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Special Feature

Dialysis dose and frequency

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Abstract

Background. From the beginning of the dialysis era, the issue of optimal dialysis dose and frequency has been a central topic in the delivery of dialysis treatment.
Methods. We undertook a discussion to achieve a consensus on key points relating to dialysis dose and frequency, focusing on the relationships with clinical and patient outcomes.
Results. Traditionally, dialysis adequacy has been quantified referring to the kinetics of urea, taken as a paradigm of all uraemic toxins, and applying the principles of pharmacokinetics using either single- or double-pool variable volume models. An index of dialysis dose is the fractional clearance of urea, which is commonly expressed as Kt/V. It can be calculated from blood urea concentration and haemodialysis (HD) parameters, according to the respective urea kinetic model or by means of simplified formulas. Similar principles are applicable to peritoneal dialysis (PD), where weekly Kt/V and creatinine clearance are used. Recommended minimal targets for dialysis adequacy have been defined by both American and European guidelines (DOQI and European Best Practice Guidelines, respectively). The question of how to improve the severe outcome of dialysis patients has recently come back to the fore, since the results of two recent randomized controlled trials led to the conclusion that, in thrice weekly HD and in PD, increasing the dialysis dose well above the minimum requirements of current American guidelines did not improve patient outcome. Daily HD (defined as a minimum of six HD sessions per week), in the form of either short daytime HD or long slow nocturnal HD, is regarded as a possibility to improve dialysis patient outcome. The results of the studies published so far indicate excellent results with respect to all outcomes analysed: optimal blood pressure control, regression of left ventricular hypertrophy and amelioration of left ventricular performance, improvement of renal anaemia, optimal hyperphosphataemia control, improvement of nutritional status, reduction in oxidative stress indices and improvement in quality of life. The basis for these beneficial effects is thought to be a more physiological clearance of solutes and water, with reduced pre- and post-HD solute concentrations and interdialytic oscillation, compared with traditional HD. Apart from concerns regarding reimbursement and organizational issues, no serious adverse effects have been described with daily HD. However, the evidence accumulated is limited mainly to retrospective cohorts, with small patient numbers and no adequate controls in most instances. Therefore, large prospective studies with adequate controls are required to make daily HD accepted by reimbursing authorities and patients.
Conclusions. Given the available observational and interventional body of evidence, there is no reason to reduce arbitrarily dialysis dose, particularly dialysis treatment time in HD patients treated three times weekly. Daily HD represents a very promising tool for improving dialysis outcomes and quality of life, although its impact on patient survival has not yet been proven definitively.

Keywords: daily dialysis; dialysis adequacy; dialysis dose; Kt/V; long slow nocturnal daily dialysis; short daily dialysis; survival; urea kinetic model

Introduction

The uraemic syndrome can be conceptualized as resulting in part from accumulation in body water

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of solutes that are normally eliminated by the kidneys and have concentration-dependent toxicity. In 1826, Quinan [1] and in 1829 Christison [2] reported elevated blood urea concentrations in patients with degeneration of the kidneys. These findings were interpreted to implicate urea as the major toxin of uraemia. The urea theory of uraemic toxicity was challenged very early on and, in light of an increasing number of observations that in renal disease numerous solutes were accumulating in blood, the symptom complex was termed uraemia by Piorry to indicate 'urine in the blood' [3]. Over the subsequent years, many solutes have been shown to accumulate in renal insufficiency and a recent tabulation by Vanholder *et al.* [4] of the major retained organic substances lists more than 40 compounds ranging in molecular weight from 60 (urea) to $>10^6$ Da. Unfortunately, for only some of these retained solutes, has organ-specific toxicity been established in the uraemic syndrome. Nonetheless, since the very beginning of the dialysis era the debate arose as to the adequacy of the new available treatment of uraemia. During the early years of intermittent haemodialysis (HD) treatment, the definition of adequate dialysis was based on the two essential goals of dialysis: eradication of signs and symptoms of uraemia and rehabilitation. As early indicated by de Palma *et al.* [5], dialysis treatment is defined adequate when it permits the patient to be fully rehabilitated, to have a satisfactory nutritional intake and a sufficient production of red blood cells, to maintain normal blood pressure values and to prevent the development of neuropathy. This holistic approach to assessing dialysis adequacy, although still valid, is subjective, requires careful monitoring of patients and has the drawback of a possible late diagnosis of underdialysis. Hence the search for a more objective definition of dialysis adequacy by means of laboratory parameters used to calculate quantitative indices of the delivered dialysis dose and the ongoing debate as to which targets of dialysis dose should be reached to ensure the best patient outcome. This debate started from the National Cooperative Dialysis Study (NCDS) [6] and culminated in the recently published Hemodialysis (HEMO) Study [7]. The latter randomized controlled trial apparently concluded that there were no benefits to patient outcome from higher dialysis doses than those recommended by the present guidelines, and from the use of high-flux membranes; we are certainly not satisfied with the current results of dialysis treatment. In the HEMO Study, of 1846 randomized patients, 871 died during the follow-up, an incidence rate of death of 16.6 per 100 patient-years. In line with the HEMO Study, the United States Renal Data System indicates that mortality of elderly patients undergoing dialysis is similar to that of patients affected by malignancy [www.usrds.org/adr_1998.htm]. This is certainly in part due to the baseline demographic and clinical characteristics of the present dialysis population. It is composed of elderly patients affected by a heavy burden of comorbid conditions, mainly pre-existing diabetes and cardiovascular disease, which affect the prognosis negatively [8]. Nephrologists, who are treating such a patient population, are challenged by the search for the best – or, in other words, 'adequate' – dialysis treatment to improve, as much as possible, survival and quality of life. Also in light of the apparently negative results of the HEMO Study, the debate on higher dialysis frequency, in the form of daily HD, continues, considering the promising preliminary results. The rationale of daily HD is based on simple considerations coming from physiology: the natural kidneys provide homeostatic and clearance function continuously, whilst the current HD schedules provide ~10% of the clearance power of the natural kidneys in an intermittent fashion, exposing the organism to peak concentration toxicity in the pre-dialysis time.

