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Seeking an Optimal Renal Replacement Therapy for the Chronic Kidney Disease Epidemic: The Case for On-Line Hemodiafiltration

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Abstract

The prevalence of chronic kidney disease (CKD) can be expected to increase dramatically in the foreseeable future, with suggestions that it has already reached epidemic proportions. The inadequate supply of donor organs, aggravated by an aging patient population, necessitates provision of sustainable dialysis treatment modalities. These treatment modalities must not only be of established clinical efficacy and effectiveness, but must simultaneously circumvent any potential treatment disparities due to geographical, social or other concurring factors. Home therapies might represent a partial solution to the complex issue of seeking optimal strategies to cope with the CKD epidemic. However, self-care renal replacement therapy (RRT), such as peritoneal dialysis (PD) and home therapies, can only be applied to a limited portion of the CKD population. Consequently, in preparation for coping with this CKD epidemic, specific large-scale plans need to be made that involve optimization of treatments already in use for the majority of the population requiring RRT, e.g. hemodialysis (HD). Extracorporeal chronic HD relies heavily on technology for its clinical success. Like the choice of the treatment modality and the complete medical approach to CKD patient care, the particular selection of the various components of the extracorporeal circuit has a significant impact on the well-being and survival of the patients. We present a medical-technological assessment of how best to treat vast numbers of dialysis patients under the financial restraints that are predicted to become even more severe as CKD entrenches itself as a more 'permanent epidemic'. A treatment modality is proposed that optimally addresses – and resolves – the debilitating effects of uremia, as well as of key clinical conditions closely linked to it. This treatment modality successfully tackles the issues of patient well-being, efficacy, effectiveness, safety and patient-nursing staff convenience – all in relation to the overall costs incurred by payers of renal care. In short, optimal care needs to be provided with shrinking resources and without compromising the medical appropriateness of the therapy. Additionally, we believe ensuring improved quality of life is just as important as prolonging patient survival. Therefore, a balanced compromise between optimal and affordable technology is required in order to reach the targets of achieving good medical care and meeting the expectations of patients, their families, healthcare providers, and society as a whole. Under these premises, and focusing on the aforementioned targets, we believe that on-line hemodiafiltration (HDF) represents the most advanced and clinically appropriate RRT modality available to best cope with the CKD epidemic. Together with the guidance and recommendations of those taking care of CKD patients on dialysis therapy, the contribution of industry is indispensable for the availability of highly reliable and affordable solutions to the impending dilemma. As representatives of the academic-medical community and of industry, we present a joint case for the application of on-line HDF towards meeting the challenge of large-scale provision of dialysis under an increasingly restrictive financial climate.

Adequate substitution of lost capabilities of diseased kidneys remains the fundamental objective of dialysis therapy. However, both peritoneal dialysis (PD) and hemodialysis (HD) are intrinsically imperfect as they cannot match the complex functions of the healthy kidney. Furthermore, besides blood purification and fluid control, several accompanying issues need to be addressed or resolved. Today, with the chronic kidney disease (CKD) 'epidemic' becoming more widespread and involving an aging population, the core necessity – and challenge – is how best to deliver a more intensive renal replacement therapy (RRT) under increasing economical restraints imposed by stretched healthcare budgets worldwide [1, 2]. Optimal RRT must therefore be the result of a compromise between the needs of all involved in the care of CKD patients requiring dialysis. Many unmet clinical needs should be addressed together with the best utilization of available technology and financial budgets [3]. The involvement and participation of patients as well as their families is crucial if home therapies could represent a possible solution to the complex problem. However, self-care RRT, such as PD and home-based therapies, only apply to a limited portion of the dialysis population. For the remaining majority, optimization of in-center HD should be attempted, considering clinical as well as ethical and financial issues.

Hemodiafiltration (HDF) is a treatment modality applied to 14% of CKD patients on regular RRT in Europe in 2010 and, as such, significantly more patients received HDF than PD in this region [4]. The principles and clinical characterization of HDF have been known for over four decades [5]. Since then, online HDF has been validated as the most efficient extracorporeal modality for the removal of both small and large uremic retention solutes ('uremic toxins'). Today, a growing body of scientific evidence and clinical experience provides

