Editorial Review

Dialysis adequacy today: a European perspective

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Abstract

The need to improve haemodialysis (HD) therapies and to reduce cardiovascular and all-cause mortality frequently encountered by dialysis patients has been recognized and addressed for many years. A number of approaches, including increasing the frequency versus duration of treatment, have been proposed and debated in terms of their clinical efficacy and economic feasibility. Future prescription of dialysis to an expanding end-stage chronic kidney disease (CKD-5D) population needs a re-evaluation of existing practices while maintaining the emphasis on patient well-being both in the short and in the long term. Efficient cleansing of the blood of all relevant uraemic toxins, including fluid and salt overload, remains the fundamental objective of all dialysis therapies. Simultaneously, metabolic disorders (e.g. anaemia, mineral bone disease, oxidative stress) that accompany renal failure need to be corrected also as part of the delivery of dialysis therapy itself. Usage of high-flux membranes that enable small and large uraemic toxins to be eliminated from the blood is the first prerequisite towards the aforementioned goals. Application of convective therapies [(online-haemodiafiltration (OL-HDF)] further enhances the detoxification effects of high-flux haemodialysis (HF-HD). However, despite an extended clinical experience with both HF-HD and OL-HDF spanning more than two decades, a more widespread prescription of convective treatment modalities awaits more conclusive evidence from large-scale prospective randomized controlled trials. In this review, we present a European perspective on the need to implement optimal dialysis and to improve it by adopting high convective therapies and to discuss whether inertia to implement these practice patterns may deprive patients of significantly improved well-being and survival.

Keywords: convective treatments; efficacy; haemodialysis; medical care; quality

Introduction

The last two decades have witnessed a better understanding of uraemic toxicity, salt and water control, correction of anaemia and metabolic abnormalities including calcium-phosphate metabolism and dyslipidaemia in chronic kidney disease dialysis patients (CKD-5D) [1]. Additionally, advances in dialysis technology have provided a more efficient, controlled and safer therapy for patients [2, 3]. Nevertheless, poor outcomes in the haemodialysis (HD) patient population suggest that the improved patient care over this period has still not been clearly translated into measureable improvement of survival rates [4]. Mortality in CKD-5D patients remains high while wide variations across countries are observed [5]. Crude annual mortality of HD patients ranges from 6.6% in Japan to 21.7% in North America and averages 15.6% in Europe [6, 7]. Several factors contributing to such differences have been identified and schematically they belong in three categories: the first one includes factors that are non-modifiable such as age, sex, ethnicity and to some extent diabetes and comorbid conditions; the second category includes factors that are modifiable by dialysis prescription and medical intervention for improving blood pressure control, uraemia correction, anaemia management, calcium-phosphate metabolism, dyslipidaemia and malnutrition-inflammation syndrome [8] and the third category includes factors that are clearly modifiable but whose modification does not improve outcomes such as in the case of lowering homocysteine levels or have not yet been linked to a clinical benefit such as reducing gut-generated toxins by colon microbes [9, 10]. Recent studies have shown that practice patterns may have a significant impact on morbidity and mortality of dialysis patients [1, 11]. Accordingly, these facts suggest that dialysis treatment prescription and clinical attention to patient care should be considered as the first line and major modifiable factor. Himmelfarb and Ikizler [12] recently reviewed the medical, social and economic evolution of HD in USA, Europe and Japan from a US perspective, conceding that 'features of practice patterns in the United States that differ from those in the other two continents may account in part for the observed differences in the risk of death'. Such features include shorter treatment times, less frequent use of fistulas, dialyser reuse and staffing of dialysis units with patient care technicians rather than nurses. These deliberations do not,

however, fully consider the role of more recent advances in HD prescription including how to implement new dialysis modalities in the future. Based on recent findings, we wish to revisit and emphasize the paradigms of patient care and HD adequacy from a European perspective.

