# Review



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# Hemodiafiltration: Technical and Clinical Issues

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# **Key Words**

Online hemodiafiltration · Ultrafiltration · Predilution · Backfiltration · Convection

# Abstract

Hemodiafiltration (HDF) seems to represent the gold standard in the field of replacement of renal function by dialysis. High convective fluxes have been correlated with better clinical outcomes. Sometimes, however, there are technical barriers to the achievement of high blood flows adequate to perform effective convective therapies. In spite of optimized procedures, the progressive increase in transmembrane pressure (TMP), the blood viscosity due to hemoconcentration and blood path resistance sometimes becomes inevitable. We propose two possible solutions that can be operated automatically via specific software in the dialysis machine: predilution on demand and backflush on demand. Predilution on demand consists in an automatic feedback of the machine, diverting part of the filtered dialysate into a predilution mode with an infusion of 200 ml in 30 s while the ultrafiltration pump stops. This produces a sudden hemodilution with a return of the parameters to acceptable values. The performance of the filter improves, and the pressure alterations are mitigated. Backflush on demand consists in an automatic feedback of the machine triggered by the TMP control, producing a positive pressure in the dialysate compartment due to a stop of filtration and rapid infusion of at least 100 ml of ultrapure dialysate into the hollow fiber. This not only produces a significant hemodilution, but also back-

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flushes the membrane pores detaching protein layers and improving membrane permeability. These are two examples of how technology will permit to overcome technical barriers to a widespread diffusion of HDF and adequate convective dose delivery. © 2015 S. Karger AG, Basel

## Introduction

Hemodiafiltration (HDF), first introduced by Henderson in 1967 [1], is a renal replacement technique combining diffusion and convection to enhance solute removal in a wide spectrum of molecular weights. In this modality, the amount of ultrafiltration (UF) exceeds the desired flu-

Claudio Ronco, MD Department of Nephrology, Dialysis and Transplantation International Renal Research Institute of Vicenza (IRRIV), San Bortolo Hospital Viale Rodolfi 37, IT–36100 Vicenza (Italy) E-Mail cronco@goldnet.it id loss, and replacement fluid is administered to achieve the target fluid balance. The <u>relative contribution</u> of <u>con-</u> <u>vection</u> to overall <u>solute removal increases progressively</u> with <u>increasing molecular weight</u>.

Technological developments in the fields of membranes, machines and fluids have made HDF a safe and effective technique. Synthetic membranes with reduced wall thickness allowed a combination of diffusive-convective techniques. Furthermore, the development of accurate volumetric UF control systems in dialysis machines reduced the risk for fluid balance errors. Recently, online preparation of sterile and pyrogen-free solutions allowed the safe infusion of large amounts of fluid, making highvolume HDF a simple and safe routine procedure [2].

#### **HDF** Techniques

HDF can be performed with different techniques [3]. The classic HDF technique used an average reinfusion rate of 9 liters/session in the postdilution mode. A blood flow over 300 ml/min was required for sufficient rates of UF at acceptable transmembrane pressure (TMP) gradients. The equipment included an UF control system, a reinfusion pump and a scale to weigh reinfusion bags. A special form of HDF called acetate free biofiltration eliminated even small traces of acetate from both dialysate and replacement fluid inducing a significant improvement in hemodynamics of unstable patients. Another variant of HDF, called 'high-volume HDF', used 15 liters or more of reinfusion per session. The high cost of commercial replacement fluids in bags stimulated the development of a novel technique called online HDF (OL-HDF). Fresh ultrapure dialysate from the dialysate inlet line is processed with multiple filtration steps and infused as replacement fluid. Large amounts of inexpensive replacement solution are generated, and HDF can be performed with a very high fluid turnover (up to 25-30 liters/session). Fluid can be infused in either pre- or postdilution mode, or both, in different proportions. Other techniques such as internal filtration HDF, paired filtration dialysis, mid-dilution HDF, double highflux HDF and push-pull HDF have also been proposed to combine convection and diffusion conveniently [3].

