When drugs and diet alone can't reduce LDL cholesterol, H.E.L.P. therapy can.
A H.E.L.P. procedure is a **continuous, closed-loop process** involving removal of whole blood and return of cellular blood components and filtered, cleansed plasma to the patient’s circulation. Over a 1.5 to 2-hour treatment session, an average of between 2.5 and 3.0 liters of plasma is treated. The H.E.L.P. System is extremely efficient in the elimination of LDL, Lp(a) and fibrinogen from processed plasma.

Performed by a trained nurse, the H.E.L.P. process involves five basic stages:

1. Blood withdrawn from the patient is continuously separated into **plasma** and **cellular components** by passage through a capillary plasma filter.
2. A mixture of sodium acetate buffer (pH 4.85) and heparin (100 IU/ml) are added to the plasma in equivalent parts by volume. When pH is adjusted to 5.12, lipoprotein complexes form a precipitate.
3. The precipitated lipoprotein complexes are captured in the precipitate filter, which is later discarded.
4. Residual heparin is removed from the LDL-free plasma by a heparin adsorber.
5. Physiologic pH of LDL- and heparin-free plasma is corrected with bicarbonate dialysis, followed by ultrafiltration to correct volume.

As for all apheresis procedures, the three available options for venous access include (1) left and right side arm veins, (2) arteriovenous fistula and (3) central venous access.

At any given time during treatment, the total volume of cellular blood components and plasma which are extracorporeal (withdrawn from the body) never exceeds 150 mL and 400 mL, respectively — about one unit of blood. All tubing and filters are sterile, disposable and single use only.

The frequency of therapy depends on the individual patient, but heterozygotes are most commonly scheduled for treatment every two weeks. Homozygotes typically require weekly therapy to attain sufficient average LDL lowering.
REFERENCES


For more information, contact us at 1-800-848-2066, or email to rtd@bbraun.com.
Safety Profile of H.E.L.P.® Therapy

In clinical use in Europe since 1986, the safety and tolerability of H.E.L.P. therapy has been demonstrated in both clinical trials and post-approval surveillance studies involving severely hypercholesterolemic patients. Worldwide experience with H.E.L.P. therapy now exceeds 200,000 individual treatments.

The H.E.L.P. procedure has also been used successfully in the treatment of post-heart transplant patients and patients on concurrent renal dialysis. A German study of 51 patients who received 4,330 H.E.L.P. treatments over a two-year period documented no serious adverse events attributable to the procedure.

Adverse reactions associated with H.E.L.P. therapy are those typically expected with any procedure involving circulation of blood outside the body. In the U.S. H.E.L.P. trial involving 40 patients and 2,826 treatments, venous access difficulties (2.3%) and transient hypotension (1.0%) were the most common adverse events.

Venous access problems often include clotting in the needle, clotted fistula or collapsed, inadequate or sclerosed veins; all can be resolved using standard methods. Transient hypotension is usually managed by administering intravenous fluids, allowing the treatment session to be completed.

Below are all other minor adverse events which occurred in at least 0.1% of procedures:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills/Shivering</td>
<td>9 (0.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (0.3%)</td>
</tr>
<tr>
<td>Prolonged PTT or ACT</td>
<td>7 (0.2%)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>7 (0.2%)</td>
</tr>
<tr>
<td>Chest Heavy/Pain</td>
<td>4 (0.1%)</td>
</tr>
<tr>
<td>Dizziness/Syncope</td>
<td>4 (0.1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (0.1%)</td>
</tr>
<tr>
<td>Elevated Temperature</td>
<td>3 (0.1%)</td>
</tr>
<tr>
<td>Others (single events)*</td>
<td>14 (0.5%)</td>
</tr>
<tr>
<td><strong>Total treatments</strong></td>
<td><strong>2,286</strong></td>
</tr>
</tbody>
</table>

*Flushing, gastrointestinal bleed, hyperventilation, wheezing, elevation of liver enzymes, apical density on CXR, ankle swelling, prostatitis, hematuria, hypoglycemia, sympathetic reflex dystrophy, angina/2nd PTCA, endarterectomy

An indication of the inherent safety of the H.E.L.P. procedure is the rare need to discontinue it: in a study involving more than 4,330 treatments, only three had to be interrupted because of technical or medical problems, none of which was serious in nature.
Chronic LDL apheresis therapy

In a subpopulation of patients diagnosed with familial hypercholesterolemia (FH), their seriously elevated plasma LDL cholesterol (LDL) levels fail to adequately respond to a prescribed diet and maximally tolerated combinations of lipid-lowering drugs.

