

## **II.1 Haemodialysis dose quantification: small solutes**

### **Guideline II.1.1**

**A. Urea is the most suitable marker for the uraemic toxins in the range of the low MW solutes.  
(Evidence level: B)**

### **Guideline II.1.2**

**A. HD dose should be expressed in terms of equilibrated Kt/V (eKt/V) with the rate equation based on the regional blood flow two-pool urea kinetic model [41]:**

$$\mathbf{eKt/V = spKt/V - (0.6 \times spKt/V/T) + 0.03}$$

**(with an arteriovenous access)**

$$\mathbf{eKt/V = spKt/V - (0.47 \times spKt/V/T) + 0.02}$$

(with a venovenous access, i.e. absence of cardiopulmonary recirculation).  
(Evidence level: B)

C. The value for the single-pool Kt/V (spKt/V) should be derived from the formal single-pool variable volume urea kinetic model (spUKM) [42]. As an alternative, the natural logarithm equation provides the most accurate estimate of spKt/V [43]:

$$\text{spKt/V} = -\ln(\text{Ct}/\text{Co} - 0.008 \times \text{T}) \\ + (4 - 3.5 \times \text{Ct}/\text{Co}) \times \text{dBW}/\text{BW}$$

where: K = dialyzer clearance (ml/min); V = urea distribution volume (ml); t, T = treatment time (in minutes and hours, respectively); Co, Ct = start and end-session urea (or BUN) concentration; dBW = intradialytic weight loss (kg); BW = end-session body weight (kg).

D. Sampling Ct 30 min after the end of the session and applying the spKt/V equation gives the eKt/V value [44] (see also Guideline II.4.1).

### Guideline II.1.3

A. Based on the available evidence the minimum prescribed HD dose per session for a thrice-weekly schedule should be:

urea eKt/V  $\geq$  1.20 (sp Kt/V  $\sim$  1.4).

Twice-weekly schedules are not recommended.  
(Evidence level: B)

### Commentary on Guideline II.1.1

Urea is the bulk catabolite of protein, and constitutes the great majority of waste nitrogen accumulated between HD sessions [45].

- It is a low MW solute, with unchanged chemical structure.
- It is easily measured in blood.
- Its distribution volume corresponds approximately to the volume of the total body water.
- Its kinetics during HD have been definitely substantiated.
- It is readily dialysed.
- It is widely used for measurement of dialyzer and session efficiency in removal of small solutes.

HD dose, based on urea measurements, correlates with morbidity and mortality in chronic HD patients. Convincing evidence, based on large database retrospective and historical prospective studies, now accumulated that HD dose, quantified as the amount of urea removal, correlates positively with the therapy outcome, in terms of morbidity and mortality [46, 47–56]. HD dose has been associated with the major causes of death in HD population, i.e. cardiovascular, cerebrovascular, and infectious causes [57].

### Commentary on Guideline II.1.2

Recommendations about the method of HD dose quantification arise from the review of the available literature concerning: (i) the theoretical formulation of existing methods, (ii) problems related to their practical implementation, (iii) validation in experimental studies, and (iv) relationship with the major therapy outcomes reported in large randomized or historical prospective studies.

The following methods have been considered.

#### Formal urea kinetic model

Formal urea kinetic model, in its single-pool, variable volume formulation (spUKM) [42], allows the iterative, computer-based estimate of urea distribution volume (V) and urea generation rate (G), when calculations are initialized with a default value for the dialyzer urea clearance (K).

*Advantages.* When rigorously applied, the model provides reliable, simultaneous information about:

- The efficiency of the HD session, which is expressed as the fractional urea clearance Kt/V, resulting from the product of K and treatment time t, normalized for the size of the patient (by dividing the UKM-derived value for V) [58].
- The nutritional status of the patient. The normalized protein catabolic rate (nPCR), measured in g/kg/24 h, may be derived from the kinetic estimates of G and V according to ref. [59]. The derived value for nPCR provides an estimate of the dietary protein intake in steady state, and permits longitudinal analysis of the patient's nutritional status [45,58].
- An individual treatment time prescription, to achieve the target Kt/V of the session may be derived, once V and K are defined, with the equation:  $t = \text{target Kt/V} \times V/K$ .

#### Drawbacks.

- Application. Three blood samples are required for the solution of the main algorithm: pre- and post-HD blood urea for the first session of the week and pre-HD blood urea for the second session of the week.
- Dialyzer clearance value. Dialyzer urea clearance K, either derived from the dialyzer mass transfer-area coefficient (KoA), or with the classical blood-side technique, overestimates the true value of the effective mean clearance of the session [60], carrying an unpredictable error on Kt/V estimate [61]. Moreover, K may be significantly influenced by the dialysate flow rate [62,63]. Implementation of formal UKM requires additional software with an updated database to extrapolate the correct KoA value for the dialyzer, blood and dialysate flows applied in the examined treatment session.
- Urea compartmentalization. Single-pool UKM model does not account either for post-dialysis