Dialysis adequacy: increasing the time and/or frequency of dialysis sessions

Dialysis efficacy relies on solute mass balance (removal of accumulated solutes) achieved during the HD with the ultimate objective of each dialysis session being to restore the patient's homeostasis and realizing a zero sodium and water balance. 'dialysis dose', defined as the net product of 'solute clearance' (K) and 'treatment time' (t), is a useful index for assessing treatment delivery. Gotch [13] developed the concept of dialysis quantification based on urea clearances to evaluate the dialysis dose delivered to patients and to assess its impact on outcomes. Despite its limitations, the 'dialysis dose' normalized to body water (urea) volume, only referring to urea Kt/V, is a widely used tool to assess delivery of dialysis efficacy in everyday clinical practice [14]. From a clinical perspective, it is important to emphasize that in this equation K and t do not have the same predictive value for outcomes of CKD-5D patients. In other words, increasing K while reducing t to maintain constant Kt/V does not have the same clinical impact on morbidity and mortality as duration of dialysis (t) which appears to be a stronger outcome determinant than K (for urea) and should always be preferred when targeting higher Kt/V [15]. It is noteworthy in this respect to underline that the HEMO study was not able to confirm the hypothesis that a higher (Kt/V >1.2) HD dose was superior to the standard dose to reduce patient mortality. In brief, this study understandably proved that CKD-5D patient mortality does not depend only on small-molecule clearance, provided a threshold minimum dialysis dose (single pool Kt/V =1.3) is delivered [16]. In addition, while in the population as a whole there was a non-significant 8% reduction in mortality in patients treated with high-flux dialysis, a *post hoc* analysis of the HEMO study in a sub-group of patients showed that the long-term use of high-flux membranes decreased serum β_2-m concentration and reduced CKD-5D patient mortality [17].

In 2009, the results of the Membrane Permeability Outcome study (MPO), a European prospective, randomized controlled, multi-centre study investigating the effect of high-flux versus low-flux dialysis on patient survival was published [18]. The primary outcome analysis of this study showed that high-flux dialysis significantly decreased mortality in incident dialysis patients with albumin levels ≤40 g/L and in a *post hoc* analysis, in diabetic patients as a whole. No effect was evident of high-flux dialysis in the population as a whole possibly because of the small number of events that reduced the power of the study for patients with albumin levels >40 g/L.

Following these results, a position statement of the working group of the European Renal Best Practice (ERBP) [19] recommended that synthetic high-flux membranes should be used to delay long-term complications of HD in patients at high risk (serum albumin ≤40 g/L; level 1A: strong recommendation, based on high-quality evidence). In view also of a reduction in an intermediate marker (β_2-microglobulin), synthetic high-flux membranes should be recommended also in low-risk patients (level 2B: weak recommendation, low-quality evidence).

By applying multiple compartmental kinetic modelling analysis of middle-molecule solutes (e.g. β_2-microglobulin) or inorganic phosphate, the limitation in removal of these compounds is mainly due to their high intra-corporeal mass transfer resistance [20, 21]. In other words, optimizing removal of middle molecules or phosphate by dialysis requires both enhanced convective clearances using highly permeable membranes as well as extended treatment time and/or increased session frequency to achieve more effective body (or effective) rather than dialyzer clearances.

Treatment schedule of any HD prescription is further critical towards dialysis efficacy and tolerance. Owing to logistical issues, scarcity of nursing staff, economical constraints and patient requests, the practice of shortening dialysis sessions has unfortunately become a clinical reality in many dialysis units worldwide. Nowadays, extending dialysis duration and increasing sessions frequency appear to be a more physiological approach to enhance efficiency, to improve vascular stability, to reduce left ventricular hypertrophy (LVH) and to preserve quality of life, but with organizational and logistic difficulties [22]. Two recent studies have shown that longer treatment time was associated with better patient survival. In the DOPPS study, longer treatment time, possibly by reducing the ultrafiltration rate and minimizing hypotensive episodes, was associated with a lower mortality in HD patients independently from the dialysis dose [23, 24]. Interestingly, by increasing treatment time by 30 min the relative risk of mortality was 7% lower. In the Australia-New Zealand data registry study, it has also been shown that longer treatment time was associated with better survival [25]. The interpretation of such impressive results on CKD-5D patient survival has been attributed to the decreased ultrafiltration rate, reduction in hypotension episodes, better control of extracellular fluid volume and the higher dialysis dose delivered [26].

