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Chapter 6

Update on Clinical Evidence Supporting Hemodiafiltration

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Additional information is available at the end of the chapter

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Abstract

The aim of this chapter is to define hemodiafiltration target efficiency, to clarify the concept of "optimal convective dose," and to facilitate hemodiafiltration (HDF) implementation in clinical practice by addressing the need for the establishment of best clinical practices for HDF. The approach taken was to conduct a comprehensive summary of clinical evidence supporting HDF. Convective dose is the total ultrafiltered volume and is complementary to diffusive dose (urea Kt/V) as a dose-dependent parameter. It can be quantified and adjusted to patient characteristics. Factors affecting convective dose are discussed: patient characteristics, prescription-dependent factors, and technical and machine-dependent factors. The key issue of HDF prescription and implementation of best practices is addressed as are intermediary and endpoint clinical outcomes. The main messages are as follows: (1) HDF is safe and effective provided that best clinical practices are followed and the right convective dose is delivered; (2) HDF is easy to perform with new technology; and (3) depending on the convection volume, HDF reduces all-cause and cardiovascular mortality. Open challenges remain, namely, the implementation of best practices to (a) achieve optimal convection volume, (b) define patient subsets that would benefit more from HDF, and (c) evaluate new tools that fine-tune HDF prescription according to individual patient needs.

Keywords: convective dose, substitution modality, treatment outcome, convection volume, clinical evidence

1. Introduction

Conventional diffusion-based dialysis modalities, namely, low-flux and even high-flux hemodialysis (HD), are limited in their capacity to effectively remove large uremic toxins and to improve outcomes for chronic kidney disease (CKD) patients [1]. By increasing convective solute transport, hemodiafiltration (HDF) enhances solute removal capacity over a broad range of middle- and large-size uremic toxins implicated in the pathophysiology of CKD [2, 3]. In addition, convective-based modalities have been shown to improve hemodynamic stability [4, 5] and to reduce patients' inflammation profile—both factors implicated in CKD morbidity and mortality [6–8]. Growing clinical evidence indicates that HDF-based modalities provide CKD patients with a number of clinical and biological benefits, including improved outcomes. Interestingly, it has recently emerged that the clinical benefits associated with HDF are positively associated with the total volume of fluid removed by ultrafiltration per session or per week [9–12]. This finding adds a new component to the conventional dialysis adequacy concept, namely, convective dose.

In this chapter, we elucidate the concept of convective dose and discuss the threshold above which an improvement in CKD patient outcome can be expected. In addition, factors implicated in the achievement of an optimal convective dose in the sense of best clinical practice are reviewed and clinical evidence supporting the use of HDF today is summarized.

1.1. Why is hemodiafiltration needed?

From a nephrologist's perspective, it is disappointing to observe that outcomes of end-stage kidney disease (ESKD) patients remain poor despite significant progress in hemodialyzer performances, HD machines and monitoring devices, better understanding of uremic toxicity, and improved patient management. Even without an in-depth analysis of root causes and reasons for renal replacement therapy (RRT) limitations, several factors are easily recognizable as contributing to this outcome. It is usually convenient to group these into two categories: "nonmodifiable factors," such as age, gender, ethnicity, comorbidity profile, and kidney disease history, and "modifiable factors," such as RRT modality and treatment adequacy. Changing the renal replacement treatment paradigm and improving practice patterns to ensure customized and better care are the only ways to improve the outcomes of ESKD patients.

In this context, two main options are available. First, HDF is today's most innovative, promising, and advanced alternative to high-flux HD. By combining diffusive and enhanced convective solute mass transfer, HDF offers the most efficient RRT today over a wide spectrum of uremic toxins including middle- and large-sized solutes. Using ultrapure dialysis fluids (water and dialysis fluid), HDF constitutes a highly biocompatible system and suppresses the occurrence of microinflammation processes [13–15]. By reducing the incidence of hypotensive episodes as well as dialysis intolerance symptoms [16–18], HDF may reduce or prevent repetitive cardiovascular insults and their deleterious long-term consequences. By giving access to an unlimited amount of substitution fluid at the cost of ultrapure dialysis fluid, online HDF provides a cost-effective approach for optimizing and customizing HDF treatment

prescription to the patient's metabolic needs. Provided that best clinical practices and hygienic rules are applied, HDF offers a reliable, efficient, and cost-effective RRT tool.

Second, the extension of treatment time is the more physiologic approach to improving patient outcome, even if not the most popular one. Increasing treatment time and/or frequency is the best way to facilitate sodium mass removal and thereby restore extracellular fluid volume, to ensure removal of uremic compounds with low intracorporeal mass transfer coefficients or tightly bound to albumin, and to minimize "nonphysiological" changes due to the aggressive nature of intermittent treatment schedules. These two approaches, HDF and extended treatment time, should not be considered competitive but rather complementary. Only a few studies have combined the solute mass transfer capacity of HDF with increased treatment time [19–21] and all clinical trials have confirmed the tremendous benefits of such combination on intermediary and long-term outcomes.

1.2. What is the clinical evidence for hemodiafiltration?

Although many studies associate HDF with significant improvements in ESKD patient outcomes, still some conflicting data or cost concerns have hampered general clinical and widespread acceptance of this method. Here, we attempt to reconcile facts and concerns regarding HDF. To begin, it should be stressed that a differentiated understanding of HDF should be adopted as opposed to considering HDF to be a generic term that covers all convection-based renal replacement modalities. The differentiation necessary lies in the magnitude of the convection dose that must be delivered to improve outcomes of ESKD patients. Based on published literature and our own experience, we revisit the current definition of convective dose and its threshold value for improved patient outcome, we review the factors affecting convective dose delivery, we summarize the best clinical practices in HDF prescription, and we summarize the main studies addressing clinical outcomes.