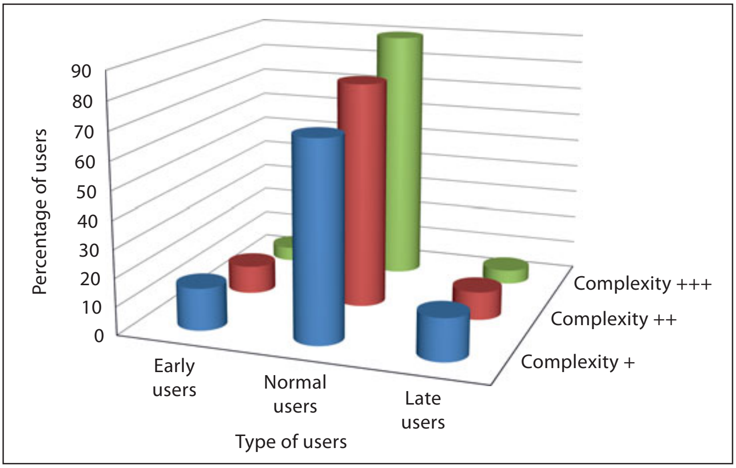

Fig. 1. Gaussian distribution of technology users based on technology complexity. Early users are mostly stimulated by curiosity, desire of progress and willingness to try new approaches. Mass users are generally following the clear evidence of a benefit for a given technology. Late users are generally resistant to changes even in the presence of good evidence for a benefit offered by a technology. In some cases this resistance implicates other factors including insecurity, specific resistance to something new, or even extra medical factors including business or conflict of interest.

a better understanding of this treatment modality, and a host of clinical benefits have been documented [6]. Moreover, constant technical refinements have made on-line HDF safe and easy to perform in routine clinical practice [5]. Nevertheless, an even wider application of the technique is precluded by the defense of more traditional techniques and the perpetual demand for more conclusive survival data from large-scale, prospective, randomized, controlled trials (RCTs) [7, 8]. This, however, is a typical evolution in the utilization of most new technologies where there is a well-distributed gaussian curve, as depicted in figure 1.

In the presence of an overwhelming body of clinical experience and data in favor of on-line HDF, including indications of a survival benefit (albeit the level of evidence is deemed not to be sufficient to satisfy the criteria of the purist) how, then, could on-line HDF be expected to evolve? We believe that the extended clinical experience, scientific validation and technological maturity of on-line HDF offers the best opportunity to satisfy the collective interests of the patient, the family, all healthcare providers and of society as a whole [9]. As representatives of the academic, medical and industry communities, we consider a joint case for the application of on-line HDF towards meeting the challenge of large-scale provision of dialysis under an increasingly restrictive financial climate [2].

Renal Replacement Therapy in the New Millennium: Unmet Clinical Needs

All the prognoses regarding dialysis patient growth made over the last two decades proved to be inaccurate and underestimated the magnitude of the CKD epidemic. Despite significant prolongation of life of CKD patients due to dialysis, major medical issues regarding adequacy and effectiveness are still open with many clinical problems still unresolved [2]. The endless cyclicity of dialysis therapy and its intermittent nature compared to the continuous functioning of the natural kidney causes permanent alterations in the hemodynamic and cardiovascular functions of the patient. This, together with the accumulation of uremic toxins of various molecular weight ranges and the impairment of the hormonal and regulatory functions of the native organ, may lead to long-term complications, especially causing skeletal, metabolic and cardiovascular disorders [10]. These and other unmet clinical needs are the cause of treatment inadequacy and unsatisfactory long-term outcomes. Even when life is prolonged for several years, the overall health status of the patient may be impaired considerably with insufficient quality of life (QoL).

Renal Replacement Therapy in the New Millennium: Social, Ethical and Financial Issues

In spite of enormous efforts targeting the optimization of technology and directed towards the individualization of treatments and treatment schedules, many patients in the world still do not have access to basic RRT facilities. Even when RRT is provided, discrimination due to age or geographic origins may occur. These problems are exacerbated in modern society by lifestyle conditions and financial constraints that make healthcare providers unable to cope with the discrepancy between expectations and resources. Today all these issues are further complicated by a worldwide economic crisis, growing patient numbers and inadequate healthcare planning. In these circumstances, both industry and clinical medicine are confronted with moral and ethical issues and are expected to offer suitable solutions. In chronic dialysis, we propose on-line HDF as a reliable technique capable of meeting the main current clinical and financial challenges as well as the diverse expectations of multiple stakeholders (patients, physicians, industry, healthcare providers and funders). Another important issue is the relative distribution of available resources between dialysis technology and the pharmacological requirements of dialysis patients. It seems that, with the allocation of fixed budgets for the entire therapy, an optimal combination of these two components must be achieved, i.e. solutions must look for an integration of both components rather than a competitive substitution.

