



# Towards a tailored prescription of dialysis adequacy: the key role of incremental haemodialysis

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Dialysis therapy is aptly referred to as kidney replacement therapy (KRT), as it aims to keep patients with very little or no kidney function alive. It may appear unbelievable that after nearly 60 years since the start of maintenance haemodialysis (HD) there is still no consensus on some important aspects, such as the timing and modalities of initiation and the duration and frequency of the dialysis sessions, among others. The main reason for the lack of consensus on the above aspects is probably derived from the fact that most of the randomized controlled trials (RCTs) performed so far have been inconclusive [1]. Among them, the National Cooperative Dialysis Study (NCDS), the first milestone RCT on dialysis, was conceived with the specific aim of determining ‘if quantitative relationships between residual morbidity (hospitalisation) and the magnitude of dialysis prescribed could be established’ [2]. The NCDS was also designed to solve the controversy of whether it is preferable to aim for the preferential dialysis removal of small molecular weight toxins (such as urea, with a molecular weight of 60 Da) with short and efficient dialysis or removal of toxins of larger molecular weight (such as vitamin B<sub>12</sub>, with a molecular weight of 1355 Da) with long and lower efficiency dialysis [2].

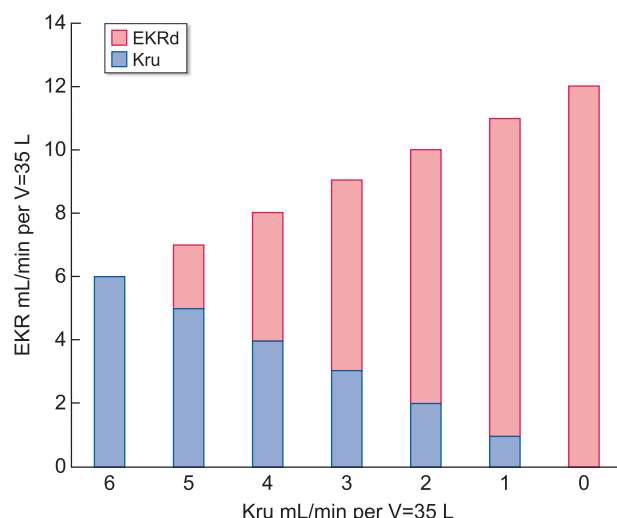
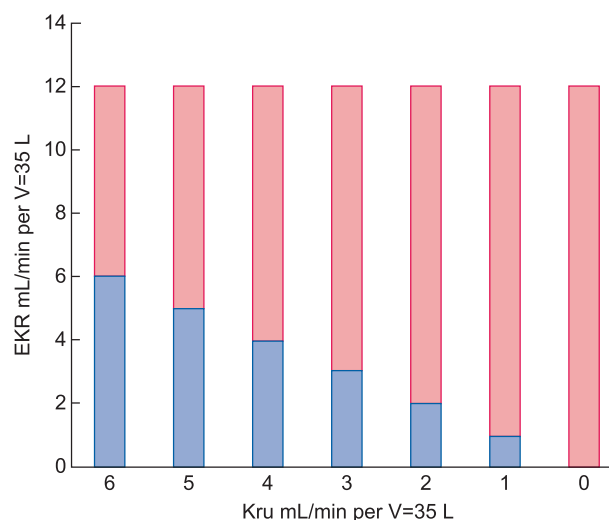
The quest for a reliable dialysis adequacy index/criteria has been a constant feature through the decades in dialysis. While agreeing that evaluating dialysis adequacy should not rely on a single index, we would like to point out the need to keep the urea kinetic model (UKM) as the gold standard,

as it is the only established tool for assessing and prescribing dialysis [3, 4].

Recently there has been growing interest in an incremental approach to HD for incident end-stage kidney disease patients, starting with one or two sessions per week [5]. Such an approach could potentially preserve residual kidney function (RKF) and improve health-related quality of life with similar or higher survival rates than those observed in patients receiving the standard thrice-weekly HD regimen [5].

The term ‘incremental HD’ essentially means that, in the presence of substantial RKF, both dialysis dose and frequency can be low at dialysis inception but should be progressively increased to compensate for any subsequent reduction in RKF. The current principle for calculating the amount of dialysis required to compensate for RKF reduction is based on the constancy of a given target value of total (renal + dialytic) equivalent continuous weekly clearance, as expressed by the equivalent continuous clearance (ECC) of urea. The above principle has been advocated by both the Kidney Disease Outcomes Quality Initiative (KDOQI) [3] and European Best Practice guidelines [4].