urea rebound (PDUR), resulting from intercompartmental solute re-equilibration occurring at the end of the session [64,65], or for recirculation through the vascular access [66–68]. As a consequence of the underestimation of  $V$ , single-pool based calculation of HD dose ( $spKt/V$ ) will invariably overestimate the effective delivered dose ( $eKt/V$ ) [44,64,65,69,70] and the actual value for  $nPCR$  [67,69]. The magnitude of PDUR, measured as the per cent increase in urea concentration from the end-HD to the equilibrated value, varies between 10 and 17% in standard HD sessions [64] and 24% after high efficiency treatments (urea clearance 500 ml/min) [70], up to values of as much as 45% in some patients [70]. Among the relatively few predictive factors for PDUR the efficiency of the session (high dialyzer  $K$ , or high  $Kt/V$ ) influences directly the magnitude of urea rebound [65,69,70]. Also, short-time sessions (<3 h), HD sessions in small  $V$  patients [71,72], or complicated by haemodynamic instability [73] are followed by greater rebound. A difference of  $\sim 0.2$  U between  $spKt/V$  and  $eKt/V$  was found in standard HD [67]. This difference increases unpredictably in high efficiency treatments [67,70,74].

The following approaches have been proposed to simplify the use of the formal  $spUKM$  model, or to overcome the drawbacks implicit in its use:

- Two-sample  $spUKM$  [75] prevents the need for sampling at the beginning of the second session, by inferring on a steady-state weekly urea profile, but it carries the same drawbacks as the formal three-sample  $spUKM$ .
- A modified algorithm of  $UKM$ , in which an arbitrary value for  $V$  is assumed to initialize iterative calculations of  $K$  and  $G$ , avoids the imprecision about assumptions or measurement of  $K$  [76]. However, this method may introduce another type of error, related to erroneous assumptions of  $V$  value from nomograms or anthropometric formulae [77].
- Other solutions have been proposed to obviate for the errors resulting from neglecting PDUR:
- Substitution of the end-HD urea concentration  $C_t$  with its equilibrated value  $C_e$ , and assumption of an arbitrary  $V$  to calculate iteratively  $K$  and  $G$  [76], provides the effective mean  $K$  and  $eKt/V$  values of the session [78]. However, this method is impractical, requiring a urea measurement at least 30 min after the end of the session [64].
- Estimate of PDUR with an intradialytic blood sample taken 70 min following the start and an equation derived from the two-pool model [79]. This method requires an additional blood sample. Small errors in the intradialytic sample result in larger errors in  $C_e$  estimate [80], and wide limits of agreement with the kinetic  $eKt/V$  have been demonstrated with the application of this method [81].
- A different approach introduces the ‘patient clearance time’ [65] ( $tp$ ), a single time constant

accounting for cardiopulmonary recirculation and intercompartment re-equilibration and representing the time needed to clear all body compartments when the dialyzer clearance is infinite.  $tp$  calculated after short haemodiafiltration (HDF) and standard HD was similar and averaged 35 min. The true HD dose ( $eKt/V$ ) may be calculated from the product of  $spKt/V$  by  $t/(t+tp)$ , where  $t$  is the length of the session in minutes. Results of this method agreed with those calculated using a 60-min post-HD sample [65]. However, more extensive validation is lacking.

#### *Two-pool model*

Both the cell membrane two-pool model [82], and the regional blood flow two-pool model [83] provide a more physiological description of urea (and other solutes) kinetics [84]. In the cell model, concentration disequilibrium between intracellular and extracellular space during HD is the effect of the limited solute permeability of the cell membrane. The regional blood flow model theorizes delayed solute diffusion from low perfused to highly perfused organ systems. In both cases PDUR is the effect of the intercompartmental re-equilibration occurring at the end of HD [64,83]. Clinical application of multicompartmental models for  $Kt/V$  estimates requires too many input parameters [85], some of which (i.e. the intercompartmental solute clearance) are of impossible individual calculation. Thus, the use of these models is restricted to experimental studies.

#### *Short equations*

Several simplified equations, that are approximate algebraic solutions of the differential equations used in  $UKM$ , estimate HD dose from the pre- to post-HD urea nitrogen ratio, variably accounting for ultrafiltration (UF), session length ( $t$ ), and PDUR (for an extensive review see [86]). Among them:

*The logarithmic estimate of  $spKt/V$*  also accounts for the effects of time and intradialytic body weight loss on the amount of solute convected by UF. This equation shows good correspondence with the results of the kinetic  $spKt/V$  calculations in a range of  $spKt/V$  values between 0.7 and 2.1 [43,44]. It has been widely adopted in clinical practice. HD dose estimated in terms of  $spKt/V$  with this method has been related to morbidity and mortality in large database studies [47,49–53,57,87]. As such, this method may be considered the most correct alternative way to calculate  $spKt/V$ , when the use of formal  $UKM$  is unavailable.

*An estimate of the  $eKt/V$*  has been derived from the  $spKt/V$  using a rate equation based on the regional blood flow two-pool  $UKM$  [88]. This method avoids the error implicit in single-pool calculations, neglecting PDUR and overestimating the HD dose. Results of the application of this equation show narrow limits of agreement with  $eKt/V$  calculated kinetically [44,81,89],

even if it is less predictive in high efficiency treatments and in patients with very high PDUR [67]. Similarly to  $\text{spKt/V}$ , increasing values of  $\text{eKt/V}$ , as an index of HD dose, have been related to a reduced risk of death in at least two large registry studies [53,56]. The  $\text{eKt/V}$  is the method for quantifying the HD dose adopted in the ongoing HEMO Study, a US NIH (National Institutes of Health) multicentre, randomized prospective trial to test the effects of HD dosage and membrane flux on morbidity and mortality [89].