On-Line HDF: Short- and Long-Term Clinical Benefits

It is important to reiterate the case for on-line HDF, which has established itself as a consolidated therapy over the last two decades [5–7]. The main benefits attributed to on-line HDF include efficient elimination of larger uremic toxins, anemia correction with an associated reduced requirement for erythropoiesis-stimulating agents, lower calcium-phosphate product levels, increased hemodynamic stability and better blood pressure control [8, 9]. A reduced incidence of side effects and an improvement of nutritional status have also been documented [11]. The reduced activation of inflammation and oxidative stress pathways with convective therapies, linked mainly to a reduced uremic toxin load, has been postulated to have a protective effect on both the vasculature and endothelium. Collectively, these mechanisms seem to contribute to a reduction in the frequency and severity of the cardiovascular complications that affect the majority of dialysis patients. Finally, there is considerable evidence indicating an improved QoL for patients on on-line HDF compared to conventional therapies.

On-Line HDF: Evidence of Survival Benefits

A number of investigations have reported reduced mortality rates amongst patients treated with on-line HDF. A review of all the current trials on high-flux HD and HDF has recently been published [7]. An observational study by Canaud et al. [12] involving over 2,000 patients indicated a 35% improved survival with high-volume on-line HDF independently of its higher dialysis dose. Prospectively collected data from 56 clinics in four European countries (EuCliD database) confirmed these results in terms of potential survival benefits with on-line HDF [13]. Two other RCTs (the Turkish HDF vs. high-fux-HD study and the Dutch CONTRAST study with HDF vs. low-flux HD) examining the impact of on-line HDF on patient survival have just been completed [14, 15]. Preliminary results did not show a significant difference in survival rates as a whole between HDF-treated patients and those treated with either high-flux HD or low-flux HD. However, in both studies, the volume of substitution delivered (17–20 liters per session) during the entire HDF session was identified as an independent risk factor, confirming earlier findings of the DOPPS study [12]. The volume of substitution, a surrogate of the convective dialysis dose, should thus be considered as a critical factor that may impact patient mortality rates. While acknowledging that these results only indicate an association between survival and therapy modality, and that selected patients may have received the largest amount of substitution fluids because of better cardiovascular stability and a better vascular access, one has to recognize that three independent, large-scale studies have now indicated that high-volume on-line HDF may represent a survival advantage.

On-Line HDF: A Therapy Meeting Multiple Requirements

On-Line HDF Fulfils the Quest for More Intensive Dialysis

The need for more intensive dialysis is widely recognized. Efficient detoxification of blood, i.e. removal of relevant uremic retention solutes, remains the fundamental objective of all HD therapies. Uremic toxicity is better understood today, yet there are still no clear indications as to specifically which substances need to be removed during HD [16]. With individual substances often controversially acquiring overt attention in terms of their potential in vivo toxicity and clinical relevance [17], the only certainty is that, irrespective of their number or identity, small *and* large accumulated substances need to be removed as efficiently as possible during HD therapies. As the majority (56%) of all HD patients worldwide are treated with high-flux HD (which also entails a convective component for solute removal, albeit smaller than in HDF), a more efficient removal of larger uremic toxins is considered beneficial. It has to be noted that the concept of urea Kt/V, commonly used to assess the delivered dose and efficiency of HD treatment, does not represent efficiency of elimination of larger uremic toxins that contribute to the uremic syndrome. Another general approach to delivering more intensive dialysis is to increase duration and frequency of treatment, both of which are associated with better outcomes [18]. Although not verified conclusively by prospective RCTs, more intensive HD regimens, including daily short or prolonged nocturnal (in-center or home) HD, are perceived as being advantageous in terms of both reduced morbidity and mortality. This, again, would only be applicable to a very limited group of patients and in areas where the required resources (including qualified personnel) are available. Given the theoretical and practical advantages of long or more frequent schedules and while accepting the possibility of these treatments fulfilling some of the unmet clinical needs, we do not anticipate that this represents a solution for the vast majority of the CKD population.

