



Review

One-Size-Does-Not-Fit-All: The Case of Incremental Hemodialysis

Francesco Gaetano Casino¹ and Carlo Basile^{2,*} ¹ Division of Nephrology, Hospital Madonna delle Grazie, 75100 Matera, Italy; fgcasino@gmail.com² Associazione Nefrologica Gabriella Sebastio, 74015 Martina Franca, Italy

* Correspondence: basile.miulli@libero.it; Tel.: +39-099-4773688

Abstract: Conventional hemodialysis (HD) (a 4 h session three times a week) is not appropriate for everyone and is excessive in the presence of substantial residual kidney function (RKF). However, it can be safely replaced by a softer incremental approach guided by the urea kinetic model (UKM), starting with one or two sessions a week. Observational data suggest that RKF may be lost less quickly if dialysis is initiated less frequently than 3 times a week. Incremental HD means that, in the presence of substantial RKF, kidney replacement therapy can begin with low doses and/or frequencies, which, however, must be adequately increased to compensate for any subsequent losses of RKF, keeping the total clearance level (kidney + dialysis) always above the minimum levels of adequacy. In HD, there are complexities in combining the dialysis dose with RKF, but tools have been developed to facilitate this issue. 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. Ongoing and future trials will likely generate further evidence of the clinical and healthcare benefits of incremental HD in routine practice.

Keywords: conventional hemodialysis; equivalent renal clearance; incremental hemodialysis; stdKt/V; urea kinetic model



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1. Introduction

The initiation of hemodialysis (HD) treatment affects patients with a vulnerable state of kidney failure (KF) and exposes them to a high risk of adverse events [1,2]. For example, mortality risk was found to be particularly elevated in the first two months (28 deaths per 100 person-years) after initiation of kidney replacement treatment (KRT) compared to that observed in the subsequent time period, from the third to the twelfth month (22 deaths per 100 person-years; $p = 0.002$) [1]. Frequently, the start of dialysis is induced by the worsening of the patient's clinical status; then, the severity and multiplicity of the patient's pathologies can explain, at least to some extent, the high mortality rate observed in the first few months of conventional thrice-weekly HD (3 HD/wk) regimen. Furthermore, it has also been hypothesized that the abrupt transition from non-dialysis-dependent KF to a 3 HD/wk regimen could promote the loss of residual kidney function (RKF), which, in turn, could contribute to the high mortality rate observed in the first few months of dialysis [3–5].

2. The Key Role of RKF

The presence of RKF in dialysis patients allows better control of water, salt, and the acid–base balance, as well as greater removal of phosphorus and molecules not easily cleared by dialysis. Furthermore, the endogenous production of vitamin D and erythropoietin is better preserved [6,7]. Surprisingly, even low levels of RKF are important for the removal of some uremic solutes, especially middle molecules such as β_2 -microglobulin: in fact, patients with residual kidney urea clearance (Kru) < 0.5 mL/min have significantly higher serum β_2 -microglobulin levels than those with values of Kru between 0.5 and 1 mL/min [8]. Furthermore, more and more importance is attributed

to the residual renal tubular function in the removal of some toxic solutes, especially the protein-bound ones, such as hippurate, phenylacetylglutamine, indoxyl sulfate, and p-cresol [9,10].

RKF loss is associated with reduced survival [11,12] due to several factors, such as lower clearance of uremic toxins [13], alteration in body volumes and blood pressure control [13,14], increased requirement of erythropoietin [15], increased levels of inflammation, [11] and higher left ventricular mass [16]. Kru preservation offers much greater benefits than those attributable to the simple increase in small molecule clearance: this may be argued from the higher survival of patients on HD with Kru of 1 mL/min compared to anuric patients who received the same clearance of urea of 1 mL/min provided by dialysis, probably because of a lower retention of medium molecules and a better control of volume and blood pressure by the native kidney [13].

Consistent with the hypothesis that the rate of RKF decline after starting dialysis may depend on factors associated with HD is the finding of a more rapid reduction in RKF in patients who received nocturnal dialysis 6 times a week compared to those who instead received a 3 HD/wk regimen [17]. In contrast, retrospective and observational studies have demonstrated better RKF preservation when starting dialysis with a twice-weekly regimen than with a 3 HD/wk one [18,19].