Chronic LDL apheresis therapy offers motivated patients a highly effective means to reduce and maintain the LDL level in a safer range, thereby minimizing its atherogenic effects and associated risks of coronary heart disease, peripheral vascular disease and premature death.

The U.S. Food and Drug Administration approved the Heparin-induced Lipoprotein Precipitation (H.E.L.P.®) System for clinical use in September 1997. To date, more than 200,000 H.E.L.P. treatments have been performed worldwide to help improve the cardiovascular health of FH patients, with an excellent safety profile.

Once you have had an opportunity to review the information in this Physician Guide, we hope you will decide that H.E.L.P. therapy should be part of your armamentarium for the management of carefully selected patients with severe drug-refractory hypercholesterolemia.

Drug–Refractory Familial Hypercholesterolemia: The Treatment Imperative

A direct causal relationship between plasma cholesterol levels and coronary heart disease (CHD) risk has been firmly established through extensive population-based and interventional studies. The current ATP III guidelines recommend an LDL goal of <100 mg/dL for patients with CHD and CHD risk equivalents.1

As confirmed in other studies, men with an LDL level of about 240 mg/dL can expect to have a 12-year CHD-related mortality experience at least three-fold higher than those with an LDL level of about 130 mg/dL.

In untreated persons with heterozygous familial hypercholesterolemia (FH), total cholesterol levels are typically elevated more than two-fold over normal, typically ranging from 350 to 550 mg/dL.2 For these FH patients, who have sharply elevated blood cholesterol levels from birth – and commonly have a CHD history by the time they are diagnosed – the mortality risk at elevated LDL levels is higher than in the general population. Intensive lipid-lowering drug therapy is usually successful in reducing LDL, both for primary and secondary prevention of CHD.

In a subset of heterozygotes (as well as rare homozygotes with two defective alleles for the LDL receptor), dietary and maximally tolerated combinations of two or more lipid-lowering drugs fail to lower LDL to an acceptable range. Assuming good patient compliance, this generally occurs either because (1) the patient is resistant or refractory to drug therapy or (2) the patient cannot tolerate optimized drug combinations.

For these patients, chronic LDL apheresis offers a safe and effective means to achieve and maintain a substantially reduced mean LDL level.

When LDL apheresis is performed with B. Braun’s Heparin-induced Extracorporeal Lipoprotein Precipitation (H.E.L.P.) System, circulating levels of certain other atherogenic and prothrombotic plasma elements are substantially reduced as well, providing additional CHD risk reduction benefits.
**Fibrinogen levels and CHD event risk: evidence from the literature.**

While fibrinogen levels start to rebound immediately after each H.E.L.P.® treatment session, on a time-averaged basis fibrinogen is reduced by roughly 40%. Elevated fibrinogen levels have increasingly been cited as an inflammatory marker and a risk factor for CHD; it promotes adhesion of platelets and erythrocytes to the endothelium, increases plasma viscosity and participates in thrombus formation.

A landmark prospective study following several thousand patients with angina pectoris over a two-year period revealed that higher baseline concentrations of fibrinogen were associated with an increased incidence of myocardial infarction or sudden death. Below are coronary events data for three fibrinogen level tertiles:

<table>
<thead>
<tr>
<th>Plasma fibrinogen level</th>
<th>Coronary events/ patients</th>
<th>Risk of coronary events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;270 mg/dL</td>
<td>12/864</td>
<td>1.4%</td>
</tr>
<tr>
<td>270 – 330 mg/dL</td>
<td>35/846</td>
<td>4.1%</td>
</tr>
<tr>
<td>&lt;330 mg/dL</td>
<td>42/853</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

Remarkably, in the patients with fibrinogen levels under 270 mg/dL, coronary event risk remained low even in the presence of elevated serum cholesterol levels: the risk of coronary events was 1.3% in patients with total cholesterol <224 mg/dL and was 1.2% in those with >263 mg/dL.

