treatment goals, whether to target an LDL-C level of less than 100 or 130 mg/dL or to aim to achieve a 50% reduction in LDL-C from baseline.

For homozygous FH, the American Heart Association has recommended that lipid apheresis should be considered by five years of age or earlier in exceptional circumstances and should be used after maximally tolerated pharmacotherapy fails to achieve target LDL-C levels. The LDL-C selection criteria for lipid apheresis include a reduction in LDL-C of less than 50% by other treatments and residual severe LDL-C elevation of more than 300 mg/dL or more than 200 mg/dL with prevalent cardiovascular disease.

No guidelines on therapeutic apheresis with selective high-density lipoprotein delipidation and plasma reinfusion were identified.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

National Coverage Decision 110.14 on apheresis 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.

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REFERENCES


**POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2011</td>
<td>New policy</td>
<td></td>
</tr>
<tr>
<td>December 2012</td>
<td>Replace policy</td>
<td>Literature search, no new references added; no change in policy statements.</td>
</tr>
<tr>
<td>December 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature search; reference 8 added no change in policy statements</td>
</tr>
<tr>
<td>December 2014</td>
<td>Replace policy</td>
<td>Policy updated with literature review; references 7-8 and 10-11 added; added policy statement indicating therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion is investigational; title change to Lipid Apheresis</td>
</tr>
<tr>
<td>December 2015</td>
<td>Replace policy</td>
<td>Policy updated with literature review through July 2, 2015; references 1, 5, and 15-16 added. Policy statements unchanged. Rationale reorganized.</td>
</tr>
<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through March 5, 2018; references added; references 20-21 updated. Policy statement on high density lipoprotein apheresis was clarified. “6-month trial” removed from the second medically necessary policy statement. The investigational statement on LDL apheresis for other uses revised to include non-FH, sudden sensorineural hearing loss, severe diabetic foot ulcerations, peripheral artery disease, and non–arteritic acute anterior ischemic optic neuropathy. The Policy Guidelines section was revised by deleting the statement “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, fibric acid derivatives, or niacin/nicotinic acids.”</td>
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