#### **Dialyzer and Membrane Characteristics**

A prerequisite to perform HDF efficiently and safely is the selection of an adequate membrane and hemodiafilter. The diffusion process can be impaired if there is a mismatch between blood and dialysate flow distribution in the dialyzer. For this reason, it is important that central and peripheral blood and dialysate flow velocities in the filter do not differ significantly. Single fiber flow velocity should be similar in the center and the periphery of the bundle. Likewise, dialysate flow in the central region of the dialyzer and in the peripheral areas should be similar. In this way the best blood-to-dialysate flow countercurrent configuration is obtained, and the diffusive process is optimized. Attempts to optimize flows have been made in the blood compartment designing specific blood ports while in the dialysate compartment different options have been proposed such as space yarns (spacing filaments preventing contact between fibers) or the moiré structure (waived shape of fibers to prevent contact between adjacent fibers) [4, 5].

Membrane performance, in terms of solute clearance and biocompatibility, is of paramount importance when choosing a dialyzer. Technological advances in membrane design, chemical composition and sterilization methods have led to enhanced performance. The membrane and the dialyzer are the center of the extracorporeal treatment. Thus, the choice of membrane and dialyzer among the wide selection available on the market is the key to obtain the desired blood purification for each individual clinical need. Criteria for selection may be the type of membrane, surface area, sterilization, permeability and cutoff point for molecular size.

The membrane allows to broaden the spectrum of uremic toxins that can be removed thanks to its chemical and physical characteristics. Nevertheless, the way each membrane is utilized inside a filter and the way each filter is utilized in the extracorporeal circuit can make a great deal of difference. Membranes can be divided by chemical composition. The polymer that composes membranes essentially determines its chemical and physical behavior and its possible use in the extracorporeal technique. Natural polymers derived from cellulose have progressively been substituted by synthetic polymers in which recent nano-controlled spinning techniques have contributed to enhanced performances. The ideal membrane should be biocompatible, physically strong, characterized by excellent diffusive and convective properties and by resistance to chemical and physical sterilizing agents. The optimal permeability profile should allow high sieving coefficients for large solutes with minimal or absent albumin loss. Some membranes are also characterized by high adsorption capacity, and this may further contribute to solute removal properties. The structure of the membrane should be thin enough to allow good diffusivity coefficients while the number and size of the pores should be standardized and optimized per unit of surface area. The inner surface of the membrane should be smooth and constructed to avoid interactions with blood components, especially platelets. Low thrombogenicity is a key feature to reduce heparin requirements and platelet activation.

The choice of the hemodiafilter should also be made according to specific criteria, such as the type of membrane and sterilization, surface area and design. The ideal filter for HDF should be highly effective regarding solute removal exhibiting constant performance over the whole treatment session. Steam or gamma sterilization avoids adverse reactions due to residuals of ethylene oxide. Today, almost all hemodiafilters are provided with hollow fiber configuration. Modern housing containing the bundle is generally light in weight and well designed to avoid dead spaces. The structure of the bundle is also important, as the number and length of fibers determine the crosssection of the dialyzer and its resistance. Therefore, in each dialyzer, the size and design of the fiber bundle determine its performance. The priming volume must be as low as possible, and each fiber should be surrounded by a uniform stream of dialysate during dialysis. The number of fibers and the fiber bundle density represent an important parameter to determine the filter dimension for a given surface area. To ensure a minimal activation of humoral and cellular systems of the blood, it is necessary to use a completely inert potting compound and a smooth cutting of the heads to form a smooth surface. These end surfaces are covered on both sides by end caps that contain the blood inlet and outlet ports. The composition of the potting compound has changed over the years in order to minimize risks associated with toxic compounds sometimes induced by the sterilization process, as in the case of irradiation with beta or gamma beams.

The main purpose of developing synthetic membranes was to create more porous membranes which could better simulate the filtration process of the natural kidney. In this way we can improve the removal of middle- and high-molecular-weight uremic toxins ( $\beta_2$ -microglobulin). All synthetic polymers (with the exception of ethylene vinyl alcohol copolymer) currently on the market are hydrophobic and have to be made more hydrophilic during their production by using additives or copolymers. On the other hand, derivates of cellulose-based membranes tend to be more hydrophilic but they need to have an improved porosity and higher sieving coefficients.