Two versions of ECC exist, the standard Kt/V (stdKt/V), i.e. the pre-dialysis averaged concentration (PAC)-based ECC [6], and the time averaged concentration (TAC)-based ECC (EKR) [7]. The assumption of a constancy of the total ECC (renal + dialytic), the so-called fixed target model (FTM), necessarily implies perfect clinical equivalence between the dialysis urea clearance (Kd) and the residual renal urea clearance (Kru) [8]. This assumption is incorrect because Kru has a much greater clinical weight than Kd, in agreement with basic physiology [9]. The assumption is derived from extrapolation to the clinical domain of the equivalence between Kru and Kd in the UKM, in which 1 ml/min of RKF, represented by Kru, removes the same amount of urea as 1 ml/min of Kd [10]. A ‘variable target model’ (VTM) has recently been introduced to overcome the limitations of the

**A Variable target model****B Fixed target model**

**Figure 1:** Total EKR expresses the total clearance (dialytic + renal), i.e. the sum of the contribution of the dialyser urea clearance ( $K_d$ ) to EKR (EKRd) and of the residual renal urea clearance (Kru). According to the FTM, the total target EKR should remain constant: 12 mL/min/35 L. This means that each mL/min of Kru should be replaced by increasing EKRd by the same amount. In contrast, according to the VTM, the total target EKR is 12 mL/min/35 L – Kru, i.e. it varies from a minimum value at the start of HD treatment (in this case Kru = 6 mL/min/35 L) to a maximum value when Kru = 0 (modified from Figure 1 of reference [15]).

FTM [8]. The total EKR is given by the sum of  $K_d$  and Kru. According to the FTM, the total target EKR in a patient with a urea distribution volume (V) of 35 L should remain constant:

$$\text{total EKR} = 12 \text{ mL/min/35 L}$$

or approximately 1.2 equilibrated  $K_t/V$  ( $eK_t/V$ )  $\times$  3 sessions/week (Fig. 1) [8]. This means that each mL/min of Kru should be replaced by increasing the dialysis component (EKRd) by the same amount.

In contrast, according to the VTM, the total target EKR is:

$$\text{total EKR} = 12 \text{ mL/min/35 L} - \text{Kru mL/min/35 L},$$

that is, it varies from a minimum value at the start of HD treatment (in this case Kru = 6 mL/min/35 L) to a maximum value when Kru = 0. This value corresponds to the adequate  $eK_t/V$  in an anuric patient on a thrice-weekly HD regimen (Fig. 1) [8]. Of note, a total EKR of 12 and 10 in an anuric patient corresponds to a  $\text{stdKt}/V$  of 2.3 and 2.1, respectively, which are the target value and the minimum value, respectively, advised by the KDOQI guidelines [4]. This leads to an overestimation of dialysis needs in the presence of substantial RKF, requiring achievement of such high values for both RKF and dialysis dose ( $K_t/V$ ) that it would be very difficult to prescribe less frequent treatments [8].

However, the key clinical questions are: can incremental/less frequent HD preserve RKF, improve health-related quality of life and increase patient survival? A long-term (20 years) observational study performed in a dialysis centre in which, by policy, all incident patients try to start their KRT with one or two sessions per week has recently been published [11]. It showed that 57.9% of 202 enrolled patients started with a 1 HD session/week regimen (G1), 22.8% with a

2 HD sessions/week regimen (G2) and 39 (19.3%) with a 3 HD sessions/week regimen (G3). All patients underwent a monthly urea kinetic study with urine output measurements, if any. The treatment frequency was increased in the presence of a marked reduction in Kru and/or the appearance of 'uraemic' symptoms or signs not treatable with medical therapy [11]. G1 patients remained on 1 HD session/week for  $11.9 \pm 14.8$  months and then transferred to 2 HD sessions/week for a further  $13.0 \pm 20.3$  months. G2 patients remained on 2 HD sessions/week for  $16.7 \pm 23.2$  months. Altogether, 22 045 sessions were saved of the 47 988 that would have been delivered if the patients had been on a 3 HD sessions/week regimen (45.9%). Gross mortality of the entire group was 12.6%, comparable to the mean mortality of the Italian dialysis population (16.2%) [11]. This observational study resembles the intervention arm of an RCT of incremental HD that demonstrated nearly 81% of patients could be started on a less frequent treatment that could be maintained for 1–2 years, with clinical and financial benefits and no increase in mortality risk [11]. On this basis, one could suggest trying to start all clinically stable patients on 1 or 2 HD sessions/week and stay on that regimen only if RKF and diuresis are maintained in the absence of uraemic symptoms and/or signs.

Arguably, further RCTs are needed to demonstrate the safety and clinical efficacy of the incremental approach. Only two RCTs have been completed, perhaps indicating the challenges in performing an RCT on this topic [12, 13]. Notably, the first one was a feasibility study and concluded that a large and definitive trial comparing the outcomes of the incremental (2 HD sessions/week) vs the standard approach is feasible, safe and requires lower financial costs in patients with sufficient RKF [12].

Some RCTs are planned or ongoing. Of note, a Spanish-Italian RCT (already under way) [14] and an RCT planned by the EuDial Working Group of the European Renal Association (REAL LIFE) [15] were designed to evaluate the adequacy of incremental HD (1 and 2 HD sessions/week) compared with the standard thrice-weekly HD by using the VTM [8].

Last but not least, among medical treatments, the environmental consequences of dialysis seem to be particularly significant, suggesting that the nephrology community has an important role to play in identifying environmentally responsible health practices: we suggest that incremental HD can be one of them.

In conclusion, incremental HD allows a tailored prescription of dialysis adequacy. Overall, the literature findings lend support to the safety of incremental HD and highlight the potential for this method to be implemented as a new standard of care in dialysis patients with substantial RKF [11]. Ongoing trials are likely to generate further evidence of the clinical and healthcare benefits of incremental HD in routine practice.

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## CONFLICT OF INTEREST STATEMENT

None declared.

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