This report is focused on the most important and debated topics on dialysis dose and higher HD frequency in the form of daily HD. The accord reached on key points is given finally.

History and principles of dialysis quantification

'Dialysis is an empirical therapy of end-stage renal disease based on the rationale that the uremic syndrome is dependent on the concentration of toxic solutes accumulating in renal failure. Although these molecular toxic have not been defined, urea has been successfully used as a toxic solute marker to define adequate dialysis therapy through urea kinetic models' (F.A. Gotch, 1994).

These sentences well summarize the basic concept of dialysis dosing: as the real toxins that account for the uraemic syndrome are not known, the clearance of urea can be used to gauge the effectiveness of dialysis, since the clearance of all toxins correlates to some extent with urea clearance.

The methods for quantifying dialysis using urea kinetics were developed by Frank Gotch and John Sargent (a mathematician) in the early 1970s [9]. The mathematical tools for modelling urea kinetics were derived originally from pharmacology and are based on the principle of matter preservation. Urea was chosen as a solute marker for dialysis quantification for the following reasons: its blood concentration is increased during uraemia; it has a low molecular weight (60 Da) and, therefore, diffusion between compartments is rapid and a simple single-pool model is adequate for most applications; its distribution volume is total body water; it crosses dialysis membranes easily; its concentration is easy to measure in the blood and in the dialysate; and, finally, it is the final product of protein metabolism and, therefore, urea kinetics can be correlated with dietary protein intake.

During HD, diffusion can be considered as a first-order kinetic process (i.e. the quantity of solutes distributed in a given volume decreases exponentially as a function of time), where the solute transport across dialysis membranes is a function of the concentration

gradient. Assuming a fixed distribution volume (zero ultrafiltration) and no generation during the dialysis session, the concentration of any solute during HD can be described by the equation:

$$C_t = C_0 \times e^{-\mathrm{Kt/V}}$$

where C_t is the blood concentration of the solute at any t time, C_0 is the blood concentration at the beginning of HD, K is the clearance due to the dialysis membrane and residual renal function, t is the time of dialysis treatment and V is the distribution volume. It derives that (a) $\mathrm{Kt/V_{urea}}$ represents the urea clearance at t time of dialysis treatment per unit of urea distribution volume and (b) the delivered $\mathrm{Kt/V_{urea}}$ can be calculated theoretically from blood determinations of urea concentration at time t and time t_0, according to the equation:

$$\mathrm{Kt/V} = \ln(C_0/C_t)$$

In fact, the V_{urea} is not fixed but variable (according to intradialytic ultrafiltration and interdialytic water accumulation) and C_t depends not only on urea removal, but also on urea generation (G) along time. The single-pool, variable-volume urea kinetic model (UKM) from determinations of blood urea concentration at the beginning and at the end of a given HD session and at the beginning of the subsequent one [10], allows the estimation of V and G and the calculation of $\mathrm{Kt/V_{urea}}$ and protein catabolic rate (PCR), which in stable patients equals dietary protein intake. After high-efficiency HD became used widely, it became manifest that urea follows a double-pool kinetics, rather than the single-pool one. *Urea rebound* at the end of HD sessions was reported. It was first explained as due to the delayed flow of urea from the intracellular to the extracellular compartment [11], subsequently as the consequence of urea sequestration in low-perfusion tissues, such as muscles, skin and bones [12]. Equilibrated $\mathrm{Kt/V_{urea}}$, correcting for urea rebound, is actually a more accurate measure of dialysis dose and is usually 0.15–0.20 lower than single-pool $\mathrm{Kt/V_{urea}}$ [13]. As equilibrated $\mathrm{Kt/V_{urea}}$, calculated according to UKM, requires complex calculations and the need for delayed post-HD blood samples, different simplified formulas have been proposed to estimate single- and double-pool $\mathrm{Kt/V_{urea}}$. The most accurate is the Daugirdas formula [14], allowing the calculation of single-pool $\mathrm{Kt/V_{urea}}$, which can be adjusted to double-pool $\mathrm{Kt/V_{urea}}$ by means of the Daugirdas–Schneditz equation rate [15].

The same principles for quantifying the dialysis dose in HD have been applied in peritoneal dialysis (PD), where weekly $\mathrm{Kt/V_{urea}}$ and creatinine clearance are both used. These indexes combine the contribution of the peritoneal clearance with that of the residual renal function. As the quantity of urea and creatinine removed are directly measurable in the dialysate, the calculation of the adequacy indexes is easier in PD than in HD.

Which targets of dialysis dose should be achieved?

The question as to the targets of dialysis dosing has been hot and controversial since the beginning of the long-term dialysis treatment era. In the late 1970s, the National Institutes of Health (USA) sponsored the NCDS to establish objective, quantitative criteria for the adequate dose of dialysis [6]. It included patients dialysed with low-permeability membranes and had a 2×2 factorial design: the patients were randomized to two different treatment times (2.5–3.5 *vs* 4.5–5.0 h) and two different $\mathrm{TAC_{urea}}$ levels (100 *vs* 50 mg/dl). Morbidity, indicated as treatment failure, was used to judge the quality of dialysis. The primary analysis demonstrated the effect of $\mathrm{TAC_{urea}}$ on treatment failure, but no significant effect of treatment time was found, although there was a clear trend towards a benefit from longer dialysis ($P = 0.06$). The secondary 'mechanistic' analysis of the NCDS data by Gotch and Sargent introduced the issue of $\mathrm{Kt/V_{urea}}$ [16]. In Gotch's model, the probability of dialysis failure was a constant step function of $\mathrm{Kt/V_{urea}}$: it was higher when $\mathrm{Kt/V_{urea}}$ was ≤ 0.8 and abruptly decreased when it was >0.9. As a consequence, $\mathrm{Kt/V_{urea}}$ >1.0 per HD treatment was considered of no apparent clinical value. However, a subsequent analysis of the same NCDS data by Keshaviah [17] concluded that there was an exponential decrease in the probability of failure as $\mathrm{Kt/V_{urea}}$ increased and also suggested the benefit of a $\mathrm{Kt/V_{urea}}$ >1.2. Although hospitalizations tended to be less likely in patients on longer dialysis, the length of dialysis was not considered an important factor in dialysis adequacy as long as $\mathrm{Kt/V_{urea}}$ remained unchanged. This represented, in part, the theoretical premise to shorten progressively the duration of HD sessions as more efficient dialysers were developed.

