

## Current view: indications for extracorporeal lipid apheresis treatment

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### Abstract

**Background** One of the first investigations concerning extracorporeal treatment of hypercholesterolemia was performed in 1967 by plasma exchange in patients with homozygous or severe heterozygous familial hypercholesterolemia (FH). In the following decades, several specific lipid apheresis systems were developed to efficiently eliminate low-density lipoprotein (LDL) cholesterol and Lp(a) cholesterol in hypercholesterolemic patients. In the early 1980s, the main clinical indication has been homozygous FH including mainly children and pregnant women. In consideration of the current development of lipid-lowering regimens and scientific knowledge of preventing progression of cardiovascular diseases, the spectrum of indications to initiate lipid apheresis was extended due to still insufficient lipid-lowering therapy in some clinical cases. However, a generally accepted indication for lipid apheresis treatment is still under discussion. In Germany, the target-oriented distribution of increasingly limited health-care resources demand data which support the benefit of established treatment procedures such as lipid apheresis. In recent years, the Federal Joint Committee (G-BA),

a paramount decision-making body of the German Health-care System, issued to reassess the approval of chronic lipid apheresis therapy for regular reimbursement. Therefore, in 2005, an interdisciplinary German Apheresis Working Group has been established by members of both the German societies of nephrology. One of the first goals of this working group was a revision of the indications for lipid apheresis corresponding to current guidelines and recommendations for the treatment of lipid disorders. In addition, recently new pathophysiological perceptions of the impact of lipoproteins on atherogenesis and thrombosis were also considered.

**Methods and Results** Since 2005, the working group met on a regular basis to substantiate the first defined goals. The indications for lipid apheresis were critically revised with respect to actual results from clinical investigations, cardiovascular guidelines, and scientific knowledge and were accepted by the members of the apheresis working group.

**Conclusions** There is consensus between the medical societies and health insurance funds regarding the need for general accepted guidelines for lipid apheresis. Recommendations for the indications of lipid apheresis were developed, but additionally these results should be confirmed by medical societies to transform them to guidelines. However, due to limited data showing that lipid apheresis has effects on the progression of cardiovascular diseases all members of the apheresis working group support a project for creating a lipid apheresis registry. This apheresis registry has been developed and recently started. The primary goal is to substantiate prospective long-term data on clinical outcome of chronic lipid apheresis treatment and to support additional clinical research activities in this field. In addition, this registry should comply with the actual requests of the Federal Joint Committee (G-BA).

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## Introduction

First investigations dealing with extracorporeal treatment of hypercholesterolemia were performed in 1967 by plasma exchange [1]. During the following decades, more specific lipid apheresis systems were developed to efficiently eliminate low-density lipoprotein (LDL) cholesterol and Lp(a) by adsorption, precipitation, and specific filtration technique [2–12].

Therefore, the currently established lipid apheresis systems are effective extracorporeal lipid-lowering treatment procedures for selected patients suffering from progressive cardiovascular diseases induced by severe hyperlipidemia, in particular hypercholesterolemia and Lp(a) hyperlipoproteinemia [13].

In the early 1980s, the main clinical indication for lipid apheresis has been focused on homozygous familial hypercholesterolemia (FH) including mainly children and pregnant women [13]. Because of a better understanding of the correlation between high LDL cholesterol and Lp(a) cholesterol concentrations and an obvious progression of cardiovascular diseases, the demand of effective lipid reduction was increased [14, 15]. In recent years, well-designed investigations with hypercholesterolemic patients suffering from coronary heart disease (CHD) showed a better survival, when LDL cholesterol was efficiently decreased [16]. Therefore, new lipid thresholds were defined in hypercholesterolemic patients suffering from progressive cardiovascular diseases, which include a clear recommendation to initiate treatment with lipid-lowering drugs [17, 18]. Against the background of the current development of lipid-lowering regimens and the knowledge that progression of cardiovascular diseases can be prevented by adequate therapeutic means, the spectrum for lipid apheresis indications was extended to severe clinical cases, in which lipid-lowering drug therapy is insufficient or severe drug-associated side effects have occurred.