*The urea reduction ratio (URR).* The URR [90] has been shown to be a predictor of morbidity and mortality in HD population [48,52]. However, its application in individual therapy quantification introduces variable and significant errors [91–94]. Its fixed, single-pool formulation does not account for PDUR due to recirculation and re-equilibration, and for the effects of UF and residual renal clearance. The linear correlation between URR and  $\text{spKt/V}$  shown in the range of commonly observed  $\text{Kt/V}$  values (0.6–1.3) becomes exponential for  $\text{Kt/V} > 1.3$  [95]. As an effect of the above factors, a broad range of  $\text{Kt/V}$  values may be observed at each URR value, and differences become even broader with increasing URR values  $> 65\%$  [91,96]. Even of simple calculation, URR is an unacceptable index to prescribe and monitor HD therapy, in that its important drawbacks may negatively impact on therapy outcome [91]. A method of correcting URR for PDUR, by using the equilibrated end-session urea concentration has been suggested [97,98], but not extensively validated.

#### *Other methods*

*Direct dialysate quantification.* With this method, the total mass of urea removed is quantified by collecting the total spent dialysate. The model, in its modified formulation (mDQ) [99], obviates the error of the original model [100], and permits an accurate estimate of  $V$  and the effective  $K$  of the session, accounting for the re-equilibration process. Mass balance equations, applied to the interdialytic interval, are used to calculate  $G$  (and  $n\text{PCR}$ ). mDQ results are close to those of the two-pool model [101]. However, its bulky application prevents its widespread use in clinical practice. Other derived applications, based on fractional dialysate collection [102,103], or two dialysate samples at the beginning and end of the sessions [104], may simplify the practical use of DQ model. Extensive validation of these methods is lacking.

*Solute removal index (SRI).* SRI [105] is the per cent amount of pre-HD urea body content that is removed during the treatment session and recovered in the total spent dialysate. Its major advantage over  $\text{Kt/V}$  is that it provides a unified index valid for comparing therapy modalities (HD, CAPD, APD), different in frequency and duration [106]. Moreover, SRI obviates clearance corrections for access and cardiopulmonary

recirculation, and compartmental disequilibrium, and does not require a variable scaling factor to correct for therapy frequency. Even if SRI is theoretically correct, it is rarely used and its validity has not been proven in large studies.

*Product urea clearance  $\times$  time (Kt).* When HD dose is measured with  $\text{Kt/V}$  or URR, paradoxical observations may arise [55] like that of an increased death-risk at the highest dose (J-shaped curve [94]).  $V$ , as proxy for nutritional status, has survival-associated properties of its own [107], and indexing  $\text{Kt}$  to  $V$ , two measures related inversely and independently to mortality, can lead to erroneous statistical inferences. Paradoxes can be managed if  $\text{Kt/V}$  is disaggregated into two separate outcome-based measures: HD dose and body mass. In a retrospective analysis of a large US database the product  $\text{Kt}$  has been strongly associated with survival over its entire range, whether adjusted for body size estimates or not. On this basis,  $\text{Kt}$  has been proposed as a more rigorous index of HD dose [55]. A gender-dependent minimum mortality risk, computed in cross-sectional analysis, shows that no additional benefit above a  $\text{Kt}$  of 40–45 and 45–50 l/treatment for females and males, respectively, may be expected irrespective of size and volume of the patient [55]. Nevertheless, a large observational longitudinal study, in which patients have been stratified by body size, indicates no statistical evidence that the association between  $\text{eKt/V}$  and mortality differs by body size. Yet, at any level of  $\text{eKt/V}$ , patients with larger body size have less mortality risk than smaller patients [56], possibly as an effect of a better nutritional status. However, small size caused by genetic factors cannot be distinguished by small body size caused by malnutrition [56]. Thus, the complex interactions between volume, nutrition, and HD dose are not yet fully clarified.

#### *Devices for on-line monitoring of HD efficiency*

Technological progress now offers promising tools to obtain on-line reliable and easy measures of HD efficiency.

*Conductivity-based method for determining  $\text{Kt/V}$ .* This method automatically determines on-line the effective ionic dialysance (ID), corresponding to the effective urea clearance ( $K$ ), without the need of blood and dialysate sampling [108–112]. This method is easy, non-invasive and inexpensive. However, the actual correspondence of the ID with the effective urea clearance of the session has not yet been demonstrated. Moreover, an extensive validation of this method is still lacking.

*On-line urea monitoring of the effluent dialysate,* with an automatic urea sensing monitor operating on spent dialysate, has been only validated in a study with a small number of patients [99,106]. Dialysate measurement, on which this method is based, has the

advantage of avoiding the difficulty to quantify urea disequilibrium during each treatment.

### Commentary on Guideline II.1.3

#### *Minimum and prescribed dose*

Based on the reports evidencing the association of the delivered dose of HD with the death risk [48,49,50–52], most published Best Practice Guidelines for HD therapy indicate the minimum dose of HD to be delivered, indexed by spKt/V or URR, and the mean suggested doses to achieve the target (Table 1).

Prescription in terms of eKt/V ( $>1.05$ ) is given by the Guidelines of the Italian Society of Nephrology [116].

#### *Effects of increasing HD dose beyond the recommended limits*

The relative risk (RR) of death did not decrease further beyond values of Kt/V  $>1.3$  or URR  $>70\%$ , either adjusting [52], or not for co-morbid conditions [48].