Generally, the material used to make hollow fiber membranes includes cellulose-based materials (cellulose

acetate, cellulose triacetate), polysulfones, polyethersulfone, cellulose triacetate, polymethylmethacrylate, ethylene vinyl alcohol or polyacrylonitrile. Nowadays, the use of poorly biocompatible unmodified cellulose dialyzer membranes is discouraged. In fact, most dialyzers are made from synthetic polymers from the family of polysulfone/polyethersulfone or from highly modified cellulose-based membranes.

## **Theoretical Considerations**

The choice of a filter for HDF depends on the selected technique. Although some techniques require a captive dialyzer, in general the selection is based on simple and clear criteria. The dialyzer should have a surface area sufficient to achieve the desired Kt/V per session, and for this purpose, a minimum filter KoA of 1,000 should be prescribed. If large filtration rates are anticipated, as is the case in high-volume HDF (convection volume >20 liters/ session), a membrane with a minimum permeability of 30 ml/h/mm Hg/m<sup>2</sup> should be considered. Crucial aspects, of course, are a high resistance to elevated TMP values and a low tendency to fouling and clotting. For this purpose, first, optimization of blood flow is of paramount importance. Thereafter, both Kt/V and convection volume per session should be checked carefully. If results are not satisfactory, necessary corrections should be made in treatment time and in the flow rates of dialysate and blood. When targets are still not reached after these maneuvers, another dialyzer can be selected with a different membrane or a larger surface area.

Sometimes, technical barriers are encountered that prevent the achievement of the desired amount of convective clearance. When TMP and end-to-end pressure drop tend to increase beyond a certain threshold in spite of blood flow optimization, a beneficial effect has been claimed of a filter flush in the predilution mode with 200 ml of saline in 30 s while the UF pump stops (predilution on demand). The sudden hemodilution, which is achieved with this maneuver, may induce a return of the parameters within acceptable values.

Initial barriers to the use of HDF have been overcome thanks to significant advances in technology. In particular, the problem of replacement solution required in large amounts has been solved by the online production of microbiologically safe fluid, adequate as a substrate for infusion. New machines and specifically designed software are conveniently combined to make HDF safer and simpler with the new online technique (OL-HDF). The sub-

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**Fig. 1.** Relationship between the convective dose in HDF and survival according to recent findings.

sequent step was to prove the concept that a more efficient dialysis technique such as OL-HDF is the basis for a significant improvement in morbidity and mortality in dialysis patients. In the last decade, many studies have demonstrated important improvements in inflammation, cardiovascular stability,  $\beta_2$ -microglobulin-related complications and many other clinical outcome measures including mortality. In particular, the most recent and well-conducted analyses have indicated that significant benefits may be achieved in dialysis patients if a higher volume of fluid exchange is obtained in postdilution HDF [6]. Looking at the single studies, and evaluating the outcomes based on the amount of convective clearance achieved, one could build a relationship with survival based on the concept of 'convective dose' (fig. 1).

#### **Barriers to Achieve High-Volume HDF**

Several factors influence the solute transport across the membrane in HDF. Blood flow greatly affects the clearance of small solutes like urea, while the UF rate mostly affects the removal of larger solutes like inulin. Convection requires a fluid movement caused by a TMP gradient. Therefore, the convective flux of a solute will depend on the UF rate, the solute concentration in plasma water and the solute sieving coefficient, being under ideal conditions  $S = 1 - \sigma$ , where  $\sigma$  is the reflection coefficient of the membrane. These definitions present convection and diffusion as two separate phenomena. However, it is impossible to precisely define the contribution of each single process in the removal of solutes because of their continuous interactions. Moreover, especially in treatments that present a combined utilization of diffusion and convection, there is a continuous interference between the two transport mechanisms.

