

Dialysis Prescription: A Modifiable Risk Factor for Chronic Kidney Disease Patients

Bernard Canaud^{a, b} Peter Wabel^c Ciro Tetta^c

^aNephrology, Dialysis and Intensive Care Unit, and ^bAider and IRFD, Lapeyronie University Hospital, CHU Montpellier, Montpellier, France; ^cFresenius Medical Care, Research and Development Intl., Bad Homburg, Germany

Key Words

Dialysis prescription · Mortality · Dialysis adequacy

Abstract

Recent surveys of hemodialysis studies strongly support the fact that dialysis prescription is a modifiable risk factor. Six tracks to improve dialysis patient outcomes have been identified: change in vascular access option strategy and restricting catheter use; increasing time or frequency of dialysis sessions; assessment and management of fluid status; favoring removal of middle and large molecules by high-flux and convective clearance; considering ultrapurity of dialysis fluid purity as a new standard and a part of hemodialysis biocompatibility, and improving quality care and patient follow-up. By modifying dialysis prescription and by implementing a continuous quality assurance program it appears possible to improve dialysis patient survival.

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Introduction

Despite significant improvements in the management of hemodialysis (HD) patients due to a better understanding of uremia toxicity, improvements in dialysis

technology, better correction of anemia and metabolic abnormalities, as well as implementation of best practice guidelines, it is quite frustrating to note that no significant improvement has been achieved in patient survival over the last decade [1]. The mortality of chronic kidney disease (CKD) HD patients remains high while wide variations across countries are observed [2]. The crude annual mortality of HD patients ranges from 6.6% in Japan to 21.7% in North America and averages 15.6% in Europe [3]. Several factors contributing to explain such differences have been identified, schematically they belong to 2 categories: the first one includes factors that are not modifiable, such as age, sex, ethnicity, diabetes and comorbid conditions; the second category comprises factors that are modifiable, such as hypertension, uremia, anemia, dyslipidemia and inflammation. In addition, recent studies have shown that practice patterns may have a major impact on the mortality and morbidity of dialysis patients. Accordingly, these facts suggest that dialysis treatment prescription and clinical attention paid to patient care should be considered as a first-line and major modifiable risk factor. This review summarizes recent findings proving that dialysis prescription alteration may be associated with significant reduction in the morbidity and mortality of dialysis patients. The beneficial role of adjunctive therapy such as erythropoietic stimulating fac-

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Prof. B. Canaud
Nephrology, Dialysis and Intensive Care Unit
Lapeyronie University Hospital, CHU Montpellier
371, Avenue du Doyen G. Giraud, FR-34295 Montpellier Cedex 5 (France)
Tel. +33 467 33 84 95, Fax +33 467 60 37 83, E-Mail b-canaud@chu-montpellier.fr

tors, statins, vitamin D supplementation or phosphate binders will not be covered by this review. In other words, our objective here is to show that by modifying dialysis prescription and practice patterns, and by implementing a quality assurance program, significant improvement in patient survival might be achieved.

In this field, 6 tracks of improvement for dialysis patient care are clearly identified in the recent literature. They include the change in vascular access option strategies, the increase in the time or frequency of dialysis sessions, the assessment and management of optimal weight and fluid status, the enhancement of middle-molecule uremic toxins, the prevention of subclinical chronic inflammation and the improvement in global patient care.

Changing Vascular Access Option Strategy

Vascular access contributes highly to the morbidity and mortality of HD patients [1, 4, 5]. Changing vascular access creation and management are practice patterns that may significantly reduce the relative risk of death in HD patients [6]. Worldwide best practice guidelines are recommending early creation and first use of native autologous fistula (AVF) for HD patients [7]. This is a first-line approach that has been proved to be very efficient in reducing vascular-access-related morbidity. In case of multiple AVF failure, vascular access alternatives including PTFE graft or central venous catheter (CVC) might be envisaged [8]. However, it must be considered that PTFE graft has a high failure rate requiring frequent revision to maintain potency on mid term. Long-term tunneled CVC use is associated with a 5–7 times higher infectious risk and their use should be restricted to rescuing situations or specified indications. Moreover, CVC always bears the risk of host vein stenosis compromising further construction of arteriovenous access [9]. Timely referral of CKD patients to nephrologists and surgeons to create native AVFs should be considered as the best medical practice as soon as advanced CKD has been recognized. Adequate mapping of the arm and forearm vascular network (venous and arterial) by imaging methods (ultrasonography, phlebography) is highly suitable for guiding vascular surgery [10]. In any case, refraining from using CVC as long-term vascular access is highly desirable to reduce catheter-related morbidity [8]. Specific expertise of surgeons or nephrologists dedicated to CKD patient care is suitable to enhance both the success rate of construction and outcomes of AVF [11]. The international Dialysis Outcomes and Practice Patterns Study