The NCDS was performed using low-flux, cuprophan membranes and acetate buffer, whilst the subsequent dialysis technology has increasingly used high-flux, substituted cellulose or synthetic membranes and bicarbonate buffer. Moreover, the characteristics of the dialysis population have changed dramatically compared with the NCDS dialysis population, with a sharp increase in elderly patients and diabetics. Therefore, the radical changes in the HD technology and population have challenged the external validity of the NCDS, i.e. its applicability to the present dialysis panorama.

A number of subsequent observational studies have investigated the relationship between $\mathrm{Kt/V_{urea}}$ and mortality. In 1993, Owen *et al.* [18], analysing 13 473 patients in a retrospective fashion, concluded that a urea reduction ratio (URR) of <60% and a serum albumin of <4 g/dl were associated with an increased mortality risk. Contemporarily, a survey of the medical literature of the US Renal Physicians Association reported an increase in the quality-adjusted life expectancy of HD patients with increasing $\mathrm{Kt/V_{urea}}$ up to a value of 2 [19]. Collins *et al.* [20], in another retrospective analysis of 1800 patients (691 of whom were diabetics), showed that single-pool Kt/V was independently associated with patient survival. The relative

risk of death in non-diabetic patients was 0.65 ($P=0.0012$) for Kt/V_{urea} of 1.2–1.4 and 0.67 ($P=0.0029$) for $Kt/V_{urea} \geq 1.4$, compared with Kt/V_{urea} of 1.0–1.2 as reference. In the diabetic cohort, the relative risk of death was 0.70 ($P=0.009$) for Kt/V_{urea} of 1.2–1.4 and 0.59 for $KT/V_{urea} \geq 1.4$, compared with Kt/V_{urea} of 1.0–1.2 as reference. In the diabetic patients, $Kt/V_{urea} \geq 1.4$ was associated with a lower risk of death even compared with the Kt/V_{urea} range of 1.2–1.4.

More recently, a progressively decreasing risk of death with increasing single-pool Kt/V_{urea} values up to 1.8 has been reported by a survey of the Japanese Patient Registration Committee from data of over 50 000 HD patients [21]. Held *et al.* [22] analysed 2311 patients from 347 dialysis centres in the United States and showed a 7% reduction in mortality for each 0.1 increase in Kt/V_{urea}, at least until a Kt/V_{urea} (single pool) of 1.33. The recent preliminary results of the DOPPS study are in line with the theory of a progressive benefit from increasing dialysis dose, by showing that increasing Kt/V_{urea} is beneficial up to a double-pool Kt/V_{urea} of ≥ 1.4 (roughly corresponding to a single-pool Kt/V_{urea} of 1.6) [23].

The two most important studies addressing dialysis dose in PD are both observational. In the CANUSA study, patient survival was continuously correlated with the dialysis dose, expressed either as weekly Kt/V_{urea} or as weekly creatinine clearance: every increase in weekly Kt/V_{urea} of 0.1 was associated with a reduced relative risk of death of 5% and every increase in weekly creatinine clearance of 51 with a reduced relative risk of death of 7% [24]. The Maiorca study also showed a progressive decrease in mortality until weekly Kt/V_{urea} values of 1.96 [25].

International guidelines on dialysis dose

Based on literature reports, the American guidelines were issued first (DOQI, 1997; K-DOQI, 2001), followed by the European Best Practice Guidelines (2002). The K-DOQI Guidelines recommend a minimum single-pool Kt/V_{urea} of 1.2, roughly corresponding to a minimum prescribed URR of 65% for thrice weekly HD [26]. The European Best Practice Guidelines recommend higher values: double-pool Kt/V_{urea} of at least 1.2, single-pool Kt/V_{urea} of at least 1.4 [27].

For continuous ambulatory PD, the DOQI Guidelines recommend a minimum weekly Kt/V_{urea} of 2.0 and a minimum weekly creatinine clearance of 60 l/1.73 m^2 [28]. The recommended minimal dose targets are higher in nocturnal PD (a minimum weekly Kt/V_{urea} of 2.2 and a minimum weekly creatinine clearance of 66 l/1.73 m^2), given the intermittent fashion of this PD modality.

Recent randomized controlled trials on dialysis adequacy: the HEMO and ADEMEX studies

Observational evidence suggested a continuous benefit from increasing the delivered dialysis dose well above the minimal targets recommended by the international guidelines. However, although observational studies can suggest associations, they never prove causation as they are exposed to confounding biases. Consequently, in the late 1990s, the argument came to the fore as to whether increasing dialysis dose *per se* could reduce patient mortality. This issue was addressed in two recently published randomized controlled trials, one performed in HD and the other in PD patients: the HEMO Study [7] and the ADEMEX study [29], respectively.

In the HEMO Study [7], 1846 patients were randomly assigned to a standard or high dose of HD and to a low- or high-flux dialyser (2×2 factorial design). The standard HD dose goal was an equilibrated Kt/V_{urea} of 1.05, which is equivalent to a single-pool Kt/V_{urea} of 1.25 and to a URR of 67%, according to that recommended by the DOQI Guidelines. The high dose goal was an equilibrated Kt/V_{urea} of 1.45 (equivalent to a single-pool Kt/V_{urea} of 1.65 and to a URR of 75%). The primary outcome was death due to any cause, while the main secondary outcomes were the rate of all hospitalizations (excluding those related to vascular access) and the composite outcomes of the first hospitalization for a cardiac disease or death due to any cause, the first hospitalization for an infectious cause or death and the first decline of >15% of the serum albumin concentration from baseline value or death. Over a mean follow-up of 2.8 years, the following results were reported:

(i) The risk of death from any cause, i.e. the primary outcome, was the same in the high- and standard-dose groups (relative risk for high *vs* standard dose: 0.96; 95% confidence interval: 0.84–1.10) and in the high- and low-flux groups.
(ii) The risk of the main secondary outcomes was also the same for both dialysis doses and flux groups. In the high-flux group, there were significant reductions, compared with the low-flux group, in the risk of death from cardiac causes and the combined outcome of first hospitalizations or death due to a cardiac cause. However, as already mentioned, total mortality was the same in the two flux groups.
(iii) Subgroup analysis revealed a significant survival benefit for women receiving a high dialysis dose (19% lower risk of death than women in the standard-dose group) and for patients with >3.7 years of dialysis receiving high-flux dialysis (32% lower risk than the low-flux group). However, men receiving high dose HD had a 16% higher risk of death than those receiving standard dose HD and the strength of the interaction between flux and years of dialysis was weakened when years of dialysis was treated as a continuous variable.