On-line HDF is the most intensive form of HD treatment available by virtue of its ability to more thoroughly remove a broad spectrum of substances involved in uremia. Convective (unlike diffusive) transport across appropriate high-flux membranes facilitates removal of larger uremic solutes; together with higher ultrafiltration rates – and thus increased convection made possible by usage of larger volumes of replacement fluid in on-line HDF – more efficient blood cleansing is achieved. The finding in three survival studies that a survival advantage is evident only at high-volume on-line HDF is thus consistent with these mechanistic considerations [12, 14, 15]. The degree of convective transport is thus decisive from an overall clinical point of view. Prolonged (e.g. nocturnal)

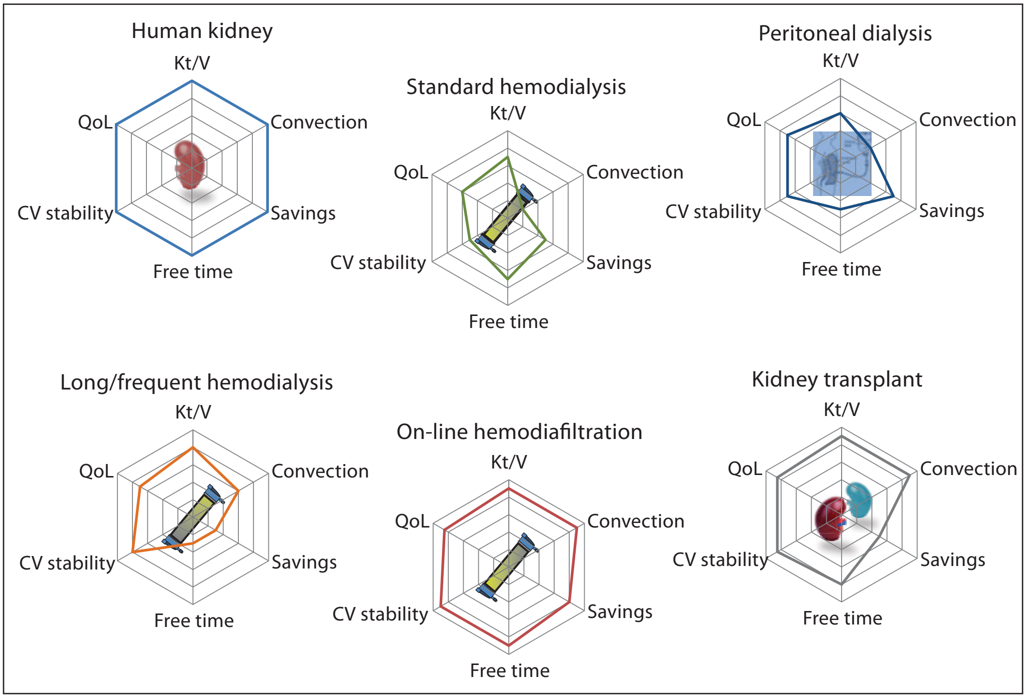

Fig. 2. Radar graph describing the performances of six different conditions: normal kidney, standard HD, PD, long/frequent HD, on-line HDF, and kidney transplant. Given a full score for the normal kidney function, we can see that on-line HDF is the therapy replacing the native organ in the most efficient way after kidney transplant. Kidney transplant, PD and long/frequent HD are performing well but their applicability is limited. Savings for all therapies includes healthcare costs, hospitalization, comorbidities and use of EPO and other expensive drugs. QoL includes survival and rehabilitation.

dialysis in the form of either high-flux HD or on-line HDF would only partially enhance detoxification processes for larger solutes by overcoming the limitations of transport of intracellular toxins into the blood compartment. This, however, would be at the expense of increased time spent on dialysis, an unacceptable social life and higher costs for the society. Thus, even assuming that a small set of patients could benefit from long or daily dialysis, on-line HDF appears to incorporate most of the advantages of long and slow treatments while taking only a few hours of patient's time and keeping the costs under control. Again, a complex compromise is the result of optimization of different performances of a therapy (fig. 2). In figure 2, radar plots of different treatments modalities are presented, comparing performance indices with the performance of the human kidney. Not only are the results with on-line HDF superior to those with other treatments in specific aspects, but on-line HDF as a whole shows a more homogeneous distribution of the different performance indices.

On-Line HDF Combines the Need for Efficient Detoxification with Reduced Inflammation

CKD is a pro-inflammatory condition; underlying inflammation corresponds with progression of renal failure [19]. Several conditions related to CKD (including malnutrition, anemia, mineral bone disease and vascular access) correlate with imbalances of various immune regulatory pathways leading to accelerated vascular disease and atherosclerosis. As cardiovascular disease and complications are the major cause of mortality in dialysis patients, curtailing underlying inflammation and associated oxidative stress is emerging as a strategy to improve patient outcomes.