A still larger UK study of 4,860 middle-aged men confirmed the association between fibrinogen level and coronary events: the age-adjusted relative risk of ischemic cardiac events for men in the top 20% of the fibrinogen level distribution compared to the bottom 20% was 4.5.

Lp(a): another atherogenic factor reduced by H.E.L.P. therapy.

A number of investigations report a strong association between elevated levels of lipoprotein (a), or Lp(a), and increased incidence of coronary artery disease. Because Lp(a) levels are under genetic control, efforts to modify elevated levels through diet and exercise have not proven successful. Niacin alone or in combination with a bile acid sequestrant or neomycin can reduce Lp(a) levels, but HMG-CoA reductase inhibitor therapy does not appear to offer benefit. H.E.L.P. therapy acutely reduces Lp(a) levels by the same low pH heparin precipitation mechanism that selectively removes LDL and triglycerides.

Reduced blood viscosity: lower CHD event risk.

Immediately following H.E.L.P. treatment, patients experience a 15% mean reduction in blood viscosity. This blood viscosity effect is substantially attributable to reductions in levels of fibrinogen, plasma LDL and other lipoproteins. Due to its large size (341 kD) and length, fibrinogen in particular contributes 20% to 25% to plasma viscosity. Conversely, elevated blood viscosity has been shown to be positively associated with initial and repeat CHD events.

While additional trials are needed to evaluate the relation between reduced blood viscosity by LDL apheresis and its effects on vascular disease, a single H.E.L.P. treatment has been shown to increase endothelial function and enhance coronary vasodilatory capacity and increase exercise capacity.

**Stabilization or regression of coronary stenoses.**

A number of studies have demonstrated that LDL-lowering drug therapy can reduce or halt the progression of coronary atheromas. Similarly, in a multicenter evaluation of 187 coronary segments in 33 patients undergoing H.E.L.P. therapy, 103 segments with >30% stenosis had a mean 4.3% reduction (p<0.001) in stenosis after two years of regular treatment.

**Reduced incidence and severity of angina pectoris.**

In a German study evaluating the H.E.L.P. System in 39 patients with existing coronary heart disease, the share of patients who were free of anginal symptoms increased from 18% prior to treatment, to 38% over two years of regular H.E.L.P. therapy.

In a separate post-marketing surveillance study involving 413 patients over a mean 5-year period, chronic H.E.L.P. therapy reduced complaints of angina pectoris, and appeared to be protective in non-anginal patients at first examination:

**Evidence of reduced risk for acute cardiovascular events.**

A pair of long-term studies in patients with pre-existing CHD and hypercholesterolemia offer strong suggestive evidence that H.E.L.P. therapy mediates a sharp reduction in the risk of myocardial infarction and other major cardiovascular events.
For properly selected FH patients who do not adequately respond to medications and diet, chronic H.E.L.P. therapy achieves a substantial reduction in time-averaged LDL level.

H.E.L.P. therapy also selectively reduces the circulating levels of a number of other atherogenic and prothrombotic blood elements implicated as risk factors for CHD-related events: While each H.E.L.P. procedure marginally reduces plasma high-density lipoprotein cholesterol (HDL) by 10–15%, the level of this “good” cholesterol generally returns to baseline within two days.

Over several months of H.E.L.P. therapy, the pretreatment HDL level rises to exceed the baseline level by an average of 15%. The mechanism responsible for this beneficial HDL effect is not known.

The highly selective H.E.L.P. procedure also conserves antibodies, albumin, coagulation factors and other important circulating blood elements.