From these results, one should consider, as a new standard in HD, that the minimal treatment time of 270 min (4.5 h, depending on the patient's weight or V) be delivered and an ultrafiltration rate of no >10 mL/h/kg applied for patients treated on a thrice-weekly schedule [27].

New paradigms in dialysis adequacy

Uraemic toxins

The issue of which uraemic toxins need to be removed remains unclear. Numerous substances have been studied *in vitro* and deemed to exert toxicity *in vivo* by the demonstration of an association with outcomes and classifying them as risk factors [28]. With an ever-expanding list of

Table 1. Potential strategies to improve haemodialysis efficiency

Strategies	Variables		
	>Duration (T)	>Frequency	>TBK (S & M)
Nocturnal HD	Yes	No	Yes
Daily HD	No	Yes	Yes
Extended (>6 h)	Yes	No	Yes
Haemodiafiltration	Yes/no	Yes/no	Yes (small/middle molecules)
Haemofiltration	Yes/no	Yes/no	Yes (middle molecules)

T, time; TBK, total body clearance; S, small molecules; M, middle molecules.

uraemic toxins, there appears to be no available recommendations categorically specifying the substances that need to be preferentially removed during dialysis. Moreover, uraemic toxins range from very small metabolites, including sodium and phosphate, increasingly recognized as major toxins, to much larger peptides and proteins that all need to be removed as efficiently as possible to restore the *internal milieu* (Table 1).

Assessing and managing more effectively fluid status

Assessment of fluid status, whether over- or under-hydration, is crucial in the management of CKD-5D patients. Optimal post-dialysis dry weight is still 'clinically' determined as the lowest body weight a patient can tolerate without intra-dialytic symptoms or hypotension. A more adequate definition of 'dry weight' could be 'the post-dialysis body weight at which the patient remains normotensive, without antihypertensive medication, until the next dialysis session, in spite of interdialytic fluid retention' [29].

The HEMO study estimated that 72% of CKD-5D patients exhibit hypertension despite intervention with antihypertensive medication [30]. Severe fluid overload was found in 25% of CKD-5D patients in Europe, even though it is likely that this excess fluid could be removed with ultrafiltration [31]. Fluid overload plays a major role in the development of LVH, which is highly prevalent in the CKD-5D population and is associated with significant numbers of deaths [32]. Management of fluid overload and hypertension remains a challenge in many patients, but where improvements in the treatment strategy have been effective, LVH appears to be potentially reversible [33]. One reason why better outcome is difficult to achieve is that the tools for the assessment of major cardiovascular risk factors, such as fluid overload, are not adequate [34]. Blood pressure measured at the time of dialysis (pre- and post-HD) is largely used as a clinical indicator of fluid excess in the assessment of CKD-5D patients, but it has severe limitations. Although some forms of hypertension are undoubtedly the consequence of fluid overload corrected by aggressive fluid overload management [35], several studies have shown that there are patients where such a relationship does not hold true [36]. On the other, the arterial stiffness due to vascular calcification is another factor that limits the validity of

brachial blood pressure as reflecting the central systolic blood pressure [37]. As the interpretation of blood pressure can be problematic, better ways to obtain objective measurement of blood pressure (central blood pressure, ambulatory blood pressure monitoring and self-assessment) and fluid status have long been sought. The inferior vena cava diameter, biochemical markers [e.g. atrial natriuretic peptide, brain natriuretic peptide (BNP) and its precursor NT-pro BNP], blood volume monitoring and single-frequency bioimpedance can be applied for assessing various aspects of volume status. However, advances in body composition analysis technology [38] have led to more precise measurement of fluid overload. Long-term severe fluid overload over a 3.5-year follow-up caused an increased risk of mortality (hazard ratio = 2.1) [39].