(DOPPS) has shown that the use of CVC was associated with an increased risk of AVF failure and subsequently a higher mortality risk [12]. In this study, starting dialysis with a CVC was related to an increased relative risk of mortality up to 30%. It must be noted, however, that this figure may be significantly altered by CVC type and practice patterns of the dialysis unit [13]. It has been reported that applying strict hygienic rules for CVC handling and filling catheters with a dual antiseptic-antithrombotic locking solution, the incidence of catheter-related infection might be minimized [14–16]. Interestingly, CVCs are now easily used as permanent vascular access in elderly subjects or CKD patients presenting with exhausted vascular access site or limited time expectancy [17].

From a clinical perspective, it is recommended to construct an autologous AVF early on, to guide vascular surgery for site of implantation and type of VA by noninvasive imaging technique. CVC should be restricted to vascular access rescuing situations and specific recommendations should be applied for catheter handling.

Increasing Time and/or Frequency of Dialysis Sessions

Treatment schedule prescription is a critical factor for dialysis efficacy and tolerance of dialysis. Due to logistical aspects, economical constraints and patient requests, shortening of dialysis sessions has been commonly applied worldwide. Faced with this therapeutic challenge, enhancement of instantaneous solute fluxes by increasing flow rates and using high-performance hemodialyzers has been a generalized trend of dialysis prescription. From a physiologic perspective, it is, however, surprising to note that the continuous rush after technical improvements has completely blunted the role of patient/HD interaction as the main limiting factor for clearance and tolerance. One must bear in mind that for a given solute the body clearance is not equivalent to the hemodialyzer clearance. Nephrologists have forgotten that the main barrier to HD efficacy and tolerance was the patient itself due to its complex body composition and to limitation of the hemodynamic adaptation.

Dialysis efficacy relies on solute mass balance (removal and load) achieved during the dialysis session with the ultimate objective of periodically restoring the patient's homeostasis. 'Dialysis dose' defined as the net product 'solute clearance' (K) and 'treatment time' (t), is a convenient index for assessing treatment efficacy. Gotch [18]

developed the concept of dialysis quantification based on urea to evaluate the dialysis dose delivered to patients and to assess its impact on the outcomes. Despite its limitations the dialysis dose, referring to urea Kt/V , is a worldwide tool used to assess dialysis efficacy in practice [19]. It has been proposed to overcome Kt/V pitfalls by implementing online direct quantification biosensors on dialysis machines [20]. From a clinical perspective, it is important to underline the fact that in this equation K and t parameters have clearly not the same predictive value for CKD patients. In other words, increasing K while reducing t to maintain constant Kt/V has not the same clinical impact on morbidity and mortality. Duration of dialysis (t) appears to be a stronger clinical determinant than K and should always be privileged when targeting high Kt/V . It is noteworthy that the Hemodialysis (HEMO) study was not able to confirm the hypothesis that high dialysis dose was superior to low dialysis dose to reduce patient mortality. In brief, this study tends to prove that HD patients' mortality does not depend on small molecule clearance provided a threshold minimum dialysis dose ($Kt/V \approx 1.3$) is delivered [21]. In addition, a post-hoc analysis of the HEMO study in subgroups of patients has shown that the long-term use of high-flux membranes lowers the serum β_2 -microglobulin concentration and reduces HD patient mortality [22]. Recently, the Membrane Permeability Outcome study has shown in incident dialysis patients that high-flux dialyzers were beneficial for subgroups of high-risk patients, namely diabetics and hypoalbuminemic patients [23]. By applying kinetic modeling analysis to middle-molecule solutes (inorganic phosphate, β_2 -microglobulin, ...) it has been proved that removal limitation of these compounds was mainly due to their high intracorporeal mass transfer resistance [24, 25]. In other words, optimizing middle-molecule removal by dialysis requires both enhanced convective clearances using highly permeable membranes and extended treatment time and/or increased session treatment frequency to match hemodialyzer and body clearance.