2. Convective dose concept—from minimal to optimal dosage

According to the EUDIAL group recommendations, convective dose is the total volume of ultrafiltration achieved per HDF session (L/session) and summed to week (L/week), standardized to postdilution convection volume for the various other dilution modalities (i.e., pre-, mixed, or mid-HDF), taking differences in the fluid volumes into consideration [22]. This is an easy and clinically relevant surrogate indicator of the convective component. Knowing that only hemodialyzers containing membranes that are highly permeable to both water (Kuf>50) and solutes (sieving coefficient β2-microglobulin [β2M] >0.6) are used for HDF, it is possible to calculate the convective component of solute clearance. An alternative proposal was to focus more on the biological effect of middle-molecule removal using biomarkers that reflect the convective action of the HDF. Among uremic toxins, β2M, a 12-kDa peptide, seems to be the most clinically relevant representative of the middle-molecule uremic toxins and strongly implicated in both morbidity and mortality of CKD patients.

Following international guidelines, urea Kt/V has been established as the principle dialysis dose quantifier and is regularly used as a quality-control tool for treatment delivery. To be valid, this approach requires certified methodology (appropriate urea sampling method and time, suitable formula) and appropriate timing of measurements (minimum of once monthly) to capture early deviation in dialysis efficacy. The ionic dialysance (iK) measurement embedded in some HD monitors is an option. This offers an interesting and cost-effective alternative that may be performed routinely at each session providing a true continuous quality-control tool. Using then the simplified concept of iKt, where iK stands for the average ionic dialysance measured by HD monitor and t stands for the duration of the dialysis session, one can estimate the total diffusive dose delivered per session (L/session).

The effective total dialysis dose (i.e., diffusive and convective) delivered to the ESKD patient can be easily assessed. Convective dose as estimated by total ultrafiltered volume per session (L/session) could be considered as a complementary component of the diffusive dose delivered and estimated by iKt (L/session).

A systematic review of studies [retrospective cohorts, prospective randomized controlled trial (RCT)] exploring the relationship of convective dose and patient outcome has shown that survival benefit is observed only when a minimum threshold ultrafiltration volume has been delivered [23]. The critical ultrafiltration volume per session (or per week) required for better patient outcome is between 20 and 22 L/session for a typical European ESKD patient. More recently, it has been shown that total ultrafiltered volume per session (or per week) acted as a continuous variable mimicking a sigmoidal dose-response curve [24].

The normalization of the convective dose to the patient's anthropometric characteristics has been proposed to match with patient metabolic needs and also to facilitate the generalization of this relationship with different patient profiles (e.g., Asian and American). In fact, such normalization attempts using different scalings (i.e., body weight, height, body surface area, and total body water) have been adopted in different studies, including the Estudio de Supervivencia de Hemodiafiltración On-Line (ESHOL) [25] and the individual personal data meta-analysis that was part of the European pooled project [26]. Interestingly, none of these scaling factors have enhanced sensitivity in predicting the relative risk (RR) of mortality. Crude convection volume per session (or per week) or convection volume scaled to body surface area or total body water tend to perform best in predicting survival benefits or mortality risks where HDF is concerned.

3. Factors affecting convective dose

Best clinical practices are essential in daily practice to achieve optimal ultrafiltration flow and the total ultrafiltered volume targeted. Schematically, three basic components need to be considered: patient-dependent factors, prescription-dependent factors, and technical or machine-dependent factors.

3.1. Patient-dependent factors

3.1.1. Vascular access

The achievement of "high" blood flows (>350 mL/min) depends on the type of vascular access (i.e., central venous catheter, arteriovenous fistula, or graft) and on the provision and maintenance of vascular access patency. Vascular access is defined as inadequate when an extracorporeal blood flow of at least 300 mL/min cannot be reached. Basically, patients treated with online HDF require a vascular access capable of delivering a consistent extracorporeal blood flow between 350 and 400 mL/min or higher. Such extracorporeal blood flows could be reached with large bore tunneled central venous catheters and with arteriovenous fistulas or grafts delivering access flows of ≥500 mL/min. High blood flow is essential to ensure that a sufficient amount of blood is processed during the treatment session. Vascular access flow performances and needle sizes assume a fundamental role in preserving the advantages of applying a high convection volume.

3.1.2. Individual patient criteria

Hematocrit and protocrit (the volume fraction of plasma proteins that may be calculated as the product of 0.000718 and the total protein concentration of plasma proteins in g/mL [22]) affect negatively the plasma water volume and plasma water flow. High hematocrit (e.g., resulting from anemia management and hemoglobin targets) and high total protein concentration (e.g., due to the particular nutritional and inflammatory status of the patient) enhance viscosity tremendously, reduce ultrafiltration capacity (filtration fraction), and provide unfavorable conditions for ultrafiltration flow. The additional ultrafiltration applied to achieve a given weight loss is an additive factor that may affect total ultrafiltration. Finally, a dynamic interaction between blood flow (shear rate and shear stress), blood components (hematocrit and protocrit), filtration fraction (ultrafiltration flow to blood flow ratio), and membrane surface (protein layer formation) is crucial to facilitate ultrafiltration flow. Many of these factors are taken into consideration in modern dialysis machine technology.

3.2. Prescription-dependent factors

3.2.1. Blood flow

The effective extracorporeal blood flow delivered is a fundamental determinant of all extracorporeal cleansing therapies. Among factors that determine the efficiency with which uremic solutes are removed during dialysis, extracorporeal blood flow, whether instantaneous (flow rate) or cumulative (total blood volume processed over the session), is the most critical. Treatment efficiency assessed either in terms of solute clearance or solute mass removal is then dependent on the total blood "processed" within a dialysis session.