Assessing and correcting underlying chronic inflammation

In CKD-5D, chronic inflammation is independently associated with malnutrition and anaemia, leading to accelerated atherosclerosis, cardiovascular complications and death [40]. Among other causes (e.g. uraemia, dialysis treatment, microbial dialysate contamination, oxidant stress [24], vascular access is a frequent site of infection or of ongoing inflammation. An important aspect in CKD-5D patient outcomes is vascular access, the Achille's heel of HD therapy. Most unfortunately, central venous catheters (as opposed to native autologous fistulas) are still widely used (74% of the incident patients in USA) and (22% [12] in Europe [41] represent a higher risk for dialysis). The European Renal Best Practice (ERBP) guidelines recommend early creation and first use of native autologous fistula for CKD-5D patients [42, 43]; the ERBP position statement contains not only a section on treatment, but also one on prevention and is entirely devoted to HD catheters [44, 45]. Clinically, an important step in patient care is to differentiate true infection (e.g. vascular access, catheter) and silent inflammation sustained by thrombosed graft or failed kidney transplant [46]. Both retrospective analysis and prospective studies have shown that the use of synthetic membranes, ultrapure dialysis fluid and convective or mixed convective/diffusive techniques improved treatment biocompatibility and reduce the chronic inflammatory state and mortality (Tables 1 and 2). It has been postulated that high convective transport may have a role in modulating the mechanisms involved in inflammation in CKD-5D patients and in addition by reducing intra-dialytic hypotensive episodes convective therapies may reduce both cardiac stunning and gut ischaemia with subsequent translocation of endotoxins [47–49]. Recent studies have highlighted the association between increased inflammatory indexes and resistance to erythropoietin stimulating agents (ESA) [50, 51].

Are there optimal treatment options for renal replacement therapy in the future?

In Europe, where HD is still considered an established specialty for nephrologists and the staff, the emphasis on

Table 2. Clinical studies examining the influence of haemodiafiltration on patient survival

First author/year of publication	Study design	Type of study	No. of patients	Survival between treatment modalities	Comments
Locatelli et al./1996 [58]	LF-HD versus HF-HD versus HDF	Prospective, randomized multicentre	380	No difference	Primary aim to compare LF polysulfone and cuprophan
Locatelli et al./1999 [59]	HD versus HDF versus HF	Historical, prospective multicentre	6444	10% reduction in relative risk	Non-significant trend towards better survival
Wizemann et al./ 2000 [60]	LF-HD versus HDF	Prospective randomized single centre	44	No difference	
Bosch et al./2006 [61]	HE-HD versus HF-HD versus HDF	Prospective observational, single centre	183	Improved survival with HDF than national average	Standardized mortality ratio relative to USRDS data
Canaud et al./2006 [52]	LF-HD versus HF-HD versus HDF (Low-/ High-efficiency)	Historical prospective observational, multicentre	2165	35% improvement	Survival improvement observed for high-efficiency HDF versus LF-HD
Jirka et al./2006 [62]	LF-HD versus HF-HD versus HDF	Prospective observational, multicentre	2564	35% improvement	Study part of European Clinical Database (EuClid)
Schiffl/2007 [63]	HF-HD versus HDF	Prospective randomized, single centre	76	No difference	Ultrapure fluids used for both HF-HD and HDF groups
Panichi et al./2008 [64]	LF-HD versus HDF	Prospective observational multicentre	757	15% improvement	Improved survival independent of dose
Vilar et al./2009 [65]	HF-HD versus HDF	Retrospective observational, monocentre	858	34% improvement	Incident patients studied over 18-year period
Tiranathanagul et al./2009 [66]	HF-HD versus HDF	Prospective observational, single centre	22	No difference	Study evaluated tolerance and patient acceptance
Locatelli et al./2010 [53]	LF-HD versus HF-HD versus HDF	Prospective, randomized	146	No difference	Primary aim cardiovascular stability

Criteria used to include the published studies reported in this table: all studies dealing with survival involving high-flux haemodiafiltration, irrespective of study type, design or sample size.