Dialysis tolerance refers mainly to hemodynamic stability during the dialysis session (crash hypotensive episodes) and during the interdialytic period (hypotension, fatigue). On the one hand, clinical tolerance of dialysis session depends on the ultrafiltration rate (extracellular fluid removal) applied during the dialysis session and, on the other hand, on the patient's hemodynamic response that includes vascular refilling rate, peripheral vascular resistance adaptation and cardiac output increase. Optimized ultrafiltration rate by customizing HD treatment schedule (longer treatment time, adjunct isolated ultra-

filtration), as well as reducing interdialytic weight gain by dietary counseling and salt intake restriction are very simple and efficient prescriptions to correct fluid overload and improve hemodynamic tolerance [26, 27]. Preserving the residual renal function by using biocompatible material and ultrapure dialysis fluid is regularly advocated as an additional means to restore extracellular volume equilibrium in HD patients but convincing evidence is missing [28]. Nowadays, extending dialysis duration and increasing session frequency appears to be an easy and physiological approach to improve vascular stability, to preserve quality of life and to reduce left ventricular hypertrophy [29]. This simple approach, which consists in customizing the treatment schedule to the patient's needs, is, however, challenged by patients and nurses for personal convenience and logistical consideration. Two recent studies have shown that longer treatment time was beneficial for patient survival. In the DOPPS, longer treatment time by reducing ultrafiltration rate and minimizing hypotensive episodes is associated with a reduced mortality in HD patients independently of dialysis dose [30]. Interestingly, by increasing the treatment time by 30 min, the relative risk of mortality was reduced by 7%. In the Australia New Zealand data registry study it has also been shown that longer treatment time was associated with better survival expectancy [31]. In this study, a treatment time of 4.5–4.9 h was associated with 20% reduction risk of death independently of dialysis dose. Such impressive results on HD patient survival might be related to the decrease of the ultrafiltration rate, the reduction in hypotension episodes, the better control of extracellular fluid volume and the higher dialysis dose delivered [32].

From this section one should consider as a new standard in HD that a minimal treatment time of 270 min (4.5 h) should be delivered and a maximal ultrafiltration rate of 10 ml/h/kg should be applied for patients treated on a thrice weekly schedule.

The Assessment and Management of Fluid Status

The HEMO study has estimated that 72% of the chronic HD patients exhibit hypertension despite intervention with antihypertensive medication [33]. Severe fluid overload has been found to be present in 25% of the chronic HD patients in Europe, even though it is likely that this excess fluid could be removed with ultrafiltration [34]. Hypertension and fluid overload play a major role in the development of left ventricular hypertrophy, which is

known to be highly prevalent in the HD population [35], and studies have attributed significant numbers of deaths to left ventricular hypertrophy [36, 37]. The management of hypertension and fluid overload remains an ongoing challenge in many patients, but where improvements in the treatment strategy have been effective, left ventricular hypertrophy appears not to be an irresolvable problem [38–40].

One reason why a better outcome is difficult to achieve is that the tools for the assessment of major cardiovascular risk factors such as fluid overload are not sufficiently adequate [41]. Blood pressure is used universally as a clinical indicator of excess fluid in the assessment of chronic HD patients [42], but it has severe limitations. While some forms of hypertension are undoubtedly the consequence of fluid overload, several studies have shown that there are many patients where such a relationship does not hold true [43–47]. Several reasons could explain this contrariness of findings: cardiac insufficiency [48, 49] or antihypertensive medication could blunt the sensitivity of blood pressure as a reliable marker of fluid status [43] or other factors besides fluid overload that influence the blood pressure [38]. As the interpretation of blood pressure can be problematic, better ways to obtain objective measurement of fluid status have long been sought. Unfortunately, of the methods available, some are indirect while others are too subjective, and without exception it is difficult to define clinically relevant endpoints [50–53]. However, advances in body composition analysis technology [54, 55] have led to the development of a new device (body composition monitor) that allows objective and quantitative measurement of fluid overload for the first time. It has been demonstrated that the sensitivity and specificity of this method are superior to established clinical methods [56]. The output parameters of this device have been validated extensively in both healthy subjects and dialysis patients [57]. Since the advent of the body composition monitor, a number of interesting findings have been reported. Of a representative cross-section of 500 chronic HD patients in Europe, 25% revealed severe fluid overload [52]. The long-term impact of severe fluid overload and mortality over a 3.5-year follow-up has been studied [58]. The results of this study indicated a significantly increased risk of mortality (hazard ratio = 2.1) for patients in whom the pretreatment fluid overload exceeded 2.5 liters.

Is it possible to transfer the objective assessment of the fluid status into an adjusted dialysis prescription with the target to modify the risk factor of fluid overload?

In a recent prospective trial, normohydration weight calculated as the difference between the pretreatment weight and the fluid overload was used in the dialysis prescription [59]. Through use of this modified prescription, the fluid status of the overloaded patients (fluid overload >2.5 liters) was reduced by an average of 2 liters over a longer time period. In these patients the systolic blood pressure was lowered significantly by 25 mm Hg despite reductions in antihypertensive medication. Additionally the ejection fraction improved. Intradialytic adverse events remained low and unchanged in frequency.