High blood flows are critical in HDF, as they have a dual action, one being to maximize the amount of solute removed and the other being to preserve membrane permeability by retarding the formation of a protein layer on the membrane (secondary layer formation). The

choice of needle size matters in HDF. Following Poiseuille's law, needle size is a barrier to high blood flow: 15-gauge needles (optimally 14-gauge needles) are required to sustain blood flow of ≥350 mL/min at an acceptable pressure regimen.

3.2.2. Choice of hemodiafilter

The choice of a specifically designed hemodiafilter is important to optimize ultrafiltration flow and prevent dysfunction or alarms occurring on the HDF monitor due to hemorheological changes in the dialyzer. Preferred hemodiafilter features, apart from being equipped with highly permeable membranes, should favor the following to reduce internal convective processes: low blood flow resistance (large lumen diameter of fibers (e.g., 200 μm), short length of dialyzer housing, and increased number of fibers per sectional surface area.

3.2.3. Anticoagulation

Methods of anticoagulation will not addressed here in detail. However, anticoagulation is required to prevent thrombosis of extracorporeal blood circuit and to ensure a safe and efficient HDF session. Different kinds of antithrombotic agents can be used systematically by intravenous (IV) injection.

Unfractionated heparin (UH) is administered as an IV bolus dose (30–50 IU/kg) at the start of the HDF session followed by continuous IV infusion (500–700 IU/h). The heparin dosing regimen for HDF does not differ from that in regular HD.

The use of low molecular weight heparin (LMWH) is nowadays favored by many centers because of its ease of use and its better risk profile. In this case, LMWH should be preferably administered IV into the venous line and not into the arterial line to prevent significant loss during the first hemodialyzer passage.

3.2.4. Treatment time prescription

The prescription of HDF treatment time duration and frequency is usually based on the patient's metabolic needs, extracellular fluid management, and cardiovascular and session tolerance. Increasing both the duration and frequency will facilitate the delivery of a high volume of ultrafiltration. A pragmatic approach is to establish a suitable convective dose for a given patient and to increase the treatment time according to the limitation of effective blood flow delivery.

3.3. Technical or machine-dependent factors

3.3.1. Transmembrane pressure management

Achieving high ultrafiltration rates and targeted ultrafiltration volumes can be challenging and requires the careful management of the transmembrane pressure (TMP) according to the treatment modality selected. In attempting to achieve high ultrafiltration volumes, hemoconcentration within the filter commonly results in high TMP, triggering pressure alarms and

potentially causing cell damage. Basically, the augmented protein layer formation occurring naturally at the blood-membrane surface during the course of the HDF session fouls the membrane pores and reduces the membrane's hydraulic permeability. In combination with the increased oncotic pressure (total protein increase) along the fibers, this tends to reduce the ultrafiltration flow. Faced with situations of high TMP increase and/or pressure alarms, nursing staff manually reduce the substitution flow and thus reduce the chances of achieving the targeted ultrafiltration volume.

3.3.2. Machine options

New features to optimize HDF performances and achieve optimal convective doses are currently available. The adjustment of the substitution mode was the most obvious and primary focus of investigation. When postdilution is problematic, switching to pre-, mixed, or mid-dilution mode may be a viable alternative. In all these cases, the targeted convection volume needs to be adjusted for the dilution factor corresponding to the HDF modality chosen (e.g., x2 for predilution HDF or x1.5 for mid-dilution HDF in manual prescription) to match efficacy with the postdilution mode.

New technical features involving specific software algorithms are currently being implemented and tested in new online HDF machines. Basically, the idea is to provide an automatic ultrafiltration control system to reduce membrane fouling and ensure maximal ultrafiltration flow considering basic operational conditions of blood flow, hemorheological conditions, and prescription setting. Schematically, the system avoids excessive hemoconcentration by the continuous adaptation of the substitution flow according to changes in blood viscosity within the dialyzer as identified by signal analyses of the pressure pulses transmitted from the peristaltic blood pump. Signal analysis is conducted several times per minute, and the substitution rate is automatically adapted based on pressure pulse attenuation and cross-membrane pressure assessment. Using such automatic control systems, it is possible to increase the ultrafiltered volume per session by 10 to 20% without harming the patient, filter, or cells.

3.3.3. Other machine-related variables

As mentioned previously, treatment time is one of the factors limiting the increase of "dialysis dose". In the current models of delivering dialysis in dialysis units, based on shifts assigned to nurses with a ratio of one nurse to three to five patients, any further increase of treatment time has an associated cost. Out of the 5.5 to 6 h of the shift length for each single nurse, it is possible to deliver a median of 4 h of treatment to three to five patients. There are two ways to achieve a cost-neutral increase in treatment time. The first is to reduce the time needed to prepare the dialysis equipment before initiating treatment. Faster disinfection of the dialysis machine is achievable with more simple hydraulic components and/or more effective disinfection processes. Also, the disinfection of the machine surface can be simpler, safer, and faster; this is achievable with especially designed equipment surfaces having as few discontinuities as possible. The second way is to reduce the number and complexity of nurse interventions. This approach may allow nurses to treat more patients, thus decreasing the cost of treatment

for each patient per hour. Consequently, it could be possible to increase the time of the shift and the treatment time in a cost-neutral manner. Is this possible? According to Tsobanelis et al. [27], new dialysis equipment under testing in HDF mode for fistula patients had a 24% reduction in the number of major handling steps compared to the previous dialysis machine from the same company.