As it is well acknowledged, the results of secondary analyses can be flawed by type-1 statistical error (i.e. false positive results simply due to chance, because of multiple testing). Therefore, they are to be taken

with caution, just as hypotheses to be tested further, in *ad hoc* designed studies. The primary outcome analysis made the HEMO Study apparently negative: no further benefit on patient survival can be expected either by increasing the dose of HD, as expressed by Kt/V_{urea} (therefore relating to low-weight solute clearance), or by increasing membrane flux (therefore increasing middle-molecule clearance). These negative findings cannot be explained by the potential failure to reach randomization targets for both HD dose and flux, as an excellent separation was obtained for all randomized groups.

The ADEMEX study [29] randomized 965 patients to either conventional-dose PD or high-dose PD, as expressed by a weekly peritoneal creatinine clearance of $\geq$60 l/1.73 m^2. Death due to any cause was the primary endpoint of the study. The secondary endpoints were hospitalizations, therapy-related complications, correction of anaemia and effects on nutritional status. Among the patients in the control group, peritoneal creatinine clearance and Kt/V_{urea} values remained constant at near baseline levels throughout follow-up, whilst in the intervention group they increased predictably and remained separated from the measurements in the control group for the entire duration of the study ($P < 0.01$). Patient survival was similar in the two randomization groups, both in the intention-to-treat and in the per-protocol analyses. However, it is worth noting that greater proportions of patients in the control group died as a result of congestive heart failure (13.4% *vs* 5.7% in the intervention group; $P < 0.05$) or a combination of uraemia/hyperkalaemia/acidosis (12.2% *vs* 5.1% in the intervention group; $P < 0.05$).

The results of these two randomized controlled trials have given rise to a renewed, hot debate on dialysis adequacy. It is possible that the positive correlation between increasing dialysis dose and patient survival shown by observational studies is due to case mix, i.e. more diseased patients are likely to die in a shorter time and are also less likely to receive high-dose dialysis (because of medical choice or more side effects experienced with dialysis delivery) than healthier patients.

Nonetheless, the HEMO and the ADEMEX studies have been criticized as to their internal and external validity. Here, the criticism moved to the HEMO Study will be reviewed, whilst for a critical appraisal of the ADEMEX study the reader is referred elsewhere [30]. The HEMO Study enrolled prevalent HD patients; 60% of them had previously been treated with high-flux HD and the mean single-pool Kt/V_{urea} at the time of inclusion was already relatively high (mean: 1.63). As a consequence, it is very likely that some of the patients enrolled in the standard HD dose group decreased their dose of dialysis and that patients previously on high-flux dialysis were subsequently enrolled in the low-flux group. Thus, a carryover effect of dialysis dose and flux prior to study initiation cannot be excluded. The magnitude of this problem cannot be neglected, considering that the mean time on dialysis at study enrolment was 3.7 years and that the mean follow-up time was shorter (2.8 years). The dialysis vintage at study enrolment and the lower age (57.6 $\pm$ 14.0 years) of the study population compared with the general US HD population implies the selection of long-term survivors. Due to the study exclusion criteria, very heavy weight patients (97% of patients who underwent randomization weighed $<$100 kg) and severely malnourished/ill patients were excluded (mean serum albumin: 3.6 $\pm$ 0.4 g/dl). All of the previous considerations support the possibility of a selection bias reducing the power of the study. This may have led to a type-2 statistical error (i.e. the failure to detect a really existing difference among the study groups) [31].

Apart from these considerations, the HEMO Study stimulated a rethink on Kt/V_{urea} as an appropriate measure of dialysis adequacy. Two major concerns on Kt/V_{urea} have been raised to attention: (I) the effect of time *per se*, independent of the product $K \times t$ and (II) the independent clinical meaning of V_{urea}.

The effect of HD time

The Kt/V_{urea} index pools urea clearance with dialysis time in a product that expresses the total urea clearance per HD session. However, a burden of evidence indicates that dialysis time *per se* is associated with adequate blood pressure control and good patient survival, whilst reductions in dialysis time may adversely affect volume status, hypertension and ultimately patient outcomes, as convincingly taught by the Tassin experience [32]. In other words, dialysis time should not be determined solely by the need to achieve a given clearance target. Rather, it should also be strongly influenced by the need to optimize volume status and blood pressure control. With respect to this, it is worth keeping in mind a lesson from the past. In the 1980s, a surprising observation came to light: the survival rate of European and Japanese dialysis patients was better than that of patients treated in the US. An analysis of dialysis prescriptions made in 1986 and 1987 found not only that the prescribed dialysis dose in US was substantially lower than in Europe, but that the most striking feature of these lower HD doses was the progressive decrease in the duration of HD sessions, which were 23.5% shorter than in Europe and 40% shorter than in Japan (where reimbursement was proportional to the duration of dialysis). This lesson subsequently led to a prolongation of the duration of HD sessions in the US in the recent past [33]. It is important not to repeat the same mistake we made in interpreting the NCDS results: as time of HD was not significantly associated with improved outcome, its importance was neglected and time on HD was shortened, without considering the associated risks [33].