Favoring Removal of Middle- and Large-Molecule Uremic Toxins

The toxic role of middle molecules has been regularly advocated for >30 years in the uremic syndrome to explain the severity of CKD. The middle-molecule hypothesis has clearly stimulated clinical research and promoted the development of highly permeable membrane and convective treatment modalities. Unfortunately, clinical research in this field has remained relatively disappointing since no strong and predictive marker of middle molecules has emerged. The lack of middle molecule biomarker may explain why the Kt/V urea has been extensively used despite its poor predictive value. Time has changed and recent experimental data gathered by the Eutox group has revived the interest in middle-molecule toxicity [60]. The vascular endothelium appears to be a privileged target for these compounds contributing to promoting and accelerating atherosclerosis and vascular calcification processes [61].

Interestingly, 2 compounds, inorganic phosphates (PO_4) and β_2 -microglobulin, might be considered as good surrogate markers of this category of toxins, both of them being characterized by their clinical relevance and their high intracorporeal mass transfer resistance. Inorganic phosphates have a small molecular weight (33 Da) and by definition do not belong to the middle-molecule group. Indeed due to their physical properties (hydration, polarity) phosphates mimic middle-molecule kinetics in the dialysis patient. Optimal correction of inorganic phosphate concentration is of critical importance in dialysis patients. By promoting passive and active vascular calcification, hyperphosphatemia is a well-recognized factor implicated in the cardiovascular risk of CKD patients. Adequate control of hyperphosphatemia, a primary target of dialysis adequacy, is rarely achieved. In the DOPPS 52% of the HD patients are above the phosphate

recommendation of the Kidney Disease Outcomes Quality Index despite the extensive use of phosphate binders [62]. Better control of hyperphosphatemia by dialysis is achievable provided the dialysis treatment strategy is revised and mass transfer is increased. Enhancing phosphate removal by dialysis requires first to increase instantaneous phosphate clearance (high flux and convective flux) and second to enhance the duration (or frequency) of treatment time. Until recently, β_2 -microglobulin toxicity was mainly associated with the risk of developing β_2 -microglobulin amyloidosis in long-term dialysis patients. Serum β_2 -microglobulin concentration is now strongly associated with mortality risk in dialysis patients. Post-hoc analysis of the HEMO study has shown that increased β_2 -microglobulin concentrations above a threshold value of 27 mg/l are predictive of an increased risk of death in HD patients [63]. β_2 -Microglobulin concentrations between 42 and 50 mg/l are associated with 60% higher mortality risk. β_2 -Microglobulin should be considered as a useful and predictive biomarker of mortality and infectious risk in HD patients [64]. For this reason the β_2 -microglobulin concentrations should be considered as quite interesting a marker of dialysis efficacy. The interest in β_2 -microglobulin may be due to its dual significance; on the one hand, it is a surrogate for middle-molecule dialysis dose, and on the other, it is a bioincompatibility marker for the dialysis system [65]. Albumin-bound toxins represent another category of uremic compounds that have been associated with dialysis patient mortality. Paracresol or paracresyl sulfate and indoxyl sulfate are the most leading compounds that are implicated in the endothelial dysfunction. Increasing removal of these compounds thus appears highly desirable. Due to the complexity of their structures and kinetics, removal of these compounds by dialysis is still a challenging concern. Two therapeutic modalities are currently proposed, one consists in using albumin-leaking membranes and the other in increasing convective clearance. Recent studies based on highly efficient convective modalities (HDF) have confirmed that low paracresol concentrations were associated with a significant reduction in dialysis patient mortality [66].

The beneficial role of high-flux membrane in patient mortality is strongly supported by recent studies. Two cohort studies have recently shown that regular use of high-flux dialysis membranes was associated with a significant reduction in HD patients' mortality [67, 68]. In a post-hoc analysis of the HEMO study it has been shown that patients exposed to high-flux membranes for ≥ 3.7 years were associated with reduced mortality and cardiovascu-

lar risks [69]. Interestingly, this effect was independent of the urea Kt/V delivered but was related to the β_2 -microglobulin concentrations. In the Membrane Permeability Outcome study, a prospective randomized trial in incident dialysis patients, assessing the effect of membrane permeability flux on mortality, the use of high-flux membranes in 2 subgroups of patients, diabetics and hypoalbuminemics, is also associated with a better survival [23].