Other aspects to be considered when targeting an increase of patient to nurse ratio are those related to safety. The risk of harm has to be reduced as much as possible, and one option is to reduce this risk by the improved design of the equipment. As an example, we can again mention the recent experience of Tsobanelis et al. [28], who reported that the tested new equipment had 27% fewer major process steps and touch points critical to hygiene compared to the current machine version. The authors found it particularly noteworthy that it was possible to avoid disconnection of the arterial line from the arterial needle with the redesigned process of blood reinfusion at the end of the session.

Finally, in the time of green economy, the authors also highlighted that the switch from an infusion line to an integrated infusion port reduced the volume of contaminated waste. The major source of waste relates to the disposables (bloodlines and dialyzers), so that newly designed, integrated disposables can facilitate a reduction of disposable waste, for example, of approximately 0.2 kg/session as reported by Schleser et al. [29], which, given an average of 10,000 treatments yearly delivered by a dialysis unit, translates into 2000 kg less waste. In terms of carbon footprint, one should also consider the consumption of water and energy and how this can be limited, for example, by having a more efficient water treatment system.

4. HDF prescription and implementation of best practices

4.1. Current status

Online HDF can no longer be considered an experimental treatment but has now developed into a mature and accepted RRT. In fact, this dialysis modality is employed for sustaining the lives of more than 160,000 ESKD patients worldwide, including 80,000 in Europe, Middle East, and Africa. Europe played a leading role in developing this therapy, where the prevalence of HDF is close to 18% (varying across countries from 0 to 100%). The annual growth rate is approximately 6% [30]. In 2013, Japan treated 31,273 patients with HDF (23,445 thereof on online HDF), representing 10% of its total dialysis population (294,605 patients; Kawanishi, personal data). The number increased by 4% between 2013 and 2014 as positively influenced by the implementation of a specific reimbursement fee in 2012. Interestingly, in Japan, the predominant HDF mode is predilution HDF (90.8% of HDF treatments).

4.2. Treatment schedule prescription

The prescription of the HDF treatment schedule is based on the usual target of providing optimal RRT to the ESKD patient. It is a composite and trade-off between patient-specific issues

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(e.g., metabolic needs, treatment tolerance and acceptance, and patient-treatment interaction), local logistical and practical issues (e.g., facility and/or modality availability), and health regulation and reimbursement policies.

The duration and frequency of sessions are based on two main components: (1) patient's metabolic needs and dialysis adequacy targets and (2) extracellular fluid management and cardiovascular tolerance depending on ultrafiltration rate. Increasing session length and frequency will facilitate the achievement of a high ultrafiltration volume. A pragmatic approach is to estimate a suitable convective dose for a given patient and to increase the treatment time according to the limitations present regarding effective blood flow or other hemorheological factors.

In clinical practice, prescription comprises the setting of the substitution rate (substitution volume per session extended to weekly volume) and adding the required weight loss to achieve the dry weight for that patient. Based on the results of recent studies, a minimal substitution volume of 60 L/week (or 40 L/m^2 body surface area) is required in individual ESKD patients to improve patient outcome. The additional ultrafiltration volume required for the correction of extracellular fluid volume excess has to be added to the substitution volume.

The hemodialyzer used for HDF must contain membranes that are highly permeable for both water (Kuf>50 mL/h/mmHg) and solutes (sieving coefficient for β2M≥0.6) with adequate dialyzer surface area. Filter design should favor a low internal blood flow resistance, thereby reducing membrane fouling and minimizing backfiltration as much as possible. A simple rule of thumb commonly applied in clinical practice is to consider 1 m^2/each 200 mL/min effective extracorporeal blood flow, meaning that a 2.0 m^2 hemodialyzer is appropriate for a blood flow of 400 mL/min [31].

In the past, the composition of the dialysis fluid differed from that of the substitution fluid. This is not the case in online HDF. Given the current definition of convective treatment adequacy, based on 23 L/session of convective dose in postdilution HDF, this equality of fluid compositions, and also the HDF mode, may affect the mass balance of electrolytes during the treatment session. Several studies dealing with the dialysate/substitution fluid prescription and focusing on sodium, calcium, and bicarbonate have been published.

Sodium: The importance of the correct sodium balancing during dialysis, preventing sodium overload with resultant thirst and water overload, has long been recognized. This risk of sodium loading also has to be considered in high efficiency treatments coupling diffusion and high volume convection. In a 1991 evaluation of HDF sessions with convective doses ranging between 9.1 and 16.7 L/week, Pedrini et al. [32] found that sodium balance was mainly affected by the sodium concentration gradient between initial plasma water and dialysate, the sodium level in the substitution fluid, and the imposed ultrafiltration rate. In the same patients treated with similar operating conditions, significantly lower net sodium removal was observed when on predilution compared to postdilution HDF [33]. Despite the complexity of managing the multifactorial equations describing the relationship between affecting variables and sodium balance (e.g., the laboratory method for the determination of sodium and the negative charge

of plasma proteins) [33], ideal modern equipment should be able to automatically address sodium balance.

Calcium: The target in the case of calcium is to maintain a neutral calcium balance, as an excessive calcium load has been associated with vascular calcification, whereas calcium depletion has been linked to worsening secondary hyperparathyroidism and decreased bone mass [34]. Here also, the modality of HDF affects the balance. Although calcium balance during postdilution online HDF does not differ from standard HD, it is usually recommended to increase the dialysate/substitution fluid calcium concentration by 0.25 mmol/L in predilution HDF mode in order [34]. In addition, discrepancies between expected and observed concentrations in the dialysate/substitution fluid play an important role in the case of online HDF. In a volumetric system based on conductivity, the sodium for the bicarbonate dialysate/substitution fluid comes in part from a basic component and in part from an acidic component. In cases of a decrease in dialysate sodium with concomitant increase of bicarbonate, a lower proportion of the acid component will produce a lower than expected calcium level in the dialysate/substitution fluid [35].