To derive the full benefits of convective therapies in terms of achieving more intensive dialysis, large volumes of substitution/replacement fluids are mandatory and, as mentioned above, have been linked to improved patient survival. Exposure of patients to such large volumes of fluids poses a potential risk of increased inflammation should the dialysis fluids be contaminated with bacterial endotoxins [20]. To avoid this, an essential prerequisite of modern convective therapies is the availability for large quantities of inexpensive and highly pure (microbiologically) substitution fluids. Ultrafilters with high endotoxin retention capacities allow the 'online' production of replacement solutions from dialysate that meet such safety and quality requirements. This has been the key factor towards reviving and facilitating convective therapies. Since most dialysis centers today already use ultrapure dialysis fluids, the transition to on-line HDF is more feasible and a growing number of HD patients could benefit from the clinical advantages of this treatment modality [21].

On-Line HDF Offers Patients a Better QoL

In addition to improved survival, patients on on-line HDF experience fewer side effects, feel more energetic, have a better appetite (and are consequently better nourished and require less erythropoietin (EPO)) and sleep better at night [8, 11]. All these secondary aspects result in a significant improvement in the QoL as perceived by the patient. Again, other therapies (such as PD or long/frequent HD schedules) may offer similar results. However, as demonstrated in figure 2, the performances of these therapies in terms of improvement of QoL are achieved at the expense of increased costs or increased time spent on dialysis. These two factors represent a burden for society as well as for the patient and the family, not to mention that such treatments are only applicable to a minority of patients. However, it is also true that some typical weak points of short intermittent on-line HDF sessions (in which high rates of fluid removal are still required) are indeed partially overcome by these treatments: the associated improvements in hemodynamic stability and the decreased sense of thirst at the end of the session result in a well-tolerated treatment and a lower incidence of interdialytic uncontrolled fluid gain.

On-Line HDF Has the Potential to Allow Curtailment of Long-Term Costs of HD Therapy

Healthcare systems all over the world face considerable challenges resulting from the current demographic and economic developments [1, 2]. The growing prevalence of chronically ill patients, including CKD and particularly those needing RRT, is increasingly considered as a critical public health problem: in the last decade the prevalence of end-stage renal disease (ESRD) in Europe grew at an annual average rate of 5.3% and, at the end of 2010, the number of patients treated for ESRD was estimated to be 642,000 in Europe. Of these patients, approximately 426,000 (around 66% of all ESRD patients) receive RRT [4].

Despite the rising burden of illness and the growing total cost of RRT, the quest for sustainable strategies of care for this patient population has still not satisfactorily been addressed and a comprehensive understanding of the economics of CKD is still unavailable. This is due to lack of an integrated approach to CKD as a chronic illness and a missing balance between clinical and economic goals. Optimization of RRT in the presence of constrained resources nevertheless requires coupling of highest possible medical standards with highest efficiency and ethical distribution of resources. Still today, the costs of different therapeutic interventions at different stages of CKD have not been comprehensively addressed. On the contrary, the tendency can be observed in numerous publications to focus exclusively on costs related to a single dialysis treatment or medication, ignoring the perspective of long-term costs, social costs and overall outcomes. This problem, while understandable in the context of a fee-for-service refunding frame, underestimates the complexity of CKD as a chronic illness that impedes an understanding of the true nature of costs of care for patients with CKD. Furthermore, the ongoing confrontation of the seemingly irreconcilable perspectives of growing total cost of RRT and the need for high quality standards often hinders openness for the optimization potentials that result from the skillful orchestration of the various aspects of care. Optimization efforts in renal care have different dimensions: both the intertemporal cost interdependencies as well as the interdependencies of cost in different care settings (especially ambulatory versus inpatient cost-of-care) need to be considered. In addition, in the simultaneous pursuit of the objectives of sustainable quality and total care efficiency, the consequences of therapeutic decisions and choice of technological solutions during every single treatment have to be addressed. In the case of on-line HDF, the simultaneous short- and long-term effects of treatment must be evaluated looking at overall outcomes, safety, convenience as well as direct and indirect expenditure and benefits for the society. It is pertinent to note here that a number of studies have indicated that on-line HDF allows correction of anemia at reduced EPO doses, with the results of the recent trial of Ok et al. [14] showing a 20% reduction in EPO requirements while maintaining the target hemoglobin and hematocrit levels [8].