UF values are predicted according to the theoretical porosity and hydraulic permeability of the membrane, but they also largely depend on the operational conditions of the system and interaction with the plasma proteins. Two conditions may occur: in the presence of low UF rates, an electrochemical link makes a thin protein layer deposit on the internal surface of the fiber. This characterizes the biocompatibility of the membrane that, once it has absorbed the protein layer, lets the blood flow on an autologous material surface. At the same time this adsorption slightly reduces the membrane sieving coefficient with a rather constant trend. In case of high UF rates, or better, high filtration fractions, a thick protein deposit on the membrane is induced by the additional phenomenon of polarization. This progressively reduces the membrane permeability and the solute sieving becomes proportional to a new reflection coefficient ( $\sigma$ 1) of the membrane. This layer is a function of several variables, and above all the value of 'shear rate' at the wall. As the blood enters the hollow fiber, the shear stress generates different layers of blood from the bulk phase to the membrane interface flowing at different velocities. The ratio between the speed variations of the fluid threads in the fiber and the variation of the distance from the center of the fiber ('shear rate' expressed in liters/second) is a function of blood viscosity and of the shear stress. The shear rate is also proportional to the blood flow per single fiber. The thickness of the protein layer at the blood membrane interface depends on the wall 'shear rate' value and is extremely important for the membrane performance. The shear rate value linearly correlates with the shear stress in case of Newtonian fluids, and the velocity profile is regularly parabolic. Blood approaches the Newtonian behavior only at shear rates higher than 200/s. UF and solute sieving coefficients are considerably influenced by the wall shear rate because it contributes to keep the polarization layer very thin. This is particularly important for solutes in the middle-high range. Diffusion is also affected by the value of shear rate since high shear rates contribute to maintain the diffusion distance from blood to dialysate within minimal values. This is because concentration polarization and the secondary layer of proteins lead to the formation of a pseudomembrane whose thickness is added to the thickness of the original membrane. In the clinical practice high wall shear rates are obtained with high blood flows and adequate device ge-



**Fig. 2.** High-volume postdilution HDF may induce a series of hydraulic consequences that affect filter survival and performance and lead to a progressive increase in TMP and end-to-end pressure drop (E-E  $\Delta$ P) throughout the session. CS = Cross-sectional.



**Fig. 3.** Typical setting and layout of a circuit for OL-HDF. When UF rates increase, new technologies may be required to perform a safe and effective high-volume postdilution HDF session. A = Arterial line; V = venous line; Do = dialysate outlet; Di = dialysate inlet; Uf = ultrafiltration.

ometry and result in higher UF rates and solute clearances. In studies carried out with dye injection in the blood compartment of different hollow fiber dialyzers, we could demonstrate in peripheral fibers blood flows and shear rates much lower than those observed in the central fibers of the bundle unless high blood flows are prescribed and flow distribution is optimized by high-performance hemodialyzers. These observations must drive the selection of operational parameters and hemodialyzers in the case of HDF. Furthermore, the site of reinfusion (predilution versus postdilution sites) may affect the final performance of the system. In postdilution HDF, efficiency is maximized compared to predilution techniques but, depending on filtration fraction, an excessive protein concentration polarization at the membrane interface and/or an excessive hemoconcentration along the length of the hollow fibers occur. The first phenomenon results in a decay of membrane permeability with requirements of increasing TMPs to maintain scheduled filtration rates. The second produces an increased viscosity of blood inside the dialyzer with a progressive increase in end-to-end pressure drop and predialyzer pressure (fig. 2). The high cost of commercially prepared fluids in bags and the improvement in the technology of dialysate preparation and online fluid filtration has allowed in recent years to develop a technique called OL-HDF (fig. 3). In this case, a certain amount of freshly prepared ultrapure dialysate is taken from the dialysate inlet line and processed with multiple steps of filtration before being used as a replacement fluid. In this way, large amounts of inexpensive replacement solution are made available, and HDF can be carried out with a very high fluid turnover (up to 30-40 liters/session) utilizing pre- or postdilution sites or even both in different proportions. Specific adjustments had to be made in the past generation of machines, whilst the latter machines are conceived to perform OL-HDF with adequate embedded software and system controls. The need to achieve at least 22 liters of ultrafiltrate in postdilution HDF, imposed by a recent clinical trial, has spurred new interest in the strategies that may allow to achieve such results. High blood flows are the best strategy but they are not available in all patients. Therefore, special software embedded in some machines allows for a continuous measurement of pressure variations inside the

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hollow fiber filter and consequently permits an optimization of the parameters achieving the maximum volume of ultrafiltrate thanks to a complex algorithm. Nevertheless, the progressive increase in TMP, blood viscosity due to hemoconcentration and blood path resistance sometimes becomes inevitable.