Bicarbonate: a positive bicarbonate balance is targeted during the treatment session to neutralize the interdialytic accumulation of strong acid anions and to avoid starting the next session with metabolic acidosis. However, there is also a risk of postdialysis alkalosis. In a recent publication by Havlin et al. [36] analyzing 68 patients on postdilution HDF treated for 4 to 5 h with 80 to 90 mL/min of substitution fluid (19–27 L/session) with a dialysate bicarbonate concentration of 32 mmol/L, 34% of patients were acidotic at dialysis initiation, but 80% had metabolic alkalosis after dialysis. They speculated that this was due to an excessive elimination of retained and endogenous anions. According to the authors, this observation requires further investigation. In any case, several factors affect the mass balance. A significantly lower bicarbonate gain was observed in predilution HDF versus postdilution HDF [37]. As is true for all electrolytes, the difference in concentration between bicarbonate levels in the dialysate/substitution fluid and in the blood at the initiation of the session is positively correlated to the mass transfer. Therefore, to maintain the same bicarbonate balance when moving from postdilution HDF to predilution HDF, dialysate bicarbonate concentration should be increased by 2 mmol/L. In fact, in predilution HDF, bicarbonate levels of the blood entering in the dialyzer increase, enhancing the loss across the membrane and reducing the normal gain by diffusion from dialysis fluid to blood [33].

5. Clinical outcomes

5.1. Intermediary treatment outcomes (short-term studies)

In this section, intermediary treatment outcomes stand for surrogates of primary outcomes in assessing HDF safety, efficacy, and tolerance. For this purpose, we focus on cardiovascular stability and treatment tolerance, solute removal (phosphate, β2M), and inflammation, oxidative stress, and anemia.

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5.1.1. Cardiovascular stability and treatment tolerance

In the short term, a significant reduction in the episodes of intradialytic hypotension was observed in HDF compared to conventional HD [16]. This has been ascribed to negative thermal balance (due to the infusion of relatively cool replacement fluid), a high sodium concentration of the substitution fluid, and/or removal of vasodilating mediators [4].

5.1.2. Solute removal: phosphate, β2-microglobulin

Several controlled studies have confirmed enhanced clearance and mass removal of β2M with HDF (30–40% higher than high-flux HD) accompanied by a 10 to 20% decline in circulating blood β2M concentrations [38, 39]. It must be reminded that reduction of circulating predialysis β2M takes time, as plasma levels reflect the equilibrium between production and elimination rates. Thus, 3 to 4 weeks are required to achieve a new steady-state and a serum concentration change [40]. Recently, it has been calculated in a large cohort of incident ESKD patients that each additional 10 L convection volume was associated with a 0.8 mg/L reduction of β2M [24].

Phosphate mass removal and serum phosphate is a major concern in ESKD patients. RRT accounts for 60 to 70% of the total amount of phosphate removed to restore weekly phosphate mass balance. The other 30 to 40% needs to be eliminated by feces through the combined action of diet and phosphate binders. Although still a matter of controversy, high efficiency HDF has been shown to enhance the phosphate mass removed by 15 to 20% [41] with a subsequent predialysis serum phosphate level reduction of 6%. The percentage of patients reaching target pretreatment serum phosphorus levels with HDF was reported to increase from 64 to 74% in the Convective Transport Study (CONTRAST) [42].

Higher clearances of a number of other uremic compounds have also been documented with HDF: complement factor D (a proinflammatory mediator), leptin (16 kDa; involved in loss of appetite), FGF23 (30 kDa, implicated in metabolic bone disorders and vascular calcification), various cytokines, circulating advanced glycosylation end products (AGEs), and AGE precursors [43, 44].

5.1.3. Inflammation, oxidative stress, and anemia

Inflammation and oxidative stress profiles tend to be improved in patients treated by HDF. Several prospective studies have shown that levels of C-reactive protein (CRP) and other sensitive biomarkers of inflammation (e.g., interleukin-6) and/or proinflammatory cells are reduced. In this field, the Rischio cardiovascolare nei pazienti afferenti all'area vasta in dialisi (RISCAVID) study is certainly one of the more convincing studies, being conducted in a large cohort of dialysis patients [7, 45]. A meta-analysis has recently reemphasized that the regular use of ultrapure dialysis fluid was the main driving force for such benefits [14].

The erythropoiesis-stimulating agent (ESA) dose could be reduced in HDF, as reported in several clinical studies and summarized in a systematic review [46]. The benefit was attributed to the combined effects of the higher removal of middle-sized toxins (erythropoietic inhibitor substances) and reduced inflammation due to the use of higher-quality water and dialysis fluid [47, 48]. However, this effect was not confirmed in a recent meta-analysis [49].

5.1.4. Clinical benefits

Several large cohort studies have indicated that the extended use of high-flux membranes and convective therapies has a beneficial impact on the development of β2M amyloidosis in the long term, reducing the incidence of carpal tunnel syndrome and other related manifestations [50, 51]. This beneficial effect probably results from the regular use of ultrapure water and biocompatible materials, reducing inflammation, combined with convective modalities that enhance β2M removal [52].

5.2. Endpoint outcomes (morbidity and mortality)

In this section, endpoint outcomes are hard primary outcomes in assessing HDF long-term efficacy. Consequently, the focus here is on mortality (all-cause and cardiovascular) and morbidity (hospitalization, dialysis-related pathology).