In contrast, further benefit in term of reduced mortality with increased doses of therapy has been suggested by other studies in the general dialytic population, not correcting RR for co-morbidity [50,51], and in a selected group of diabetic patients [49]. However, few patients are included in the group with Kt/V  $>1.4$  in the above databases, and the possibility of inferences on the base of such small patient groups has been argued [117].

Remarkably low mortality rates have been reported in Tassin, in association with long HD, in which the overall mean ( $\pm$ SD) levels of spKt/V were  $1.67 \pm 0.41$  [118]. Cox analysis including five co-variables confirmed that survival was linked to an optimal control of blood pressure and decreased cardiovascular mortality, favoured by a better control of dry body weight during the long HD sessions. Analysis also suggested that survival improvement might not be expected from a spKt/V  $>1.60$  [119].

A survey of the medical literature of the US Renal Physicians Association has reported an increase in the quality-adjusted life expectancy (QALE) of HD patients with increasing Kt/V up to a value of 2. However, the recommended adequate level of therapy (Kt/V  $>1.2$ ) has been based on a decision model accounting also for the cost-effectiveness of the

strategies aimed at increasing the removal of uraemic toxins [120,121].

More recently, a progressively decreasing risk of death with increasing spKt/V 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 [53]. When the RR of death was adjusted for the length of the sessions, Cox model confirmed the independent predictive effect on outcome of spKt/V [122] or eKt/V [54] over the entire tested spectrum.

Knowing that erroneous statistical inferences are possible from retrospective uncontrolled studies, with complicated case mix, and data transformations, the question of whether increasing the dose of HD improves outcome remains unresolved. Definite conclusions can be drawn only from prospective controlled studies, as the ongoing HEMO Study, comparing two well-defined levels of therapy [123] (spKt/V 1.32 vs 1.67, or eKt/V 1.05 vs 1.45). However, past observations [50,51,119], and more recent reports [53,54,122], suggest the possibility that some further benefit might be achieved with increasing HD doses. EBPG recommendations also account for the fact that careful assessment and monitoring of the treatment sessions (adequate flows and time, etc.), coupled with more efficient and permeable dialyzers, now available at trivial additive cost, may achieve easily the recommended target without relevant economical implications.

**Table 1.** Proposal for spKt/V of different Best Practice Guidelines

	Year	spKt/V		URR %	
		Minimum	Suggested	Minimum	Suggested
NKF-DOQI [113]	2001	1.2	1.3	65	70
The Renal Association [114]	1997	1.2	1.35–1.4	65	
Canadian Society of Nephrology [115]	1999	1.2		65	

## **II.2 Haemodialysis dose quantification: middle molecules (MM)**

### **Guideline II.2.1**

**A.  $\beta$ 2-m is representative in its kinetic behaviour of other MM and peptides of similar size, and may be used as a marker for such molecules.**

***(Evidence level: B)***

### **Guideline II.2.2**

**A. To enhance MM removal, synthetic high-flux membranes should be used. Additional strategies, such as adding a convective component, or increasing HD time or frequency, should be used to maximize MM removal.**

***(Evidence level: B)***

## Commentary on Guideline II. 2.1

### *MM markers*

No surrogate molecule has been identified yet with the characteristics of an ideal marker for MM uraemic toxins.

*Vitamin B12.* Vitamin B12 (1350 Da), the most used marker for *in vitro* characterization of dialyzers [124], is not useful *in vivo*, because of its extensive binding to plasma proteins. Inulin (5200 Da), even widely studied [124] requires a methodology not suitable for clinical practice.

*Gentamicin.* Gentamicin (518 Da) [125], ofloxacin (361 Da) [126], and vancomycin (1448 Da) [127] more recently proposed as marker molecules in light of their appropriate MW, minimal protein binding, and small distribution volume, lack experimental and extensive clinical validation.

*$\beta_2$ -m.*  $\beta_2$ -m is easily measured in blood. Even if its intradialytic kinetics has not been clarified definitely yet, its transport through different dialyzer membranes has been widely studied [128–137]. It is only removed through high-flux membranes, able to reduce the basal  $\beta_2$ -m concentration by 23–30% with respect to cellulosic membranes [129,138–141]. The use of high-flux synthetic membranes has been associated with reduced incidence of bone amyloidosis [142], and carpal tunnel syndrome [140,143,144].

### *Methods of MM removal quantification*

Methods used to evaluate the efficiency of a dialyzer, or a dialytic strategy in removing MM toxins, have substantial drawbacks.

*Reduction ratio.* The ratio between the final and initial plasma solute concentration of the session:  $R = (1 - C_t/C_o)$  has been used in the past for  $\beta_2$ -m [130], and recently applied to the novel uraemic retention solutes, like pentosidine [14,15,145,146], homocysteine [147,148], ADMA [35,37], and p-cresol [149].

Correction of the  $C_t$  value has been suggested to account for intradialytic change in distribution volume (the extracellular space) when calculating this ratio for  $\beta_2$ -m [150].