# Predilution on Demand

When TMP and end-to-end pressure drop tend to increase significantly beyond a certain threshold in spite of autosub plus optimization, we propose an automatic feedback of the machine, diverting part of the filtered dialysate into a predilution mode with an infusion of 200 ml in 30 s while the UF pump stops. This produces a sudden hemodilution with a return of the parameters within acceptable values. The performance of the filter improves, and the pressure alterations are overcome (fig. 4).

# Backflush on Demand

In the presence of the same phenomenon observed before, this technique utilizes the mechanism of backfiltration by an automatic feedback of the machine triggered by the autosub plus, producing a positive pressure in the dialysate compartment due to a stop of filtration and rapid infusion of at least 100 ml of clean dialysate into the hollow fiber. This not only produces a significant hemodilution, but also backflushes the membrane pores detaching protein layers and improving membrane permeability (fig. 5).

Little information is available on the different dialyzers used in clinical practice. In the randomized clinical trial CONTRAST [7], comparing HDF with hemodialysis, dialyzers with a surface area between 1.7 and 2.2  $m^2$ , an UF coefficient between 56 and 85 ml/mm Hg/h, a capillary lumen diameter between 185 and 215 µm and a capillary length between 225 and 280 mm were applied. Despite these dissimilar characteristics, convection volumes were rather similar. However, as these data are observational by nature and the dialyzers were clustered in participating centers, local practice patterns may have influenced these results [8]. In a crossover study in 18 HDF patients who were treated with an automatic ultracontrol technique (UltraC system), 4 different dialyzers were tested with constant dialysis parameters. As more or less expected, the highest convection volumes and filtration fractions were achieved by a dialyzer with the largest surface area, a high UF coefficient (75 ml/mm Hg/h), a wide capillary lumen diameter (210 µm) and a capillary length of 200 mm [7]. From this study it was concluded that, although structural characteristics of dialyzers may limit



**Fig. 4.** Predilution on demand (POD) in postdilution HDF. During the session, a periodical flush of the hollow fibers is achieved by a predilution mechanism with replacement solution. This can be done automatically based on a specific algorithm or manually on demand. Laboratory findings demonstrate good results in terms of hydraulic performances of the filter. E-E  $\Delta P$  = End-to-end pressure drop.



**Fig. 5.** Backfiltration on demand (BOD) in postdilution HDF. During the session, a periodical backflush of the hollow fibers is achieved by a backfiltration mechanism induced by a sudden pressure change inside the dialyzer. The dialysate backflushes the proteins on the inner surface of the hollow fiber restoring membrane permeability and disrupting the protein layer created by the concentration polarization phenomenon. This can be done automatically based on a specific algorithm or manually on demand. Laboratory findings demonstrate good results in terms of hydraulic performances of the filter. E-E  $\Delta P$  = End-to-end pressure drop.

their use in automatic systems, manual settings may overcome these imperfections.

A large selection of dialyzers is available on the market with different characteristics and consequently different performance features. KoA, cutoff and hydraulic permeability determine how each filter should be used and how prescription should be made. For specific techniques, captive configurations and design may be required. Based on a profound knowledge of membrane and dialyzer characteristics, the nephrologist can choose and prescribe the best device and treatment for each individual patient in relation to his clinical needs. In case of intolerance or complications, treatment parameters must be carefully checked and optimized before shifting to another device.

# **Clinical Potential of HDF**

After several decades of rapid and impressive technical development of renal replacement therapy, it has been clarified that, despite multiple adjustment for age, case mix and comorbidity, the conventional short hemodialysis treatment schedule based on a low-flux hemodialyzer is loaded with unacceptably high morbidity and mortality in chronic kidney disease patients. The run for highly efficient short dialysis schedules further aggravated dialysis intolerance and increased morbidity and mortality.