5.2.1. Observational (cohort) studies on hemodiafiltration and clinical endpoints

Locatelli et al. [50] conducted a retrospective observational study (Lombardy registry) of 6444 patients with ESKD who started RRT on HD, HDF, or hemofiltration (HF) between 1983 and 1995. A total of 1082 patients were treated with HDF or HF (first choice in the case of 188); the median follow-up time was 29.7 months. Interestingly, after adjustment for age, gender, and comorbidities (including diabetes), the RR for carpal tunnel surgery and mortality was 42% (statistically significant) and 10% lower (not statistically significant) in patients treated with HDF or HF.

In 2006, Canaud et al. [53] reported results of a prospective, nonrandomized observational study from the Dialysis Outcomes and Practice Patterns Study (DOPPS) of 2165 patients followed between 1998 and 2001 in five European countries. Patients were stratified into four groups: low-flux HD (n=1366), high-flux HD (n=546), low-efficiency HDF (n=156; substitution volume 5–14.9 L/treatment), and high-efficiency HDF (n=97; substitution volumes 15–24.9 L/treatment). Patient characteristics (including age and sex), 14 comorbidities, and time on dialysis were similar in each group. High-efficiency HDF patients had lower crude mortality rates than low-flux HD patients. After Cox regression analysis with adjustment, high-efficiency HDF patients had a 35% significantly lower mortality risk than those receiving low-flux HD.

Also in 2006, Jirka et al. published the results of an observational study of 2564 ESKD patients (394 on HDF) treated in Fresenius Medical Care clinics and followed for 12 months. Data were collected in the European Clinical Database (EuCliD) [54]. In this patient cohort, all-cause mortality was reduced by 43% and unadjusted mortality was reduced by 35% in patients treated with HDF compared to HD. Convection volume was not reported.

In 2008, Panichi et al. [7] reported the results of a prospective observational study performed in the northwestern part of Tuscany that included 757 ESKD patients (RISCAVID study) who were followed for 30 months. Treatment with low- or high-flux HD (n=424) was compared to treatment with HDF using substitution fluid delivered in bags (130 patients on low-volume HDF with acetate-free biofiltration (AFB) and 74 patients on HDF with convection volumes of

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10–15 L/treatment) and treatment with online HDF (129 patients on HDF with convection volumes of 22–25 L/session). Cox proportional hazards regression analysis showed that online HDF and bag HDF patients had a significantly better survival than HD patients, having a 22% reduced risk of all-cause mortality after adjustment.

One year later, Vilar et al. [55] reported the results of an observational study of 858 incident ESKD patients in the United Kingdom followed over 18 years. Patients treated with online HDF (n=232) received 79% of treatments with this modality and a mean filtration volume of 14.9 L/session. The control group was treated exclusively with high-flux HD (n=626) and pure dialysis fluid. The mortality risk was significantly reduced in patients receiving predominantly HDF [hazard ratio (HR) 0.45; $p<0.001$] after adjustment for age, gender, body mass index, and comorbidities.

Imamovic et al. reported the Balkan experience in 2014. In this cohort study of 442 incident patients, the risk of death for HDF-treated patients relative to high-flux HD patients was 0.87 (nonsignificant) for low-volume HDF and 0.29 (highly significant) for high-volume HDF. After adjustment for covariates, the HR for patients on low-volume HDF remained statistically not significant compared to high-flux HD (HR 0.84; nonsignificant), whereas patients on high-volume HDF had a significantly lower HR (0.29; nonsignificant) than high-flux HD. In the time-dependent analysis, the mortality risk was not lower in high-volume HDF compared to high-flux HD (HR 0.48; nonsignificant), but this may be because 44% of the patients changed treatment modality during follow-up [56].

In 2015, Siriopol et al. published a report on the Romanian experience with HDF. In this study, the group of 221 prevalent patients treated with online HDF (mean convection volume was 22.2 L) was propensity score matched to a group of 431 patients treated with HD [57]. Online HDF was associated with a reduced mortality risk (HR 0.62; statistically significant). A second cohort consisting of 265 incident patients on HDF were matched with 530 patients treated with HD. The mortality risk was significantly lower in patients treated with HDF (HR 0.22; highly statistically significant).

In another study, Canaud et al. reported results based on the EuCliD database involving 1590 incident patients in 12 European countries. The patient groups receiving high volume HDF (≥21 L/session) were propensity score matched to the group receiving HD. Patients were followed for 2 years (HD group) or 1.6 years (high-volume HDF group) [58]. In this study, a nonsignificant survival advantage of HDF was found (HR 0.88; nonsignificant). Using inverse probability of censoring weighting (IPCW) to take bias due to the large amount of modality crossover during the follow-up time into consideration (7% HDF patients switched to HD; 55% HD patients switched to high-volume HDF), a statistically significant survival advantage of high-volume HDF was found (odds ratio 0.501; highly significant).

Canaud et al. [24] recently published the results of a dose-finding study exploring the optimal convection volume required to observe an increase in patient survival. This was a retrospective analysis involving 2293 incident HDF patients whose treatments were documented in the EuCliD database. Advanced statistical tools, including cubic spline analyses, were applied for the determination of the range of convection volume over which a survival benefit was

observed. The relative survival rate of online HDF patients, adjusted for age, gender, comorbidities, vascular access, albumin, CRP, and dialysis dose, was found to increase at approximately 55L/week and to stay increased up to approximately 75L/week. Similar analysis of predialysis β2M concentrations found a nearly linear decrease in marker concentration, as convection volume increased from 40 to 75L/week. The analysis of log CRP levels showed a decrease over the same convection volume range.