This ratio overestimates the amount of solute removal, not accounting for the effect of post-HD rebound. As shown theoretically with two-pool modelling [151], intercompartmental concentration dysequilibrium during HD, and thus post-HD rebound, depends on the relationships between the dialyzer clearance  $K_d$ , the intercompartmental clearance  $K_c$  and compartment volumes for each solute. Inulin is more efficiently removed from its smaller perfused volume ( $V_p$ ) than urea, as indicated by its higher ratio  $K_d/V_p$ . Conversely, inulin refills at a slower rate from its non-perfused compartment, according to its lower  $K_c/K_d$  ratio [151]. In the more general case, these factors play in favour of a larger and more prolonged

rebound for a MM than for a small solute. The *in vivo* kinetics of a MM during and after HD may deviate unpredictably from that of a marker molecule, due to known and unknown factors. The extent and the rate of formation of protein bindings [146], removal of precursors/substrates or reduction of inhibitory activities against relevant enzymes [147] may modify the metabolic rate of a MM and interfere with its generation or removal. This might explain the flat post-HD concentration–time curve observed for pentosidine [146] and homocysteine [147], and the decrease in ADMA concentration up to 5 h after the end of HD [35]. All the above factors may unpredictably affect the reliability of the reduction ratio as a method to quantify MM removal.

*Mean  $\beta_2$ -m clearance of the session.* An equation based on a single compartment model has been proposed to estimate the  $\beta_2$ -m clearance during a session [152]. Assuming extracellular  $\beta_2$ -m distribution, negligible extra-dialytic clearance and solute generation during HD, the equation calculates an average clearance value for the whole session, including removal by diffusion, UF, and absorption.

$$K_{\beta_2\text{-m}} = Q_{\text{uf}} [1 - \ln(C_t/C_o)] / \ln(1 + Q_{\text{uf}} t/V_t)$$

where:  $C_o$ ,  $C_t$  = start and end-session urea concentration;  $t$  = session time (minutes);  $V_t$  = end-session volume of the extracellular space.

This equation, accounting for treatment time, UF, and patient size, carries fewer drawbacks than other methods. However, disregarding the effect of post-HD rebound, it overestimates significantly the effective clearance of the session. By substituting the end-session concentration value with the value taken 30 and 60 min after the end, the equation yields results closer to those calculated from the arterial and venous concentration difference across the dialyzer [152]. However, much longer re-equilibration time has been reported by other authors in the case of  $\beta_2$ -m [135].

*Dialysate quantification.* As a result of the extensive adsorption of most MM to synthetic membranes, direct quantification in the spent dialysate is not a precise method to quantify the removal of such compounds.

Apart from  $\beta_2$ -m, the definition of an ideal marker of uraemic toxicity in the different ranges of the MM is far from being satisfactory. Lack of knowledge of the kinetics of these compounds also prevents to establish an adequate index to monitor the dialytic removal of MM toxins and compare different treatments and populations.

## Commentary on Guideline II.2.2

### *MM removal: effects of flux*

Partial removal of solutes in the size of the smaller MM may be achieved by diffusion even in conventional HD

with unsubstituted cellulose membranes. This has been proven in an acute *in vivo* controlled study using ofloxacin [126] (361 Da) as a surrogate MM. A reduction ratio by 82% has been found for free pentosidine (379 Da) concentration during an acute controlled study with cuprophane membrane [146]. Similar removal (~70%) of this low MM AGE has been observed by comparing a cellulose membrane with high-flux polysulfone (PS), polymethylmetacrylate (PMMA), and polyacrylonitrile (AN69) membranes [145]. Reduction by ~30% in homocysteine (135 Da) concentration has been shown with low-flux membranes [147], and in a randomized study comparing low-flux with high-flux PS [148]. Reduction ratios varying from 20 to 65% have been reported for ADMA (202 Da) during conventional HD [34,37,153]. In these studies the time of sampling was not specified. When reported, an increase in post-HD ADMA concentration was observed, followed by a 65% reduction 5 h after the end of the session [35].

High-flux HD with highly permeable membranes yields more substantial removal of larger solutes, as shown for low MW AGEs (<6 kDa) and for AGE peptides (<12 kDa) in acute controlled studies [154,155], and for AGE-apolipoprotein-B in a randomized study comparing AN69 vs low-flux PS [156]. A significant reduction in triglycerides and increase in high-density lipoprotein concentration and lipoprotein lipase activity have been reported as an acute effect of high-flux HD with PS membranes, not shown with a cellulose membrane [157].

Further enhancement and widening of the molecular spectrum of the removed uraemic compounds may be obtained with all the available highly permeable and biocompatible membranes on both haemofiltration (HF) and HDF. This has been demonstrated for  $\beta_2$ -m [130,136,158–162], for some of the AGE compounds [14], for ADMA [163], for complement fractions, such as factor D (24 kDa) [161,164,165], fraction Ba (33 kDa) [165], C3a (8.9 kDa), C5a (11 kDa) [166], and for pro-inflammatory cytokines as TNF- $\alpha$  (17 kD) [167,168], interleukin-1 (IL-1, 17 kDa) [167], IL-6, and IL-8 [168].

The mechanism by which MM removal occurs through high-flux membranes largely depends on the membrane itself. Several studies support some general conclusions [128,130,134,136,164,166–172]. The predominant mechanism with AN69 and PMMA is adsorption [128,136,168,169,171], while cellulose triacetate shows minor adsorption, and removes MM mainly by diffusion [127,130,168]. In the middle, polyamide shows intermediate characteristics and combines diffusion and convection with a minor adsorption capacity [168]. Polysulfone shows minor adsorption and removes MM mainly by filtration [173]. In general, the degree to which convection augments total solute removal is proportional to the MW of the solute and to the rate of UF [160]. The pore diameter, structure, and chemical properties of the membrane play also an important role [130,134,170,174].