Considering these facts it has become clear that a more effective, gentle but also economically viable dialysis modality is required to improve outcomes. Ideally to achieve this objective, the best suitable treatment modality has to fulfill several prerequisites: regular use of dialyzers with a highly permeable synthetic membrane, increased diffusive dialysis dose and maximized convective dose component to favor removal of small, middle and larger uremic toxins (optimal blood and dialysate flow rates are other important factors in maximizing solute mass transfer), regular use of ultrapure dialysis fluid, a safe and flexible hemodialysis machine capable of mastering balance of fluid volume exchange with multipurpose options for customizing treatment.

Based on these considerations the OL-HDF concept was proposed as an innovative solution. By combining diffusive and convective clearances, HDF offered the most efficient modality to clear small and middle uremic toxins. In vitro and in vivo studies confirmed the superiority of HDF compared to high-flux hemodialysis and high-flux hemofiltration for removing small and middle size uremic toxins [8–10]. By using ultrapure dialysis fluid and high-flux synthetic membranes, HDF offered a highly efficient and safe biocompatible system. In vitro and in vivo studies showed the beneficial effects in reducing the activation of circulating cells, protein systems and preventing the induction of inflammation [11]. By providing a virtually unlimited amount of sterile dialysis fluid by cold sterilization of fresh dialysate, OL-HDF offered an economical and viable method to achieve high-efficiency HDF (high-volume exchange) therapy. Production of ultrapure dialysis fluid, namely sterile and nonpyrogenic fluid by UF, was first reported by Henderson and Beans [12] and Henderson et al. [13], applied successfully later on in the clinic essentially with hemofiltration methods. The 'online' term was taken from the hemofiltration methods that were developed for large volumes of substitution. Modern hemodialysis machines with builtin technical options (adjustable blood pump, fluid balancing system, conductivity meter, flow and pressure monitoring, bicarbonate-buffered dialysate) for HDF allow for a safe and effective conduction of this convective therapy keeping the complexity inside while the interface is simple and friendly.

Best practice guidelines have also been developed to recommend a safe practice of OL-HDF methods. Best practice incorporates basic hygienic rules of maintenance and disinfection for water treatment and distribution systems as well as machines in order to prevent microbial contamination and biofilm formation [14]. This regulation has been reinforced in some specific countries where the online methods were particularly developed. A specific working group (EUDIAL) has been created recently within the ERA-EDTA to evaluate and favor the safe development of online methods.

Over the last decade, a tremendous technical progress has been made by manufacturers of dialysis equipment in order to ensure safety, reliability and excellent performance while adding new options to quantify efficacy and to increase the tolerance of sessions. OL-HDF machines are benefiting now from a specific certification and CE marking by notified bodies in the European Community [15]. This official recognition of CE marking for online methods was a major advance in the field of renal replacement therapy. Indeed, it is the first time that a medical device was approved and certified for infusing intravenously a sterile and nonpyrogenic pharmaceutical product prior to any laboratory testing. By the way, OL-HDF techniques opened a new breach in the regulatory field of pharmacopoeia for intravenous fluids and solutions, which is not yet solved today. Water treatment systems representing a key and sensitive component for online methods clearly benefited from this dynamic and improved their end product. Ultrapure water is recognized and imposed to online methods but is strongly recommended to all hemodialysis modalities by most international best practice guidelines [16]. Interestingly, water treatment and distribution systems, considered as a part of the dialysis treatment chain, may be certified by the European Community.