Mercadal et al. reported a study using data from the French national Renal Epidemiology and Information Network (REIN) registry to assess the effects of HDF on mortality in the total population of incident dialysis patients (treatments were performed between 01/01/2008 and 31/12/2011 and patients were followed up to the end of 2012) [59]. Analyses were performed at both patient and facility levels. Here, 5526 out of 28,407 ESKD patients used HDF for a median of 1.2 years and 2254 of them used HDF exclusively. All-cause and cardiovascular mortality associated with HDF use were significantly reduced (HR 0.84 and 0.73, respectively). In patients treated exclusively with HDF, the beneficial effects on all-cause and cardiovascular mortality were more pronounced (HR 0.77 and 0.66, respectively). At the facility level, increasing the percentage of patients using HDF from 0 to 100% reduced the HR for all-cause and cardiovascular mortality (HR 0.87 and 0.72, respectively). The authors concluded that, irrespective of whether analyzed at patient or facility level, HDF treatment was associated with better survival.

5.2.2. Prospective RCTs

Four prospective controlled or randomized studies comparing HDF and standard HD have been reported in the past which were not designed (short term <12 months) or sufficiently powered (<100 patients) to assess mortality differences between modalities [25, 38, 60, 61]. These will not be discussed in this chapter.

The Dutch CONTRAST was performed in 29 centers in The Netherlands (n=26), Canada (n=2), and Norway (n=1) [62]. Here, 714 patients were randomized between treatment with low-flux HD and online postdilution HDF between 2004 and 2009, both with ultrapure dialysate. The primary endpoint was all-cause mortality, and the main secondary endpoint was a composite of fatal and nonfatal cardiovascular events. Of 358 HDF patients, 121 discontinued treatment during the study due to transplantation, switch to another center or therapy, or other reasons. Of 356 HD patients, 118 patients discontinued the allocated treatment. The mean follow-up was 36 months (range 5–79 months); during this period, 269 deaths occurred in 2170 person-years. All-cause mortality (HR 0.95; nonsignificant) as well as cardiovascular events (fatal and nonfatal; HR 1.07; nonsignificant) were not affected by treatment modality. Although the target convection volume was set at 24 L/treatment, the mean volume achieved was 20.7 L/session and only one third of centers achieved at least 24 L/session. Post hoc analyses based on convection volume delivered (tertiles) showed a significantly lower mortality in patients receiving the highest convection volume (>21.95 L/session). In this subgroup, mortality risk was reduced by 39% compared to HD (HR 0.61; significant), which remained after extensive adjustments.

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The Turkish Hemodiafiltration Study with 782 patients was conducted between 2007 and 2010 in 10 centers; patients were randomized to treatment with online postdilution HDF or high-flux HD [63]. Patients with central venous catheters, poor blood flow, and significant residual urine output were excluded. The primary endpoint was a composite of all-cause mortality and first nonfatal cardiovascular event. Of 391 patients treated with HDF, 110 discontinued the study (28%), including 40 (10%) who terminated early due to vascular access problems. Of 391 patients randomized to HD, 90 patients (23%) dropped out. The mean follow-up time was 23 months (range 1–38 months). The mean substitution volume was 17.2 L/session and the mean intradialytic weight gain was 2.4 L/treatment, corresponding to a mean total convection volume of 19.6 L/treatment. The RR of death and first cardiovascular event was 0.82 (non-significant), and the RR for all-cause and cardiovascular mortality was 0.79 (nonsignificant) and 0.72 (nonsignificant), respectively. In a post hoc analysis, patients who achieved a convection volume above the median of 17.4 L/session had a significant lower risk of all-cause and cardiovascular mortality (RR 0.54 and 0.29, respectively; both highly significant). This association remained after extensive adjustments for age, gender, comorbidity, and practice patterns.

The Catalonian Hemodiafiltration Study (ESHOL) included 906 Spanish dialysis patients in 27 units who were randomized to online postdilution HDF (n=456) and HD (n=450) [64]. In the HD group, 8% of the patients were treated with low-flux membranes and 92% were treated with high-flux membranes. The mean follow-up time was 23 months. Here, 355 patients dropped out of the study for various reasons and were censored at the time of loss (36% in the HD group and 42% in the HDF group). Centers involved in the study received a short training course on how to achieve the targeted convection volume. The median convection volume in HDF treated patients was 22.9 to 23.9 L/treatment. Here, 207 events were observed in 1730 patient-years. A significant 30% decrease in all-cause mortality and 33% decrease in cardiovascular mortality were observed in the HDF group. Interestingly, a post hoc analysis based on convection volume showed that the highest convection volume tertile (>25.4 L/treatment) was associated with a lower mortality risk (HR 0.55; highly significant) compared to HD patients.

5.2.3. Meta-analyses

Several meta-analyses comparing conventional HD and convective-based therapies have been published over the last decade.

Rabindranath et al. from the Cochrane group performed two analyses in 2005 and 2006. The latter included 20 trials (657 patients). Mortality results were available only in 4 trials (336 patients) and different therapies were mixed (AFB, HF, and HDF). The authors found no difference in mortality risk for patients treated with convective-based therapies [26, 65]. This systematic review was severely criticized due to its poor methodology [66, 67].

Susantitaphong et al. [49] compared convective-based therapies to standard low-flux HD. HF, HDF, AFB, and high-flux HD were all included in the convective therapy group. This meta-analysis aggregated data of 12,182 patients. Convective therapies resulted in a nonsignificant decrease in all-cause mortality (RR 0.88) and all-cause hospitalization (RR 0.91); a significant

decrease in therapy-related hypotension (RR 0.55) and cardiovascular mortality (RR 0.84) was reported. The authors concluded that convective therapies were associated with improved clearance of uremic solutes, but the potential long-term benefits of specific convective modalities could not be confirmed.