Unfortunately, the systematic investigations concerning the beneficial effects of lipid apheresis treatment such as a randomized double-blinded prospective lipid lowering study with significant statistical power are still lacking worldwide and are now difficult to perform [19] due to ethical reasons against the evidence from the current scientific knowledge. Therefore, in the last two decades, the indications for lipid apheresis treatment remained vague [20].

The Federal Joint Committee's (G-BA) assessment of medical treatments and procedures follows a standardized procedure which rests on evidence-based medicine. The generally accepted current state of medical knowledge is

ascertained for the purpose of assessing the effectiveness, quality, and economic efficiency of the diagnostic and therapeutic methods under examination.

In 2003, the German reimbursement guidelines for lipid apheresis were again revised by G-BA confirming the relevance of LDL cholesterol but denying an important role of Lp(a) cholesterol to establish the indication for lipid apheresis. Comments published with that decision prompted all medical disciplines, in particular nephrologists, to continue the critical discussion of chronic lipid apheresis therapy and to develop guidelines with broad acceptance within all related medical disciplines. To focus these discussions, an interdisciplinary German Apheresis Working Group (AWG) was founded in 2005 by members of both German societies of nephrology (Deutsche Gesellschaft für Nephrologie (DGfN), Verband Deutsche Nierenzentren (VDN)) with the goals to be a partner in the dialogue and negotiations with the G-BA and to standardize the indications for lipid apheresis [21].

Until now, the indications for lipid apheresis treatment were critically revised and adapted by AWG to substantiate benefit and cost-effectiveness of established lipid-lowering treatment procedures and to optimize lipid-lowering therapy through lipid apheresis treatment considering the increasingly limited healthcare resources [21].

Most members were previously members of an apheresis working group, which consisted of nephrologists, cardiologists, endocrinologists, and specialists of clinical chemistry and laboratory medicine [22].

## Methods and results

From 2005 until today, several meetings were held and the suggestions from actual publications as well as recommendations from national and international cardiovascular societies were critically discussed. At the end of all discussions, all attendees agreed on the following consensus statements:

### **Recommendations for maximal lipid-lowering therapy in patients suffering from severe hyperlipidemia**

All patients suffering from high LDL cholesterol concentrations according to actual guidelines, with triglyceride less than 300 mg/dl and without any evidence for remnant hyperlipidemia or chylomicronemia, should be considered for long term lipid-lowering therapy.

However, before lipid-lowering drug therapy should be considered, a basic diet with low cholesterol and rich in omega-3 fatty acids is advised for these patients, corresponding to the recommendations of EAS and NCEP.

When lifestyle modification with an emphasis on normalization of body weight and heart-healthy patterns of dietary intake and physical activity fails in hyperlipidemic patients, the lipid-lowering drug regimens should be recommended. It should be taken into account that the lipid-lowering success in these recommendations depends on attention to multiple tasks like titration of medications, management of side effects, careful use of combination lipid-altering drug therapies. Side effects associated with lipid lowering drugs or their combinations should be well documented and reported to the Drug Commission of the German Medical Association.

The initiation of a lipid apheresis treatment should be considered within a period of 3 months, when diet and lipid-lowering drug procedures remained ineffective (conservative therapy) to LDL cholesterol or Lp(a) cholesterol levels in the following situations:

- In *primary prevention*, the patients suffering from familial hypercholesterolemia with remaining LDL cholesterol concentrations >160 mg/dl (4.2 mmol/l) and cardiovascular events in close relatives.
- In *secondary prevention*, the patients suffering from progressive cardiovascular events with remaining LDL cholesterol concentrations >120–130 mg/dl (3.1–3.4 mmol/l).
- In *addition*, independent of LDL cholesterol concentrations, the patients suffering from progressive cardiovascular disease clinically assessed or by using imaging techniques with lipoprotein a (Lp(a)) concentrations >60 mg/dl.

These regulations may be flexibly applied with respect to individual clinical conditions of the affected patients. When progressive cardiovascular events occurred despite maximal conservative therapy, earlier initiation of chronic lipid apheresis should be considered.