### *Interactions between flux and biocompatibility*

As quoted above, high-flux biocompatible membranes used in convective and mixed techniques seem to extend the amount and the molecular range of toxins removed. However, the role of the high flux is often difficult to dissociate from the biological effects of biocompatibility. In spite of similar dialytic removal, basal levels of pentosidine were lower in patients treated with high-flux PS membranes than with other high-flux or cellulosic membranes, possibly as an effect of minor oxidative stress [145]. High-flux and low-flux PS resulted in similar plasma homocysteine levels in a 3-month longitudinal study, in spite of a significantly greater removal per session obtained with the high-flux membrane [148]. On the other hand, a significant reduction in homocysteine levels was obtained with superflux PS and cellulose triacetate [175]. The use of low-flux polyamide resulted in the most favourable ratio arginine/ADMA concentration when compared with high-flux polyamide during different dialytic strategies [163]. The role of flux in the improvement of lipid profiles with the use of synthetic membranes [176–179] has been claimed by some authors [178] and challenged by others [177]. As reported in a recent prospective randomized study, the use of low-flux and high-flux biocompatible membranes resulted in similar effects on lipoprotein and lipid profiles [148].

No studies have been published on the long-term biological effects of an increased AGE removal with high flux, highly biocompatible membranes. Instead, it is well established that patients treated with synthetic membranes show a reduction in basal  $\beta_2$ -m compared with patients treated with cellulosic membranes [129]. Biocompatible low-flux membranes induce a slower increase in plasma  $\beta_2$ -m with time, independent of the influence of residual renal function [180]. Pre-HD  $\beta_2$ -m concentrations are lower in high-flux HD and HDF than in conventional HD with cuprophane and low-flux biocompatible membranes [139]. Plasma  $\beta_2$ -m is further reduced in high efficiency on-line HDF vs high-flux HD [161]. The last two studies point to a prominent role of flux in the reduction of plasma  $\beta_2$ -m. Even if an intensive extracorporeal treatment fails to return  $\beta_2$ -m concentrations to normal [181], a reduction in plasma  $\beta_2$ -m reduces the incidence of bone amyloidosis [141,142] and carpal tunnel syndrome [140,143,144] (discussed in Section III). The long-term use of synthetic membranes results in a better prevention of cardiovascular events [182] inflammation, malnutrition, and improves the outcome of therapy [140,144,183–187]. It remains unclear whether biocompatibility, or high-flux, or both, may explain these results. Two historically prospective studies on large database suggest that the reduced risk of mortality is associated with the enhanced MM removal promoted by high-flux membranes, independently from the effects related to their biocompatibility [186,188].

### II.3 Haemodialysis dose and residual renal function (Kr)

#### Guideline II.3

**A. In the case of significant residual renal function (Kr), the amount of therapy to be delivered with HD may be estimated with the aid of the equivalent renal urea clearance (EKR). (Evidence level: B)**

#### Commentary on Guideline II.3

In some cases, especially at the start of chronic HD therapy, significant residual kidney function is still present. Its favourable effect on outcome of HD, as well as methods of measurement and reporting, are more extensively discussed in Section I.

The contribution of residual renal clearance to the total urea removal has been computed by Gotch and Keen [190] in terms of equivalent urea Kt/V value provided by the native kidneys: (Kt/VKr) for thrice- and twice-weekly HD, and added to the dialytic Kt/V to yield the total fractional clearance (KTV):

$$\begin{aligned} \text{KTV} &= \text{Kt/V} + 5.9 \times \text{Kt/VKr} \text{ (thrice-weekly HD)} \\ \text{KTV} &= \text{Kt/V} + 10.1 \times \text{Kt/VKr} \text{ (twice-weekly HD)}. \end{aligned}$$

More recently, a kinetic estimate of a time-averaged KT, derived from the spUKM, has been proposed: the EKR [189]. EKR is computed as the ratio of the net urea generation (G, mg/min) to the time-averaged urea concentration (TAC, mg/ml). It defines the averaged urea clearance delivered, in ml/min, as the sum of dialytic plus residual renal clearance. EKR is independent of treatment type and schedule. On the basis of the relation found between EKR and Kt/V, the minimum 'adequate' EKR, normalized for urea volume, is ~ 15 ml/min, corresponding to an spKt/V of 1.4, and can be recalculated to a value of 13 ml/min for an eKt/V value of ~ 1.2.