Wang et al. [68] conducted a systematic review and meta-analysis that included 16 trials and 3220 patients treated with convective-based therapies (HDF and HF) and with standard HD (low- and high-flux). Convection volume was not considered as a confounder in this analysis. On the one hand, the authors concluded that convective modalities did not significantly reduce the risk of cardiovascular events (RR 0.85) or all-cause mortality (RR 0.83). On the other hand, they noted that convective modalities reduced intradialytic symptomatic hypotension (RR 0.49) and reduced serum β2M levels (-5.95 mg/L).

Mostovaya et al. [69] compared exclusively HDF to HD (low- and high-flux) including 2402 patients. The meta-analysis identified six RCTs. The convective arm consisted exclusively of HDF patients treated with different HDF modes (a mixture of postdilution, mid-dilution, and predilution HDF, and of online HDF and HDF with bags) and achieving a specified minimum convection volume. All-cause and cardiovascular mortality were reduced with HDF compared to HD (RR 0.8 and 0.73, respectively).

Nistor et al. [70, 71] from the Cochrane group updated the previous systematic review of 2005 and compared HD (low- and high-flux) to convective-based modalities (HF, AFB, bag HDF, and online HDF) without considering convection volume. Thirty-five trials (4039 patients) were included in this meta-analysis and the effects on mortality were estimated. The convective group consisted of 1648 patients, but 227 of them were treated with low convection volumes. Within the limitations of the review (e.g., studies reviewed were partially old and referred to a diverse mixture of HDF modalities), the authors concluded that convective therapies had no significant effect on reducing all-cause mortality (RR 0.87), cardiovascular mortality (RR 0.75), and intradialytic hypotension (RR 0.72) but had uncertain effects on nonfatal cardiovascular events (RR 1.14) and hospitalization (RR 1.21).

5.2.4. Individual participant data meta-analysis

An alternative to the aggregated data meta-analysis approach is to perform meta-analysis of individual participant data in which the raw "individual level data" for each study are obtained and analyzed. The term "individual participant data" relates to the data recorded for each participant in a study. Individual participant data sets of four randomized trials were pooled and used to compare online HDF to HD. The four studies aggregated 2793 patients and were designed to examine the effects of HDF on mortality endpoints. Bias by informative censoring of patients was resolved. HRs comparing the effect of online HDF versus HD on all-cause and cause-specific mortality were calculated using Cox proportional hazard regression models.

In the first part of this individual participant data meta-analysis, Davenport et al. [72] analyzed the relationship between convection volume and patient outcomes. After a median follow-up time of 2.5 years, 769 of the 2793 participants had died (292 cardiovascular deaths). Convection

volumes were either not standardized or standardized to weight, body mass index, body surface area, and total body water. Data were analyzed by multivariable Cox proportional hazards modeling from 2793 patients. All-cause mortality was reduced when the convective dose was unstandardized or standardized to body surface area or total body water; corresponding HRs were 0.65 (0.51–0.82), 0.74 (0.58–0.93), and 0.71 (0.56–0.93). Standardization by body weight or body mass index was not associated with significant survival advantages. Higher convection volumes were generally associated with greater survival benefit with online HDF, but results varied across the different ways of standardization for body size. Further studies should take body size into account when evaluating the impact of convection volume on mortality endpoints.

In the second part of this analysis, Peters et al. [73] also investigated the effects of convection volume on patient outcomes. HRs comparing the effect of online HDF versus HD on all-cause and cause-specific mortality were calculated using Cox proportional hazards regression models. The relationship between convection volume and the study outcomes was examined by delivered convection volume standardized to body surface area. Online HDF reduced the risk of all-cause mortality by 14% and cardiovascular mortality by 23%. There was no evidence for a differential effect in predefined convection volume subgroups. The largest survival benefit was for patients receiving the highest delivered convection volume (>23 L/1.73 m^2 body surface area per session), with a multivariable-adjusted HR of 0.78 (95% confidence interval 0.62–0.98) for all-cause mortality and 0.69 for cardiovascular disease mortality. This pooled individual participant analysis indicates that online HDF reduces the risk of mortality in ESKD patients. This effect holds across a variety of important convection volume subgroups of patients and is most pronounced for those receiving a higher convection volume normalized to body surface area.

6. Conclusions

Online HDF can no longer be considered an experimental treatment; it is a mature RRT that is applied daily to sustain the lives of more than 160,000 ESKD patients worldwide, including 80,000 in Europe, Middle East, and Africa. Europe has played a leading role in developing this therapy, where the prevalence of HDF is close to 18% with variations across countries from 0 to 100%.

Interestingly, it has recently been also shown that clinical benefits associated with HDF were directly correlated with the total ultrafiltered volume delivered, either per session or per week. This finding adds a new component, namely convective dose, that needs to be integrated into our conventional dialysis adequacy concept. In addition, accumulating evidence from both retrospective and prospective RCT studies confirm the clinical safety and sustainability of HDF therapy and support its superiority over conventional HD in terms of morbidity and mortality.

In line with these facts, the remaining and crucial challenges today are to implement best clinical practices to achieve the optimal convective dose required, to define which subset of ESKD patients should benefit most, and to evaluate new tools facilitating and fine-tuning HDF

prescription according to ESKD patient needs (e.g., electrolyte balancing and quantification and homeostasis).

7. Compliance with ethical standards

Conflict of interest: Bernard Canaud, Aileen Grassmann, Laura Scatizzi, and Daniele Marcelli are employees of Fresenius Medical Care.

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