Revising the meaning of V_{urea}

It has been suggested that V_{urea} cannot be regarded as a mere urea container, but that it is a surrogate

for nutrition and, as such, an independent predictor of mortality [34]. The correlation of mortality with V_{urea} might invalidate Kt/V_{urea} as a parameter of dialysis dose since Kt and V_{urea} relate to mortality inversely. Thus, at any level of Kt, Kt/V_{urea} decreases as V_{urea} increases and, therefore, Kt should be considered independently as a parameter of dialysis dose. The evidence presented to support this is the observation that mortality risk computed in cross-sectional analysis fell as Kt increased and reached a gender-dependent minimum for Kt of $\geq$42 l in females and of $\geq$48 l in males, without a clear cut-off over which the mortality reached a plateau [35]. In contrast, mortality as a function of Kt/V_{urea} tends to show a reverse J-shaped curve, where at some point the higher Kt/V_{urea} is associated with higher mortality [36,37]. This has been interpreted as a consequence of the fact that malnourished patients, who are more likely to die, had low V_{urea} and, hence, high Kt/V_{urea} for the same Kt values. Therefore, V_{urea}, as an independent predictor of mortality, might act as a confounding factor in assessing the relationship between Kt/V_{urea} and mortality. Thus, the dialysis dose to be delivered should combine an adequate Kt/V_{urea} with an adequate Kt [35].

Beyond HEMO and ADEMEX: a look into the future

Notwithstanding all the arguments reviewed above, the best available evidence at present indicates that increasing dialysis dose beyond the minimal levels recommended by the DOQI Guidelines does not improve patient survival. This conclusion prompts future research towards two directions: (A) a revision of the issue of dialysis adequacy and of the quantitative indices used to synthesize it, possibly working on the large available HEMO database (as was done by Frank Gotch with the NCDS database in the 1980s) and (B) renewed interest in optimal dialysis prescription in the future. With respect to this, conventional HD is efficient, but it is intermittent. PD is often better tolerated than HD, with slow continuous fluid and solute removal more strictly mimicking the physiology of native kidneys. However, it often does not provide adequate solute removal, especially in large patients and in the presence of declining residual renal function. Whatever manipulations may be done for improving the efficiency of PD, they are ultimately limited by the surface area and permeability characteristics of the peritoneal membrane, as well as the volume it can contain. In contrast, HD can be improved easily by decreasing its intermittence; hence, the renewed interest for daily dialysis programmes.

Rationale for daily HD

With intermittent, standard thrice weekly HD, blood solute concentrations and water/sodium retention have an irregular time profile, with peak values being recorded before each HD session (particularly before the first HD session of the week) and low values at the end. The unphysiological condition of intermittent clearance profiles is potentially associated with:

(i) peak concentration toxicity, which is harmful not only over a medium–long term run, but can also be lethal in the short term (see hyperkalaemia peaks and/or pulmonary oedema);
(ii) disequilibrium syndrome, which is mainly due to urea and sodium high clearances and manifests itself mainly as headache and post-dialysis fatigue;
(iii) intra-HD hypotensive episodes, which are related to the inability to compensate for abrupt blood volume reduction secondary to high ultrafiltration;
(iv) triggering of cardiac arrhythmias due to rapid electrolyte blood concentration changes (particularly regarding potassium).

Daily HD has a solute concentration profile much less irregular and similar to that observed in PD. In daily HD, pre-HD concentrations of solutes, for example, urea, creatinine, potassium and hydrogen ions, are reduced throughout the week, as are the TACs of these solutes and – perhaps more importantly – the TAC deviations. Also intra-HD water removal is smoother and more gradual, greatly reducing cardiovascular instability. Therefore, daily HD has been claimed to be much better tolerated than thrice weekly HD. Moreover, daily HD potentially may offer higher dialysis dose ranges than those explored by the HEMO Study and that are not achievable with thrice weekly HD.

History and schedules of daily HD

Although there is currently great interest in daily HD, the idea is anything but new. The first description of daily HD was in 1969 by de Palma *et al.* [38]. They reported on seven patients that had begun HD five times a week for 4–5 h per session. The reasons for changing to more frequent HD included severe intradialytic hypotension and severe intradialytic hypertension. Both of these disturbances were solved with increasing HD frequency and all patients experienced better appetite, weight gain and better biochemistry parameters in spite of dietary restrictions being lifted. In 1979, Bonomini *et al.* [39] reported on six patients dialysed 6–12 months for 3–4 h, 5 days a week. These patients had been placed on daily HD for a variety of medical reasons, as well as severe subjective complaints, all of which improved.

Daily HD programmes have taken two main configurations: short daily HD (SDHD) and long slow nocturnal daily HD (NDHD). The former is scheduled on 6–7 days/week and lasts 1.5–3.0 h per session. Big dialysers are employed, with high blood flow (400–500 ml/min) and dialysate flow (500–800 ml/min) rates. In other words, it is a quotidian short

high-efficiency HD. The latter is scheduled on 6 nights/week and the duration of each session is 6–8 h. Small-standard dialysers are employed, with low blood (200–300 ml/min) and dialysate (100–200 ml/min) flow rates. In other words, it is a quotidian, overnight prolonged low or standard-efficiency HD. SDHD can be performed in-centre or at home, whilst NDHD has to be necessarily performed at home. Both NDHD and SDHD provide a higher quantity of solute removal than conventional thrice weekly HD and a more physiological modality of solute removal. The kinetic rationale for SDHD is based on the fact that the first half of a 4 h HD session removes the majority of urea (60–70%), due to the direct correlation between solute removal and its plasma concentration (higher at start) and the multicompartment structure of human body (rapid decrease of plasma concentration). Stopping the HD session after the first 2 h will reduce the removal capability for low-weight solutes, such as urea, by 30–40% per session, but doubling the number of HD sessions per week will increase the latter by 20–40%. At the steady state, SDHD is characterized by maintenance of lower pre-HD blood urea levels; moreover, the pre- and post-HD solute concentration oscillations are reduced, allowing an improved physiology of the HD treatment. Interestingly, lower pre-HD solute concentration concerns not only water-soluble and non-protein bound toxins, such as urea and creatinine, but also partially lipophilic and protein-bound solutes, such as 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid, *p*-cresol, indole-3-acetic acid, indoxyl sulphate and hippuric acid, that are increasingly considered in part responsible for the biochemical and functional alterations present in the uraemic syndrome and to which the kinetics of urea is not applicable [40].