The beneficial influence of enhancing convective clearances with high-flux membranes on patient survival has also been reported in several studies. The DOPPS conducted in Europe identified that the subgroup of patients receiving HDF treatment had a reduced gross mortality risk [70]. This beneficial effect has been confirmed in a multivariate analysis including age, 14 comorbidities and dialysis dose. The volume of fluid exchanged per session (liters per session) is an interesting surrogate of the convective dialysis dose delivered. In this case mortality was reduced by 7% in the low-efficiency group (7–15 liters) and 35% in the group of patients receiving high-efficiency HDF (15–25 liters). This is the first study showing that better survival was associated with increased convective dialysis dose. A recent prospective study conducted in prevalent dialysis patients has also observed a significant survival improvement after 30 months of treatment by hemodiafiltration [71]. Three prospective randomized European studies are currently running to evaluate the precise effect of HDF on the mortality of dialysis patients with a particular focus on cardiovascular events [72].

All these facts support a pathogenic role of middle molecules in mortality of HD patients. Inorganic phosphate and β_2 -microglobulin represent 2 middle-molecule compounds that should be incorporated in the biomarker panel serving to evaluate dialysis adequacy. The time has come to increase the solute convective clearance and to define a new standard for dialysis dose efficacy including blood β_2 -microglobulin concentrations [73].

Implementing Ultrapurity of Dialysis Fluid as New Standard of HD System

Ultrapurity of dialysis fluid standing for sterile and nonpyrogenic solution has been proposed to reduce microbial-contamination-related problems in HD and to facilitate the development of online hemodiafiltration methods [74–76]. The regular use of ultrapure dialysis fluid has several beneficial effects: it amplifies the beneficial role of biocompatible synthetic membrane in pre-

venting activation of circulating cells and proteins, it prevents monocyte activation and proinflammatory cytokine release, and it reduces polymorphonuclear cell burst preventing release of reactive oxygen species and minimizing oxidative stress [77]. Ultrapure dialysis fluid is newly proposed as standard for contemporary renal replacement therapies that is recommended by international guidelines to globally improve the hemocompatibility profile of the dialysis system and to minimize patient/HD interaction. A highly biocompatible dialysis system is desirable to prevent chronic inflammation and its harmful consequences in long-term dialysis patients [78]. This aim appears of crucial importance to prevent the development of dialysis-related complications including malnutrition, atherosclerosis and anemia. This fact is strongly supported by a recent mid-term prospective study showing that the reduced inflammatory profile of dialysis patients was associated with a noteworthy reduction in cardiovascular events and an improvement of patient survival [73].

Improving Practice Patterns and Dialysis Patient Supervision

Practice patterns may affect dialysis patient outcomes. This is quite original and clear-cut an observation that has been made by the DOPPS. The DOPPS is an international prospective observational study conducted worldwide in HD patients that evaluates several dimensions of practice patterns in dialysis facilities and analyzes consequences on patient outcomes. Several observations made by the DOPPS support the fact that quality care is a major determinant of patient outcomes. Physician time spent looking after patients (physician/patient time contact), number and qualification of nursing staff (patient/staff ratio), drug prescription, dialysis adequacy targets and vascular access management are among the more power-

ful and significant findings associated with better patient survival. The DOPPS findings also substantiate the fact that dialysis prescription and effective dialysis delivery are major factors for improving dialysis patient outcomes. Based on 6 targets of dialysis care, dialysis dose ($Kt/V \geq 1.2$), anemia (Hb >110 g/l), serum phosphorus ($PO_4 <1.70$ mM/l), serum calcium (>2.40 mM/l), albumin (>35 g/l) and catheter use ($<7\%$), the DOPPS has estimated that a substantial number of patient life years could potentially be saved if every chronic HD patient who is currently outside of the specified target was able to achieve these objectives partly (50%) or totally (100%) [79].

From a clinical perspective, it is then recommended to improve patient care by implementing guidelines and ensuring quality assurance processes in each dialysis facility. Selecting simple pertinent indicators of dialysis efficacy, focusing on patients outside guidelines and correcting causes of excursion would significantly improve the patient dialysis survival rate [80].

Conclusion

This review shows that large opportunities exist to improve dialysis patients' care and outcomes. Recent clinical study findings have clearly indicated that dialysis prescription is a modifiable risk factor. Among them, 6 tracks to improve dialysis patient outcomes have been identified; they include: changing vascular access option strategy and restricting catheter use; increasing time or frequency of dialysis sessions; assessment and management of fluid status; favoring removal of middle and large molecules; incorporating dialysis fluid purity in the global biocompatible concept, and improving quality care and patient follow-up. In other words, by modifying dialysis prescription and by implementing a continuous quality assurance program, it is possible to improve dialysis patient survival.

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