Wider Use of On-Line HDF Offers Refinements in Device Costs
As is true with the introduction of all advanced medical technologies, there is a degree of apprehension regarding higher costs incurred by the technical components of on-line HDF. Bearing in mind the aforementioned clinical and financial benefits to society as a whole, on-line HDF still offers potential refinements of future cost developments as penetration levels increase over the course of time. With the rapid increase of on-line HDF over the last decade, we have already observed that, as demand increases, an accompanying lowering of production costs (and prices) has been realized. This is the result of increased economies of scale, lower amortization of investments, automatization, optimization of component designs, delocalization of production and leaner production processes. This trend will continue and expand in the future: the dialysis field has encountered such trends in the past, for example with bicarbonate dialysis fluids, the demand for which led to cost reductions over time.

Potential Future Technical Refinements of On-Line HDF

Dialysis relies heavily on diverse technologies for the delivery of an adequate short- and long-term therapy. Indeed, the choice and quality of the individual components may have a significant impact on long-term outcomes. While the effects and limitations of long-term HD are recognized, we are unaware of the potential benefits of a long-term application of on-line HDF. In this circumstance, we must offer new chances to our patients. Ever since recognition of the advantages of convective transport and the birth of hemofiltration and then HDF, the technique has periodically undergone technical refinements in response to clinical needs. A significant number of therapy variations have evolved around classical HDF and on-line HDF [5, 21]. This trend will continue and further advances can be expected in the future.

On-line HDF can further be streamlined to avoid unnecessary alarms, interruptions, disruptions or discomfort during the course of treatment, and to avoid inefficient and non-effective use of resources. Intelligent technologies available today enable more precise monitoring of treatment parameters and provide the foundation for future innovations aimed at maximizing quality, dose and safety of treatment. An understanding of the following is essential to achieve such refinements:

(A) The intricate interdependencies between all components, from vascular access preparation and care, to the often 'trivial' issue of choice of needle, to how the artificial kidney and the dialysis system can work in perfect harmony.

(B) The dialyzer-machine interface and interplay between these two systems as linked by IT systems that can establish trends and the right selection of treatment parameters in response to clinical and technical signals (from treatment individualization, to profiling, to biofeedback).

Essentially, four areas of technical refinement can be identified that address unmet clinical needs, the solution of which would elevate on-line HDF to the next level of efficiency and efficacy.

Fluid Removal – How Much and How Fast?

A more effective fluid management is crucial to patient outcomes as non-physiological fluid shifts promote hemodynamic instability, development of vascular stiffness and left ventricular hypertrophy. To achieve volume control by ultrafiltration (i.e. primarily the magnitude of convective transport) in on-line HDF, the first objective is to ascertain, as precisely as possible, the overall and the net amount of fluid to be removed/replaced. The second is to ensure that the desired fluid exchange (according to patient requirements) is fully achieved in each treatment session. Online monitoring of blood parameters will allow adjustment of UFR to identify the patient-specific exchange rate possible at any given point in time in the presence of clinical stability. Determining instantaneously achievable exchange rates will therefore permit a better response to the highest achievable conditions of efficiency. The use of bioimpedance technology permits accurate, non-invasive and objective assessment of fluid status, defining the amount of fluid to be removed [22]. Furthermore, it enables a link between the fluid status and blood pressure, thereby allowing a more rational prescription of antihypertensive medication. Coupling bioimpedance with continuous and non-invasive blood volume monitoring allows not only to target overall fluid removal but also enables control of fluid removal rate. However, filter properties and other treatment parameters also need to be taken into consideration to prescribe and deliver optimal therapy. Derived measures such as filtration fraction, intravascular refilling rate and local protein concentration may all contribute to achieve the best filter performance and to design proportionally adequate filtration and reinfusion strategies.

Maximum Blood Flow Available for Solute and Water Removal

Both the total amount of fluid to be removed (allowing for weight gain between sessions) and the subsequent substitution of replacement fluid during an on-line HDF session depend upon adequate 'delivery' of blood flow from the patient into the extracorporeal circuit. An understanding of diverse vascular access-related issues is a prerequisite to attain the maximal blood flow rate through the dialyzer: the extent of solute clearance achieved is to a considerable extent determined by high effective blood flow rates (Q_b). As the fistula needles or catheters used are normally the limiting factors for the extracorporeal blood flow rates, their dimensions (inner diameter, length) are key to achievable diffusive and convective solute clearances. Advanced monitoring systems allowing the optimal regulation of blood and dialysate flows will contribute to treatment optimization. Blood flow rate can thus be automatically adapted to assure control of arterial pressure and to assure the best available blood flow delivered to the dialyzer. Of course, recirculation is an important measure in complete management of dialysis parameters and in avoiding mistakes in effective treatment delivery.