According to the relation between  $\text{EKR}_c$ , Kt/V, and  $\text{Kr}_c$  ( $\text{EKR}_c = 1 + 10 \text{ Kt/V} + \text{Kr}_c$  for a thrice-weekly schedule,  $\text{EKR}_c = 1 + 6.2 \text{ Kt/V} + \text{Kr}_c$  for a twice-weekly schedule) the minimum dialytic dose in terms of eKt/V to be delivered in presence of Kr varying from 0 to 5 ml/min can be derived with the equations:

$$\begin{aligned} \text{eKt/V HD} &= (12 - \text{Kr}_c) / 10 \text{ (for a thrice weekly HD schedule)} \\ &= (12 - \text{Kr}_c) / 6.2 \text{ (for a twice-weekly HD schedule)} \end{aligned}$$

where

$\text{Kr}_c$  (normalized for urea volume) =  $\text{Kr} \times 40 / \text{Watson V}$ . Kr can be calculated according to the following formula proposed by Gotch [190]:

$$\text{Kr} = U_{\text{vol}} \times U_{\text{urea}} / [t \times (0.25 \times B_{\text{urea}}^1 + 0.75 \times B_{\text{urea}}^2)] \text{ (for a thrice-weekly HD schedule)}$$

$$\text{Kr} = U_{\text{vol}} \times U_{\text{urea}} / [t \times (0.16 \times B_{\text{urea}}^1 + 0.84 \times B_{\text{urea}}^2)] \text{ (for a twice-weekly HD schedule)}$$

where

$U_{\text{vol}}$  = volume of urine collected between the first two dialysis session of the week,

$U_{\text{urea}}$  = urea concentration in the urine,

t = urine collection time,

$B_{\text{urea}}^1$  = blood urea concentration at beginning of collection time,

(= end of first dialysis session of the week),

$B_{\text{urea}}^2$  = blood urea concentration at end of collection time,

(= before second dialysis session of the week).

## II.4 Monitoring of treatment

### Guideline II.4.1

**A. Indices used to quantify the efficiency of HD depend upon the blood urea concentration in pre- and post-HD blood samples. Therefore, it is crucial that these samples be taken carefully with a standard method.**

*(Evidence level: A)*

### Guideline II.4.2

**A. The delivered dose of HD should be checked at least monthly.**

*(Evidence level: B)*

**B. Renal function may only be included in the assessment if it is measured monthly at the same time as the delivered dose of HD. Because renal function may change over time, historic renal function data may not be used.**

### Guideline II.4.3

**A. If a patient fails to receive the adequate HD dose, or if a significant difference between the prescribed and the delivered dose is observed, a search for the cause of the problem must be undertaken.**

*(Evidence level: B)*

### Commentary on Guideline II.4.1

Errors in sampling collection may severely affect the determination of HD dose. A survey on 15 000 HD patients of 202 HD centres in the USA participating in a Collaborative Study of the NKF [191] showed a 5.0% error in pre-HD blood drawing and an 8.4–41.6% error in the post-HD counterpart.

The following precautions should be taken to avoid errors leading to false results:

- Initial sample must be drawn from the arterial needle avoiding dilution with either heparin or washing solution, causing Kt/V to be falsely underestimated.
- Final sample must be drawn avoiding to sample access-derived recirculated blood that will falsely lower the measured blood urea and overestimate

Kt/V [192]. The following procedure should be used at the end of HD:

- Set UF rate to zero.
- Decrease the blood flow to 100 ml/min for 15 s. This is the best approximated time necessary for new, not recirculated blood to rinse the tubing between needle and arterial sampling port.
- Exactly after 15 s draw the blood sample from the arterial sampling port nearest to the patient. In this case the effect of cardiopulmonary recirculation is still present, and the first of the two equations reported in Guideline II.1.2 must be used to calculate eKt/V.
- The final sample may be drawn 1–2 min after slowing the blood pump, when the arteriovenous urea gradient due to the cardiopulmonary effect has dissipated. This method has the advantage to avoid the variability of the cardiopulmonary effect, but is associated with the risk of underestimating the spKt/V, due to the very early effect of intercompartmental urea re-equilibration.
- Equilibrated sample can be obtained 30 min after the end of the session from the arterial needle, after a careful wash-out with the blood of the patient.

- Patient intolerance (haemodynamic instability, cramps) or non-compliance.

A detailed discussion about vascular access function and methods of detecting and measuring recirculation through the vascular access will be reported in the appropriate section.

If no obvious technical procedural or clinical cause may be identified, the following steps should be taken to increase the efficiency of the treatment:

- increase blood flow or dialysate flow, or both,
- change to a more efficient dialyzer (surface, membrane),
- increase treatment time,
- change to a more efficient technique (high-flux HD, HDF, HF).

### Commentary on Guideline II.4.2

The session-to-session variation in Kt/V is small in stable HD patients. Kt/V should be measured monthly in such patients to assure the adequacy of HD [113]. Averaged values of two to three measurements [193] are required to reliably assess the dose of HD in non-compliant or unstable patients, when delivery of the prescribed dose presents frequent problems, or measurements yield variable results.

### Commentary on Guideline II.4.3

In almost 50% of HD treatments resulting in a Kt/V < 1.0, the culprit is impaired delivery of the prescribed amount of HD [194]. Non-compliance with HD, depending on the definition, occurs in 2 to > 50% of patients [195]. In two special USRDS studies on 6251 patients, non-compliance in HD was associated with a 5–35% greater risk of an adverse outcome depending on the cause [195].

The factors involved in impaired delivery of the prescribed HD dose are multiple and often elusive [191,194–197].

- Inadequately applied effective blood flow rate and blood pump speed calibration.
- Blood pump slow down for a significant time (i.e. for hypotension).
- Reduced dialysate flow rate.
- Dialyzer malfunction (channelling, fibre clotting from inadequate anticoagulation).
- Access dysfunction or recirculation.
- Sampling errors.
- Effective treatment time less than prescribed.