**Time-Averaged LDL Lowering.**

Immediately following a H.E.L.P. treatment session, the sharply reduced levels of LDL, Lp(a), fibrinogen and other proatherosclerotic and pro-thrombotic elements promptly begin to rise. This “rebound effect” generally necessitates biweekly H.E.L.P. therapy for most heterozygotes and weekly therapy for homozygotes. Confirming earlier European experience, a clinical trial documented a time-averaged LDL reduction of nearly 140 mg/dL with biweekly H.E.L.P. treatments.

Notably, pre-treatment LDL levels decline more than 50 mg/dL after regular long-term H.E.L.P. therapy, to reach a new lower pre-treatment “baseline.” Similarly, the immediate post-treatment LDL trough level continues to decline with regular therapy to a new lower steady state. This pattern applies also for plasma triglycerides, Lp(a) and fibrinogen.

*Over a six-month study period with biweekly H.E.L.P. therapy, CRP levels exhibited a mean 49% reduction from baseline in four drug- and diet-resistant FH patients with advanced coronary artery disease.*
Insurance Coverage and Billing for H.E.L.P.® Therapy

Coverage

H.E.L.P. therapy is consistently covered by Medicare and private health insurers when prescribed for the chronic management of high-risk hypercholesterolemic patients for whom dietary and maximum tolerated drug and dietary therapy fails to achieve adequate LDL cholesterol reduction.

Private insurers and state Medicaid programs generally require preauthorization before submitting claims for this service. Suggested guidelines for securing preauthorization are available at your request.

Insurance coverage policies have generally been modeled on the September 1997 FDA marketing approval for the H.E.L.P. System. Patients who have failed a minimum six-month trial of an American Heart Association (AHA) Step II diet (or equivalent) and maximum tolerated combination drug therapy are eligible for H.E.L.P. therapy when they fall into one of the following three groups:

- **Functional hypercholesterolemic heterozygotes with LDL ≥ 200 mg/dL and documented coronary heart disease (CHD)**
- **Functional hypercholesterolemic heterozygotes with LDL ≥ 300 mg/dL**
- **Functional hypercholesterolemic homozygotes with LDL > 500 mg/dL**

As a physician, you have the prerogative to recommend and provide H.E.L.P. therapy for patients whose baseline LDL levels do not happen to fall within the confines of this indication, but you should be prepared to justify its medical necessity to the satisfaction of the patient’s insurer.

Many insurers will preauthorize a specified number of H.E.L.P. treatments, or for a specified duration, at which time updated clinical laboratory results will be required to secure a new preauthorization. This is a routine policy for coverage of many chronic therapeutic modalities.

Billing

For hospital-based H.E.L.P. therapy programs, the hospital bills the technical procedure and the physician's practice group separately bills his or her professional services.

For non-hospital-based H.E.L.P. programs, a single claim is submitted. Some insurers define separate payment amounts for technical and professional components of this service, while others prefer to set a single global payment rate.

Supporting Your H.E.L.P.® LDL Apheresis Program: The B. Braun Commitment

H.E.L.P. therapy programs can be situated in either hospital or non-hospital settings, usually under the direction of a specialist in cardiology, internal medicine or endocrinology.

B. Braun Medical provides all technical support services and operator training on the H.E.L.P. System to get your team ready to deliver patient therapy.

On an ongoing basis, B. Braun commits to support your LDL apheresis program with:

- New staff training
- New clinical and scientific literature
- Reimbursement consultation
- Patient literature
- H.E.L.P. program marketing assistance

We understand that we succeed as a supplier of this enabling technology by helping you succeed as a H.E.L.P. therapy provider.

Finally, while this procedure offers the promise of extended lifespan and enhanced quality of life, it is important to emphasize to patients that it also requires a long-term commitment on their part. Good candidates for H.E.L.P. therapy are those who are also sufficiently motivated to visit your clinic for their biweekly or weekly treatment sessions on an indefinite basis.

*CHD is defined as having one or more of the following: a prior documented myocardial infarction (MI); a prior coronary bypass graft surgery (CABG); a prior percutaneous transluminal coronary angioplasty (PTCA) with or without atherectomy or coronary stent placement; and significant angina pectoris with a positive thallium or other heart scanning stress test.