Automatic Dialysate/Substitution Fluid Flow Rate Management
Both dialysate and substitution fluid flow rates (Q_d and Q_s) are optimized and individualized based on clinical criteria of how much fluid needs to be – and can be – removed/reinfused during each session. In combination with the aforementioned management of hydration status, the reinfusion rate should be adjusted to blood flow rate (thereby controlling hemoconcentration) while blood flow rate is adjusted to dialysis fluid flow rate (thereby controlling diffusive efficiency). Essentially, the task is to identify *maximum achievable exchange volume* based on patient blood parameters evaluated by online monitoring via pressure and resistance in the circuit. When pressure increases, then the machine responds by adapting Q_b (reducing) and altering Q_d and Q_s, and/or creating pulses across the dialyzer. The objective is to utilize to the maximal what the patient can offer and what the dialyzer can provide without wastage of the potential of either. As such a treatment strategy approach could impact cardiovascular disorders, drug dosing (e.g. antihypertensive medication) and be a component of strategies supporting efficient administration of EPO.

Maximization/Optimization of Available Filter Performance
It has been recognized for some time now that the potential of the dialyzer, the focal point of the blood-cleansing function of all HD therapies, has yet to be fully harnessed. Dialyzer design studies are under way to optimize dialyzer surfaces and geometries which will enable best performance based on patient parameters. New approaches are also being investigated to select optimum dialyzer properties to suit specific treatment and patient parameters, thereby optimizing interplay of all relevant parameters of the dialysis procedure. In addition, new design of dialyzer surfaces and geometries will enable best performances based on patient parameters.

Filter performance decreases over the duration of each treatment, being at its highest during the early phases of the dialysis session. This is attributed to the formation of a 'secondary membrane' comprising several adsorbed proteins as well as other blood components; its composition is determined not only by the membrane polymer and structure, but is also influenced by rheological factors including blood viscosity and fiber-filter geometry. Thus, hollow-fiber dimensions (wall thickness and lumen diameter) and filter geometry must be designed or selected to reduce longitudinal and TMP increases during treatment. Again, treatment parameters must be selected to optimize the performance of the filter; pressure monitoring sensors within the machine can identify filter properties at beginning of treatment (i.e. calibrate the filter at t = 0) and undertake measures to maintain the dialyzer performance as close as possible to this initial (optimal) performance throughout the entire treatment (i.e. maximum and consistent performance of the dialyzer). Pressure bursts would pulsate the membrane at appropriate time points, disturbing formation of secondary membrane and thus maintaining the membrane surface in a defined, consistent state. In situations where there is a tendency for blood coagulation to occur (e.g. at suboptimal heparinization regimens), pressure pulses across the membrane would further serve to unclog any clots that may have developed. Avenues are also being explored to reduce the tendency for clot formation by pulsing buffered citrate-containing dialysis fluid across the membrane to achieve a local surface anticoagulant effect that would lead to reduced need or even an absence for anticoagulant. These cross-filtration pulses might be coupled with predetermined (frequency, direction and amplitude) shock waves to further obtain disruption of laminar flow and fluid stagnation in the dialyzer [23, 24].

Thus, the vision is to refine on-line HDF as a system which is continuously self-regulating based on intelligent adaption of parameters evaluated by blood and dialysis fluid online monitoring. Realization of such targets would represent the next most important refinement of HDF therapy, following the landmark of making unlimited amounts of inexpensive and microbiologically pure substitution fluids available 'online' that facilitated application of convective transport.

Conclusions: Adding Quality to Extended Life

With the expected worldwide escalation of CKD, provision of dialysis therapy on a large-scale requires due consideration. Preemptive strategies need to be put into place regarding delivery of the most optimal form of therapy to cope with a chronic disease necessitating regular, high technology-dependent interventions for the entire lifetime of a patient to ensure survival. Clinical as well as economical factors are inseparable deliberations for the provision of dialysis therapy of the future. In essence a stable therapy, that is by no means substandard, is required for the bulk of the dialysis population. Such a treatment modality must have demonstrable clinical effectiveness, efficacy and safety. Furthermore, it must be individualized, be convenient for patients and nursing staff alike, and be affordable – not necessarily in that order. A state of preparedness (incorporating these factors and based on the dialysis experience to date) is required to cater for the projected increase of a dialysis population having more elderly people with multiple comorbid conditions.