## II.5 Dialysis schedules

### Guideline II.5.1

**A. The standard HD dose should be delivered as 3×4 h. Even if the standards of adequacy such as dose expressed as eKt/V are reached, a minimum time of 3×4 h/week is desirable.**

*(Evidence level: B)*

### Guideline II.5.2

**A. Treatment time and/or frequency should be increased in patients with haemodynamic instability or cardiovascular problems. The same may apply for the aged HD patients, who suffer more frequently from the above-mentioned conditions.**

*(Evidence level: B)*

### Commentary on Guidelines II.5.1 and II.5.2

#### *Effects of different HD schedules regarding solute removal*

Dialysis schedules of different frequency have been compared theoretically with an index, the standard  $Kt/V$  (std  $Kt/V$ ) [198], that utilizes the ratio of generated urea to peak urea concentration, and equates all HD doses to continuous therapy. The modelled dose of therapy equivalent to the recommended weekly CAPD  $Kt/V$  of 2.0 was a  $spKt/V$  of 1.2 per 3.5-h session with thrice-weekly HD, or a  $spKt/V$  of 0.4 to 0.3 with daily HD, depending on the length of the session (2–8 h) [198].

The more frequently intermittent HD is performed, the more it approaches continuous therapy. When HD was simulated at different frequency and length with a variable-volume double-pool model [151], it was shown that, relative to a standard three times weekly HD regimen:

- daily/short-time HD of similar total (weekly) duration results in modest (3–6%) increases in effective small solute and MM removal,

- daily low-flow/long-time HD substantially increases the effective removal of all solutes,
- three times weekly low-flow/long-time HD results in comparable effective small solute removal and progressive increases in MM and  $\beta_2$ -m removal.

Treatment time *per se* affects solute removal in spite of similar Kt/V for urea. This is particularly true for intermediate-size molecules [199].

#### *Impact on morbidity and mortality*

*Length of the treatment session.* An adequate removal of small solutes may be delivered in very short times (~2–2.5 h) with high flux, high efficiency treatments [200,201].

Small and time-limited experiences in single renal units [202,203] and reports on large databases [48,52,204], did not show significant effects of the length of the sessions on patient morbidity and survival, provided that patients had received an adequate HD dose (URR > 65–70% or Kt/V > 1.3). However, prescribed HD time in the majority of patients of the latter two studies covered a narrow range, with very few session-time cases of > 5 h, which makes definite conclusions impossible.

Conversely, other reports suggested an association between HD length and risk of death. It is well known that a very long survival was reported by the Tassin Group. Patients dialyzed twice or thrice weekly for a total of 22–24 h/week [118,119,205], had a better survival, less intradialytic complications and better blood pressure control than patients in Europe, the US, and Japan, treated during conventional HD times. Mean spKt/V was remarkably high in the long sessions. However, these results have been ascribed mainly to an excellent control of hypertension, with minimal anti-hypertensive therapy, favoured by a better intradialytic weight removal through smooth UF during the long sessions, and a subsequent reduced cardiovascular morbidity and mortality [206,207].

Recently, a survey on a large Japanese database showed a progressively decreasing risk of death in HD patients as the session duration increased until 5 h [53]. Dialysis duration up to 5.5 h was independently associated with survival even after adjustment of the RR of death by the dose of HD, either in terms of spKt/V [122] or of eKt/V [54]. This finding suggests that shorter HD times may be associated with increased risk of death even when an adequate dose of therapy is delivered.

*Daily dialysis.* Long, slow, nocturnal HD is performed 6–7 nights per week for 8–10 h during sleep at home. The results of a single unit, 3 years experience in 170 patients/months [208], updated to 5 years [209], reproduced the results of the Tassin experience in terms of patient well being, control of blood pressure with reduced use of antihypertensive drugs, reduced incidence of intradialytic hypotension and cardiovascular complications. Slow nocturnal HD provided, at the

same time, an increased weekly clearance of MM [210], and phosphate, with control of hyperphosphatemia without any phosphate binders [211].

*Short/standard daily HD.* Prolonged experience in a single unit with daily HD sessions of 2–2.5 h and ‘standard efficiency’ [212,213], similarly to other more limited experiences [214,215], reported better control of hypertension and intradialytic fluid removal, improved nutritional status (increase in serum albumin, and dry weight), with substantial benefits in terms of well being. These were attributed to increased small- and middle-MW solute clearances and to a lower peak concentration of uraemic toxins. The more intensive use of the vascular access did not cause an increased incidence of complications and did not reduce access survival [213]. Similar conclusions were reported in a recent publication of a retrospective data collection from nine centres involving 72 patients shifted from standard HD to a daily HD schedule (1–3 h, 5–7 times per week) and followed for 6 months [216].

No prospective randomized studies, comparing intermittent treatments at variable frequency on a large number of patients are available yet.

The best HD long-term survival rates have been reported by the groups that used the largest doses and the longer times. Effects of dose and time are difficult to disentangle. Thus, it cannot be assumed that treatment time *per se* can replace Kt/V or other quantitative indices of HD adequacy.

Prospective controlled studies on large number of patients are necessary to confirm the other claimed advantages of long daily schedules, attributed to an improved removal and lower blood level of uraemic toxins of various molecular size.

A unique index combining the effects of HD therapy and residual renal clearance should be defined and validated in order to compare intermittent HD treatments at variable frequency with continuous treatments (peak concentration hypothesis [106], standard Kt/V [198], equivalent renal clearance [189]).

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