Daily HD: main outcomes

Improving hypertension control and cardiac remodelling

The early study by Woods *et al*. [41] described retrospectively the patient outcomes after switching from standard thrice weekly HD to SDHD in a cohort of 72 patients treated at nine centres in the 1972–1996 period. Pre-HD systolic and diastolic blood pressures fell by 7 and 4 mmHg, respectively, after starting SDHD ($P = 0.02$). Also, the number of anti-hypertensive medications required fell. These results have recently been confirmed in a prospective cross-over trial comparing SDHD with thrice weekly HD, using 24-h blood pressure monitoring and echocardiography to assess cardiac remodelling [42]. Of note, left ventricular mass index decreased significantly during SDHD (SDHD: $120.1 \pm 60.4\ g/m^2$; standard HD: $148.7 \pm 59.7\ g/m^2$; $P = 0.01$). Extracellular water content also decreased from $52.7\% \pm 11.4\%$ to $47.6\% \pm 7.5\%$ ($P = 0.02$) and correlated with 24-h systolic blood pressure ($r = 0.63$, $P < 0.01$) and left ventricular mass index ($r = 0.66$, $P < 0.01$). In conclusion, this study confirmed that SDHD allows optimal control of blood pressure and reduces left ventricular hypertrophy. These effects seem to be related with an optimization of body volume status. Similar results were obtained with NDHD, concerning both improved blood pressure control [43] and regression of left ventricular hypertrophy [44]. In six cardiac-compromised patients, shifting from conventional to NDHD was associated with a significant increase in the ejection fraction and a significant decrease in the number of cardiovascular medications, whilst the extracellular fluid volume was unchanged [45].

Improvement of renal anaemia

An analysis of an ongoing, non-randomized, prospective trial of NDHD, SDHD and their cohort of conventional HD controls was recently performed. Those patients who had completed 15 months of the trial were analysed, i.e. nine patients in the quotidian dialysis group and nine cohort controls receiving conventional three times weekly HD. At 15 months, the weekly Kt/V_{urea} in the quotidian group was higher than in the conventional group ($P = 0.001$). Mean erythropoietin dose decreased in the quotidian group ($P = 0.02$) and the mean haemoglobin concentration rose from 11.5 (± 1.8) to 12.9 (± 1.4) g/dl ($P = 0.008$). There was no significant change in erythropoietin dose or haemoglobin concentration in the conventional HD group [46]. The results of this study suggest a benefit from daily HD on renal anaemia, which, however, cannot be distinguished clearly from the effect of increased dialysis dose. However, some reports showed no significant change in haematocrit or haemoglobin levels in patients undergoing daily HD and increased requirements in erythropoietin dose in NDHD, secondary to an increased quantity of blood loss, have even been reported [47]. Probably, additional studies are needed to elucidate the effects of daily HD on renal anaemia.

Improvement of phosphataemia control

Optimal control of serum phosphate concentration has been reported with NDHD, with possible necessity of phosphate supplementation due to excessive dialysis loss. The issue of hyperphosphataemia control deserves consideration, as phosphate removal by HD has always been far from adequate, given the fact that phosphate is located mainly in the intracellular compartment and, therefore, is characterized by double-pool kinetics. Consequently, in well-nourished dialysis patients, hyperphosphataemia is nearly inevitable and its consequences have characterized most of the HD panorama, with the need for phosphate binders and the development of refractory hyperparathyroidism. A recent analysis from the London Daily/Nocturnal Hemodialysis Study cohort has confirmed the adequate control of pre-HD serum phosphate levels by NDHD, allowing the discontinuation of all phosphate binders. Serum calcium levels also fell and required an increase

in dialysate calcium concentration to 1.75 mM/l to avoid hypocalcaemia [48]. This was not observed with SDHD, as expected from the consideration that increasing dialysis efficiency is not the proper way to increase removal of intracellular solutes. The effect of NDHD on hyperphosphataemia is worth emphasizing, considering that an increased body of evidence has accumulated associating hyperphosphataemia with cardiovascular calcification and increased mortality risk from cardiovascular disease [49,50]. Recently, the calcium load, to which calcium-containing phosphate binders give a non-negligible contribution, has also been associated with increased cardiovascular calcifications [51]. With respect to this, NDHD eliminated oral intake of approximately 8 g elemental Ca/week owing to withdrawal of phosphate binders [48]. In conclusion, the benefits that can be expected from NDHD are optimal control of hyperphosphataemia, reduced patient calcium load (avoidance of phosphate binders + increased dialysis calcium loss), improved control of hyperparathyroidism and prevention of the deleterious effects of the above factors on cardiovascular system. Of course, care has to be paid in avoiding the negative effects of excessive calcium and phosphorus depletion.

Improvement of nutritional status

In the study by Woods *et al.* [41], post-HD weight fell by 1.0% within 1 month of starting daily HD (indicating better control of fluid overload). After the initial drop, post-HD weight increased at a rate of 0.85 kg per 6 months, indicating an anabolic state. Accordingly, serum albumin rose by 0.29 g/dl ($P < 0.001$) between months 1 to 12 of daily HD treatment. These data have recently been confirmed by Galland *et al.* [52], who, shifting eight patients from conventional thrice weekly HD to SDHD, observed a significant increase in serum albumin, prealbumin, total cholesterol concentrations and daily protein intake. The amelioration in the biochemical parameters of nutrition was accompanied by a significant increase in dry body weight and lean body mass.

Reduced advanced glycation end-products and oxidative stress

Preliminary studies have shown that SDHD is associated with a reduction in serum markers of oxidative stress, as shown by the reduction in pentosidine-like advanced glycation end-product (AGE) compounds, AGE-related total fluorescence and protein-linked pentosidine [53]. In accordance with this study, SDHD has been reported subsequently to be associated with a reduction, compared with standard HD, in other glycation indices of plasma, measured by a new high-performance liquid chromatography method: the early product furosine and the advanced products protein-bound and free pentosidine, and two heterogeneous classes of low molecular mass AGE peptides [54]. Uraemia is characterized by an increase in oxidative stress, compared with the general population, which could be, in part, responsible for uraemic toxicity and accelerated atherosclerosis [55]. Therefore, the possibility of interfering with the generation of oxidative compounds by means of daily HD is a modern and fascinating issue in the clinical approach of uraemic patients.