Foremost, it is essential to recognize the specific needs of the today's dialysis patient. As with any chronic disease, dialysis patients wish to live full, normal lives with minimal restriction to their lifestyle, particularly in terms of family life, leisure and employment. Dialysis therapy, by its very nature, does not always permit this. In-center dialysis, or even home treatment, disrupts daily routine – as does more prolonged, more frequent or nocturnal dialysis therapy.

Meeting the complex and specific clinical needs of the dialysis patient today involves several components, each of which requires due consideration. The technological features of the dialysis procedure, while being the core of the life-saving function of dialysis, are only one of several factors around delivery of HD therapy. The entire clinical picture of each individual patient and the type and quality of overall medical care provided, including therapies for CKD-associated comorbid conditions, collectively determine morbidity and mortality outcomes. Dialysis technology, or a particular treatment modality, is not the only determinant of patient outcomes or of survival.

Prolonging survival for any disease with a particular therapeutic option has, alone, little meaning without ensuring that the patient derives an adequate QoL. Patients might prefer a higher QoL for the duration of the period they are on dialysis, rather than simply living longer but being bedridden and unable to lead active lifestyles. Dialysis patients themselves, once on on-line HDF, do not wish to revert to other less advanced modalities; increased patient well-being, with fewer complications, has been documented with on-line HDF.

Thus, prescription of a particular treatment modality should not be based on the sole criteria of whether evidence is available from large-scale prospective RCTs, showing that the modality is able to prolong life. The fastidious quest, in certain quarters, for more conclusive data indicating that on-line HDF prolongs patient survival may result in a missed opportunity to give patients a therapy that has demonstrable clinical advantages in several ways (as outlined in this communication). Clinical experience is indispensable; an extensive clinical application spanning over two decades has shown that on-line HDF therapy has been successfully prescribed for thousands of patients.

Evidence indicating reduced mortality is not mandatory for the allocation of a particular treatment option. Clinical efficacy and effectiveness, both well established for on-line HDF, are more pertinent. Nevertheless, it has to be noted that there *are* indications that on-line HDF reduces mortality rates under certain conditions – only that the evidence is deemed not to be sufficiently strong. Once the clinical viability of a therapy has been established, allocators of renal care consider the costs of delivery of the therapeutic intervention. As the true overall costs of delivery of dialysis therapy are extremely complex to calculate and are as yet unavailable, technological components, consumables or medication are usually the most obvious subject of cost-containing measures. Estimation of the potential cost-saving attributed to patient well-being is difficult to ascertain and is unfortunately not available. For instance, rehabilitation due to better general health and being more active enables patients to attain a degree of normality in their lifestyle and make contributions back to society. Ability to return to, or maintain, employment overcomes manpower shortages in certain sectors, provides income from tax contributions and makes dialysis patients less dependent on state contributions. Better general health, in short, reduces the burden to society and healthcare providers.

We are faced with the challenge of delivering an optimal therapy that meets the interests of the patient, medical personnel, as well as the care providers. Medical appropriateness has essentially to be balanced with economic sustainability for the care providers, payers and society as a whole. Under these premises, more frequent dialysis, e.g. in the form of daily dialysis, may clinically be in the interests of the patient but immediately raises (serious) issues regarding increased costs, logistics of delivery of therapy and availability of medical personnel. HD therapy is, and has always been, a balance between what should, and can, be delivered to the patient. On-line HDF may not fulfill all the criteria of an ideal treatment modality, but with the current knowledge of what dialysis can and should deliver and under the present pressures of cost containment, it is the most optimal modality in the interests of all the stakeholders involved in renal care. On-line HDF, based on sound principles and clinical experience documented in clinical databases, affords significant advantages to the patient – including QoL and possibly extended longevity. Significantly, future technological advances outlined in this article will make this therapy option even more efficient and reliable regarding improving the QoL of the dialysis patient. Since its revival, on-line HDF has followed the path of steady incremental advances and of resolving technical issues to facilitate the clinical implementation of the modality. This trend may be challenged by future developments involving recently announced leading-edge technologies, like regenerative medicine, adsorption or portable dialysis devices. These quantum leaps, if realized into reliable products, may elevate blood purification in CKD to a better and more individualized cleansing modality. However, most likely a combination of new and established best practices, such as on-line HDF, will represent the optimum approach for treating the vast patient numbers of the CKD epidemic.

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