improvement of current practices is based essentially on daily clinical, bed-side HD prescription and patient care-oriented criteria. In clinical medicine, and particularly in HD, not all current clinical practices have necessarily being supported by conclusive 'validation' from large randomized clinical trials (RCTs). Currently, about two-thirds of CKD-5D patients worldwide are treated with high-flux membranes based on the likelihood that the enhanced solute clearance of small and larger substances that can be achieved with more open membranes would contribute to improved clinical outcome. Furthermore, a significant proportion of dialysis patients who benefit from extended/daily dialysis or from more efficient removal strategies such as online-haemodiafiltration (OL-HDF) are being treated based on results from observational [52] as well as RCTs [53, 54].

OL-HDF is no longer an experimental treatment modality but a clinical reality. It is used in routine clinical practice for over 10% of the dialysis population in Europe with an increasing trend. In some countries such as Switzerland, over 60% of its dialysis patients are treated with OL-HDF, whereas in northern Europe countries ~24% of patients are treated with convective therapy. Since the first validation of its principles in the early 1970s, the treatment modality had been slow to be realized in clinical practice due to a combination of factors pertaining to technical, convenience and cost-related issues. With the advent of online production of large quantities of microbiologically pure replacement fluid

from dialysis fluid at low costs, these obstacles have been overcome and the therapy has been successfully revived.

The scientific principles and efficacy of OL-HDF are now well studied and established: it is widely recognized to be the most efficient form of extracorporeal renal replacement therapy (RRT) for the elimination of most small, but above all large uraemic retention solutes that accumulate in uraemia. Numerous publications—not the subject of this review—have dealt with specific advantages of OL-HDF pertaining to anaemia control, better haemodynamic stability, phosphate reduction, improvement of dyslipidaemia and well-being in general [55]. Significantly, OL-HDF has been shown to reduce the effects of underlying conditions of uraemic toxicity, inflammation, oxidative stress and endothelial dysfunction which are all known to contribute to cardiovascular complications and mortality that afflict CKD patients. The advantages attributed to OL-HDF most likely derive from the combination of factors related to improvements in the current HD technology and water quality, and moving to OL-HDF rather than to more frequent and/or longer HD sessions is practically much more convenient.

Preliminary results from two randomized controlled trials (Turkish HDF versus HFHD study, Dutch Contrast study HDF versus LFHD) have failed to show a significant difference as a whole with HDF-treated patients compared either with low-flux or high-flux haemodialysis-treated patients [56, 57]. Interestingly, in these two studies the volume of substitution delivered (17–20 L/session) during

the entire HDF session was identified as an independent risk factor. In other words, the volume of substitution, a surrogate of the convective dialysis dose, should be considered as a critical factor for patient survival confirming the preliminary findings of the DOPPS study [21]. We appreciate that these are association results and the possibility that the best patients could have received the largest amount of substitution fluids because of better cardiovascular stability and better functioning vascular access cannot be ruled out.

Conclusions

New paradigms for dialysis adequacy now encompass the specific removal of middle molecules beyond small solutes leading to a better control of the various metabolic alterations associated with the uraemic state: the assessment of the fluid status, the reduction in chronic inflammation and the prevention of activation of protein pathways and pro-inflammatory cells. Higher frequency and longer duration of HD are increasingly appreciated but their actuation meets with practical difficulties. Improvements in practice patterns and implementation of quality assurance tools are mandatory to reduce significant cardiovascular morbidity and mortality of dialysis patients. Optimal renal replacement therapy today benefits largely from the highly sophisticated dialysis technology that has improved dialysis dose delivery, expanded removal capacity of middle molecules, reduced vascular instability and minimized pro-inflammatory reactions. High-flux membranes and more appropriate dialyzer geometries will improve the removal of newly appreciated uraemic toxins. Despite the fact that OL-HDF may be one of the most technically advanced and versatile platforms of renal replacement therapy with promising clinical outcomes, it has to be emphasized that no technological improvement will ever replace neither the expertise of caregivers or individualized care given to CKD-5D patients.

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