Improvement of quality of life

The patient's self-reporting of improved quality of life has been constant from the beginning of daily HD. In the London Daily/Nocturnal Hemodialysis Study, 23 patients (11 patients, SDHD; 12 patients, NDHD) were compared with 22 conventional thrice weekly HD patients serving as controls [56]. All patients completed three sets of quality-of-life assessment tools. Overall, the reduction in symptoms showed better fluid management, because quotidian HD patients reported experiencing fewer and less severe crampings during dialysis, fewer headaches, less hypotension, fewer episodes of dizziness, decreased fluid restriction, decreased interdialytic weight gain, fewer episodes of shortness of breath and a reduction in the sensation of easily feeling cold. Quotidian HD patients maintained functionality throughout the study period, whereas control patients showed a significant loss. Given the choice, all patients chose to remain on quotidian HD therapy after having switched from conventional HD therapy.

Sleep apnoea is common in patients with chronic renal failure and is not improved by either conventional HD or PD. NDHD has been shown to improve significantly sleep apnoea and hypopnoea in 14 patients switched from conventional HD, accompanied by significant increases in the minimal oxygen saturation, transcutaneous partial pressure of carbon dioxide and serum bicarbonate concentration [57]. Moreover, it has been shown to partially ameliorate the quality of sleep itself, as shown by the reduced incidence of daytime sleepiness in NDHD patients [58]. It is important not to forget that sleep disturbances in dialysis patients do not simply affect the quality of life, but are also related to autonomic nervous system dysfunction and, as such, to cardiovascular events [59]. Recently, interesting results have been also reported coupling daily dialysis with online haemodiafiltration (HDF). Switching eight patients from standard online HDF (4–5 h three times a week) to daily online HDF (2–2.5 h six times per week) led to the disappearance of post-dialysis fatigue, a reduction of phosphate binders, an improvement of nutritional status and an important reduction of cardiovascular risk factors [60].

Lights and shadows of daily HD

A growing number of reports have been recently devoted to the issue of more frequent HD, either SDHD or NDHD. Most of these articles highlighted the successes obtained by these programmes, with a fragmented look at specific areas and outcomes. The present review of published results from the use of daily

HD shows that universal improvement is noted in dialysis adequacy, blood pressure control, fluid and electrolyte balance, cardiac remodelling and performance, anaemia, phosphate control, nutrition and quality of life. Considering that all of these parameters have been characterized in the literature as surrogates for patient mortality, one could anticipate that daily HD might be associated with improved patient survival as well. As a matter of fact, the report by Woods *et al.* [41] indicated an excellent patient survival (93% at 2 years and nearly 80% at 5 years). However, comparative data confronting daily HD with conventional thrice weekly HD, with respect to mortality and other hard endpoints, is still lacking. Moreover, studies on daily HD published so far share common limitations, of which the reader must be aware in order to evaluate daily HD in the correct perspective. Data reporting is often incomplete. Most studies are retrospective and do not have adequate control groups. Patient populations are often different from the standard HD population and all have small numbers that flaw statistical analysis. Non-uniformity of patient selection and study design prevent accurate comparison and pooling of patient data. In some instances, the same patients have been reported in several studies, analysing different outcomes separately (see the quoted London Daily/Nocturnal Hemodialysis Study [48,50,58]). Prospective analyses are characterized by short follow-up times. The possibility of reporting bias (i.e. only positive results are published) is always present. It is needless to underline that no randomized controlled trials have been performed with daily HD. In spite of these concerns, a very recent prospective study confirmed, again, the positive effects of switching 21 patients from thrice weekly HD to SDHD over a 4 week observation period: there were improvements in blood pressure, intradialytic and interdialytic symptoms and urea kinetics and dynamics. There were fewer machine alarms and less need for nursing interventions during dialysis. Nutrition and quality of life began to improve [61]. In our opinion, an impartial conclusion on the clinical outcomes of daily HD should be that, despite data that can be characterized as preliminary and mainly anecdotal, the pathophysiological premises and the clinical results reported so far show remarkable patient improvement with daily HD worthy of serious consideration by the renal community. However, we have not yet reached definitive proof for the conclusion, on an evidence-based ground, that daily HD is superior to conventional thrice weekly HD with respect to patient survival.

Apart from the methodological aspects, other major clinical, economical and organizational concerns have been raised concerning daily HD.

Clinical concerns

A more frequent repetition of HD may lead to increased loss of amino acids, glucose, phosphate and vitamins, with the possibility of inducing deficiency syndromes. However, the clinical reports available to date agree in reporting improved nutritional status [41,52].

Another concern regards the possibility of enhancing bioincompatibility phenomena, due to more frequent exposure of blood to bioincompatible material. Again, this concern can probably be ruled out when considering that the dialysis membranes presently in use are more biocompatible than those of the past and that a primary role in bioincompatibility is played by the microbiological quality of the dialysate, which should be paid more attention. Considering that a large part of bioincompatibility acts via inflammatory processes, one would have expected high inflammation indexes, had the more frequent blood–membrane contact been the cause of enhancing bioincompatibility. This has not been the case in the present experience with daily HD [46].

The other major concern is the possibility of enhancing complications related with daily use of the vascular access, be it an arteriovenous fistula or a catheter. Of note, Woods *et al.* [41] reported an excellent primary arteriovenous fistula patency with daily HD (92% at 2 years). Another retrospective study even reported, by both univariate and multivariate survival analysis, a higher risk for arteriovenous fistula occlusion with thrice weekly HD than with daily HD [62]. This somewhat surprising result might be ascribed to the higher incidence of hypotension episodes with three weekly HD, favouring vascular access clotting. Therefore, daily HD might not have adverse effects on vascular access closure. Moreover, single-needle technology has been developed to reduce the number of punctures and, consequently, the patients' discomfort with daily dialysis.