According to the Federal Joint Committee's (G-BA) assessment of medical treatments and procedures, the lipid apheresis can only be performed in Germany although the indication for lipid apheresis is given, if the additional administrative standardized procedures are completed. In compliance with the given G-BA guidelines, only specialists in vascular medicine like cardiologists, specialists in lipidology, and neurologists can consider the indication for lipid apheresis. Together with the patient's approval and expert opinion, all nephrologists must file their applications to an apheresis subcommittee of the Associations of Statutory Health Insurance Physicians (Kassenärztliche Vereinigungen; ASHIPs). Only after an agreement of this apheresis subcommittee, the lipid apheresis treatment can be performed for one year. However, within a year, the application procedures for lipid apheresis must be repeated in the way mentioned above [23, 24].

## Discussion

Since 1967, the lipid apheresis treatments were performed in patients with severe familial hypercholesterolemia and cardiovascular diseases. During the following years, specific lipid apheresis regimens were developed and were able to decrease LDL cholesterol for more than 60% or Lp(a) cholesterol for more than 55%, respectively [25]. However, general accepted guidelines for lipid apheresis are still lacking.

There is consensus between the medical societies and health insurance authorities regarding the need for generally accepted guidelines for lipid apheresis [19].

During the past 10 years, several review articles from different countries have discussed the indications for using lipid apheresis to treat refractory hypercholesterolemia in association with severe progressive cardiovascular damage [13, 22, 26, 27]. In addition, definitive recommendations have been published by various national as well as international societies and organizations [28–31].

The Food and Drug Administration (FDA) has approved the use of dextran sulfate-cellulose adsorption (DSA) and Heparin-induced extracorporeal LDL precipitation (HELP) apheresis system in three categories of patients in the US: Functional FH homozygotes, with LDL cholesterol >500 mg/dl (13 mmol/l); functional FH heterozygotes, with LDL cholesterol >300 mg/dl (7.8 mmol/l); and functional FH heterozygotes with documented CHD and LDL cholesterol >200 mg/dl (5.2 mmol/l) [32].

However, all former reviews have shown that there is a gap between the demand for aggressive LDL cholesterol lowering (<100 mg/dl (2.6 mmol/l), in some cases <70 mg/dl (1.8 mmol/l)), when cardiovascular damage had occurred in a hypercholesterolemic patient and the consequent application of lipid lowering therapies like diet, lipid-lowering drugs, and in special clinical cases lipid apheresis [24].

Now, recommendations for the indications of lipid apheresis were developed for Germany by the members of the German Apheresis Working Group (AWG), but additionally these results should be confirmed by medical societies condensing them to guidelines [24].

All members of the AWG agreed that the indications of lipid apheresis should be critically reviewed within one year and adapted to new scientific recommendations, findings, or drug developments.

Under actual consideration is an investigation, which identified LPA variants (LPA locus on 6q26–27) encoding Lp(a) lipoprotein that were strongly associated with both an increased level of Lp(a) lipoprotein and an increased risk of coronary disease [33], but these results need further investigations to substantiate this method as a tool to determine high-risk patients for Lp(a) associated cardiovascular diseases and consequently for lipid apheresis treatment. Further-

more, a new developed antisense apolipoprotein B synthesis inhibitor may become an additional potent agent in lipid-lowering therapy [34]. However, long-term clinical data are still lacking.

Due to limited data showing that lipid apheresis has effects on the progression of cardiovascular disease, all members of AWG support a project for establishing a lipid apheresis registry [21].

A registry represents an appropriate instrument for quality management of extracorporeal treatment. Worldwide, several registries exist with different purposes. The world apheresis registry, the Swedish, French, and the Canadian apheresis registry provide an overview of various techniques of therapeutic apheresis and their clinical applications, which for Germany is still lacking [35–37].

A German apheresis registry was recently developed and started. The primary goal is to substantiate prospective long-term data on clinical outcome of chronic lipid apheresis treatment and to support additional clinical research activities in this field.

In addition, this registry should fulfill the current requirements of the Federal Joint Committee (G-BA).

## Conclusions

The German Apheresis Working Group (AWG) has developed actual recommendations for the indications of lipid apheresis treatment in consideration of current national and international guidelines for lipid therapeutic regimens, but the general acceptance in medical societies is still lacking. In addition, AWG designed and started a German lipid apheresis registry. This registry should fulfill the requirements of the Federal Joint Committee (G-BA).

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