Several studies have shown that HDF provides significantly higher body clearances than high-flux hemodialysis both for small and middle molecule solutes [17–20]. Phosphate removal is increased by 15-20% over a weekly mass balance reducing the oral phosphate binders [21-24].  $\beta_2$ -Microglobulin is more effectively removed by HDF therapies [25-27]. By enhancing significantly middle molecule clearances, HDF is accompanied by a significant decline of circulating  $\beta_2$ -microglobulin concentrations over a mid-term period [28, 29]. Leptin (16 kDa) is a protein-bound uremic toxin that accumulates in chronic kidney disease that is implicated in malnutrition and anorexia [30]. Free leptin is effectively removed by HDF that translates in reduced circulating concentrations in HDF-treated patients [31, 32]. Cytokine removal has been shown in high-flux convective therapies both in acute and chronic end-stage renal disease patients [33]. Anti-inflammatory effects of OL-HDF have been shown in several prospective studies by reducing the number of proinflammatory monocytes and acute phase proteins [34-36]. Circulating concentration of oxidized-derived products (advanced glycation end products and advanced oxidation products) are reduced in diabetic and nondiabetic chronic kidney disease patients treated by high-efficiency HDF [37]. 3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid, a protein-bound erythropoietic inhibitor, can be reduced in HDF particularly when using proteinleaking high-flux membranes [38, 39]. Free paracresol or paracresyl sulfate or indoxyl sulfate, protein-bound endothelial toxin compounds [40], are poorly removed during high-efficiency HDF [41, 42].

Clinical benefits of HDF-treated patients have been underlined in several studies. Improvement of clinical tolerance is frequently reported with convective therapies. The incidence of hypotensive episodes is reduced in HDF and hemofiltration therapies [43]. Maltolerance (nausea, vomiting, cramps, headache) of sessions is also reduced with highly efficient HDF. Postdialysis fatigue is less frequently observed with convective therapies. These properties are particularly attractive in elderly, diabetics and cardiovascular 'high-risk' patients. Better blood pressure control with a reduced occurrence of cardiac events has been reported in two observational studies [44, 45]. Recent studies have shown that high-flux therapy and HDF modalities contributed to a better preservation of the residual renal function over time than conventional hemodialysis [46]. Anemia appears more easily corrected in HDF-treated patients. Although this fact remains still controversial [47], anemia correction tends to be facilitated in HDF-treated patients while the weekly erythropoietin dose is reduced [48]. Enhancing convective clearances is associated in the context of inflammatory cachexia with an improvement of nutritional parameters (dry weight) and somatic proteins (albumin) [49, 50].  $\beta_2$ -Microglobulin amyloidosis, a major concern in longterm hemodialysis therapy 20 years ago, has virtually vanished with the regular use of new high-flux convective therapies and ultrapure dialysis fluid. More interestingly, it has recently been shown that daily HDF promoted a normal catch-up growth curve in a population of children [51]. To our knowledge, this is the first study showing that growth in chronic kidney disease children could be recovered virtually to a normal curve by renal replacement therapy.

The reduced mortality of HDF-treated patients is more difficult to ascertain. Large cohort studies indicate that mortality is reduced by about 35% in HDF-treated patients accounting for confounding factors (age, Kt/V, comorbidities...), while small prospective studies did not find any significant differences [52-54]. Such a concern may probably be solved by prospective randomized controlled studies in the near future. Two recent randomized controlled studies (Turkish HDF, CONTRAST) reported at the ERA-EDTA indicated a significant survival benefit for HDF-treated patients only for those receiving large volumes of substitution (17-20 liters/session) [6, 55]. This observation is of particular interest for two reasons: on one hand, it confirms the previous findings of the Dialysis Outcomes and Practice Patterns Study that identified the major role of large volumes of substitution in patient survival; on the other hand, it raises the true concern of the convective dialysis dose in patient survival. According to findings of these studies the concept of convective dialysis dose should be seriously considered as an add-on in the quest for dialysis adequacy. A very recent large randomized controlled trial in which 906 chronic hemodialysis patients were assigned either to continue standard high-flux hemodialysis (n = 450) or to switch to high-efficiency postdilution OL-HDF (n = 456) showed that HDF had a 30% lower risk of all-cause mortality and a 33% lower risk of cardiovascular mortality.

In conclusion, while clinical evidence is rising in favor of OL-HDF, new technological advances make this treat-

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ment safer, more reliable and economically sustainable. It is likely that we will face a significant expansion of the utilization of OL-HDF and an increased number of countries adopting this technique in the years to come.

#### **Disclosure Statement**

The author has no conflict of interest to declare.

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