Other concerns relating to vascular access are the possibility of accidental disconnection of the lines with consequent bleeding and/or air embolism. This might effect NDHD in particular, as the patients are asleep at night. Initially, the Toronto group used a central venous catheter for vascular access (Uldall-Cook catheter), equipped with the InterLink connection system to prevent bleeding and air embolism. Recently, they have started to use arteriovenous fistulas with use of plastic cannulas instead of dialysis needles [63].

The recent study by Williams *et al.* [61] confirmed the good safety profile of SDHD: no increase in vascular access complications and no significant changes in blood chemistry and haematological parameters were observed.

Organizational and economic concerns

Patient acceptance may represent an objective obstacle to a daily HD programme, which can be overcome only by a good relationship and trust between patients and doctors. Once the patient has experienced improved well-being, it is doubtful he will deny his consent to be kept on daily HD [56].

Obviously, doubling HD frequency will imply doubling the cost of disposable materials, treatment preparation time and patient transportation and will potentially cause a problem regarding the available infrastructure. These problems can be solved, in part, by maximally favouring home daily HD and the use of continuous remote telecontrol systems to facilitate patient surveillance, while reserving in-centre daily HD for patients requiring close clinical monitoring, because of serious comorbid conditions or limited autonomy in self-caring (in the absence of a valid partner). With respect to the latter patient population it is worth underlining at this point that ill patients affected by severe comorbidities are those most likely to benefit from daily HD programmes [64].

With respect to the concerns regarding increased costs, it is worth mentioning a recent economic analysis of daily HD reports from the literature, which suggested that this treatment modality might provide better outcomes and savings when compared with conventional HD (total annual treatment costs for one US patient on conventional HD in 1998: $68 400; savings for short-daily in-centre HD: $12 500 [18%]; savings for NDHD: $15 600 [23%]) [65]. Similarly, reduced costs with NDHD compared with standard HD have been reported by Pierratos' group [66]. However, larger, more-extended controlled studies are needed to establish whether daily HD fulfils these promises.

Final accord

After intensive discussion, the panel reached consensus on the following key points.

Principles of dialysis quantification

Dialysis adequacy is a concept that overcomes simple clearance calculations from laboratory data, but includes both laboratory evaluations (indices of solute removal, anaemia status and biochemical nutrition parameters) and an evaluation of the patient's clinical status (such as blood pressure control, overhydration signs, dialysis-related symptoms, appetite and quality of life).

Given the above premise, there is a need for objective quantification of solute removal to assess delivered dialysis dose. Urea has traditionally been chosen as a marker for uraemic toxicity. From the mechanistic analysis of the NCDS, the Kt/V_{urea} index of dialysis adequacy emerged. The same principles can be applied to PD, where weekly Kt/V_{urea} and creatinine clearance are used.

As the original single/double-pool variable-volume UKM is not easy to use because of the complex calculations required, generally simplified formulas are used to quantify HD dose. The most accurate is the Daugirdas formula [14], allowing calculation of single-pool Kt/V_{urea}, which can be adjusted to double-pool Kt/V_{urea} by means of the Daugirdas-Schneditz equation rate [15]. Attention has to be paid to the modality of blood sampling for urea concentration determinations. The present international guidelines recommend minimum values of dialysis adequacy indices. For HD, a single-pool Kt/V_{urea} of $\geq$1.2 and a URR of $\geq$65% for thrice weekly HD (DOQI Guidelines) or a double-pool Kt/V_{urea} of $\geq$1.2, single-pool Kt/V_{urea} of $\geq$1.4 (European Best Practice Guidelines). For PD, a weekly Kt/V_{urea} of $\geq$2.0 and a weekly creatinine clearance of $\geq$60 l/1.73 m^2.

Recent randomized controlled trials on dialysis adequacy

Given the body of evidence coming from observational studies that increasing dialysis dose is associated with a progressive improvement in patient survival, two randomized controlled trials (HEMO Study for HD and ADEMEX study for PD) have investigated whether increasing the delivered dialysis dose well above the minimum targets recommended by the DOQI Guidelines would improve patient outcome.

The findings of both studies were apparently negative. However, the results should not be used to arbitrarily reduce dialysis dose and, particularly, HD treatment time.

Although some criticism can be made to both of them as to their internal and external validity, present evidence supports the notion that it may not be useful to increase dialysis dose above certain values in thrice weekly HD and PD.

In the search for an improvement in patient outcome, PD is hardly the solution, as it is limited by the surface area, capability volume and permeability characteristics of the peritoneal membrane. In contrast, HD can be improved by increasing its frequency.

Rationale and schedules of daily HD

Daily HD means an HD frequency of at least six treatments/week.

Daily HD is more physiological than conventional thrice weekly HD, as it allows lower pre- and post-HD blood solute concentrations and, particularly, lower oscillations in concentration. Also, sodium-water overload is removed much more gradually.

Daily HD programmes are currently divided into short daily HD (1.5–3.0 h per treatment, six treatments per week, use of high-efficiency membranes, high blood and dialysate flow rates) and nocturnal daily HD (6–8 h overnight treatments, six treatments per week, standard-small membrane, low blood and dialysate flow rates).

Daily HD: main outcomes

Daily HD has been associated with improvements in many outcomes, including blood pressure control, left ventricular hypertrophy and cardiac performance,

renal anaemia, hyperphosphataemia control, nutritional state and markers, oxidative stress markers, quality of life (including sleep) and good patient and vascular access survival.

Lights and shadows of daily HD

The clinical outcomes of daily HD have been described in preliminary and mainly anecdotal studies including small numbers of patients. Despite this limitation, the results are promising and worthy of serious consideration by the renal community.

Prospective and controlled studies, with sufficient patient numbers, focusing on morbidity, mortality and economic aspects are required: (*a*) to convince institutional payers regarding an appropriate reimbursement; (*b*) to convince dialysis patients to accept daily treatment; and (*c*) to provide appropriate infrastructures where necessary.

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