3. Incremental HD

The convention of prescribing HD on a 3 HD/wk schedule began empirically when it seemed that this frequency was convenient and likely to treat symptoms for a majority of patients. Later, when urea was identified as the main target and marker of clearance, studies supported the prevailing notion that 3 HD/wk provided appropriate clearance of urea [20].

The majority of patients on maintenance HD in developed countries are administered a relatively uniform regimen, with a 3 HD/wk schedule and a full dose, to achieve a minimum single pool Kt/Vurea (spKt/Vurea) ≥ 1.2 . The patients are indifferently incidental or prevalent in the dialysis treatment [21].

Today, national guidelines on HD from most countries recommend patients receive at least thrice-weekly therapy [20]. Although the regulatory agencies might consider the 3 HD/wk regimen as a “standard of care” and “adequate requirement”, it is by no means perfect. The 3 HD/wk regimen has been assumed, until recently, almost as a dogma in the dialysis community. Incredibly, it has been widely accepted worldwide without ever undergoing any randomized controlled trial (RCT) to examine whether less frequent HD treatments would be inadequate or harmful [22].

Recently, there has been a growing interest in an incremental approach to HD for incident KF patients, starting with one (1 HD/wk) or two sessions a week (2 HD/wk) [22]. Such an approach could potentially preserve RKF and improve health-related quality of life with similar or higher survival rates than those observed in patients receiving the standard 3 HD/wk regimen [22].

The aims of incremental HD are detailed here:

- Provide the required amount of dialysis at the right time, based on RKF;
- Is based on step-wise or incremental increase in dialysis dose as RKF falls;
- Is based on the premise that a gradual increase in dialysis dose may preserve RKF;
- Reduce the “shock” of starting dialysis.

The potential benefits of incremental HD are listed here:

- Less exposure to the harmful effects of HD;
- Less vascular access, and thus fewer complications;
- Gentle start of dialysis in the early period, in which the mortality rate is high;
- Dialysis-free time;
- Reducing dialysis frequency can help to dialyse other patients more frequently;
- Better quality of life;
- Less burden of treatment;

- Less exposure to aggressive attempts at ultrafiltration;
- Lower therapy costs.

The educational aspects of incremental HD are reported here:

- Requires patients to have education on the importance of individualized therapy and an acceptance that dialysis intensity may have to be increased in the future;
- Patient education of accurate measurement of RKF;
- Investment of time needed in the pre-dialysis education stage;
- Requires staff education—clear and consistent messaging;
- Requires investment of staff time in the measurement of RKF and the dialysis dose.

The potential pitfalls and limits of incremental HD are as follows:

- Thrice-weekly HD has been accepted worldwide as adequate. We do not have targets for less frequent dialysis;
- Concern for inadequate clearance of uremic solutes (including solutes other than urea) due to insidious and unpredictable loss of RKF;
- Undefined effects on patient survival and other important clinical outcomes;
- Concern about the insidious onset of volume overload and adverse clinical outcomes;
- Patients on frequent home dialysis feel better, so it is obvious that we should provide as much dialysis as possible;
- Uncertain patient adherence to recommended changes in HD treatment frequency or length;
- Uncertain patient adherence to serial urine collections;
- Added workload for the dialysis staff and nephrologist.

4. The Quest for a Reliable Dialysis Adequacy Index/Criteria

The ultimate goal for patients on dialysis is the prolongation of life with the best achievable quality of life. Dialysis-dependent patients require the solution of several clinical and metabolic problems, which are independent of or only partially dependent on the dialysis adequacy per se. However, the search for a reliable criterion to establish the adequacy of maintenance HD has been pursued since the beginning of its clinical introduction. Although it is now clear that the evaluation of adequacy cannot be based on a single index, we believe it is necessary to maintain the urea kinetic model (UKM) as the gold standard because it is the only consolidated tool for the assessment and prescription of dialysis [23,24].

The principle underlying the rationale of incremental HD is that, in patients with substantial K_{ru} , for instance, equal to or greater than $3 \text{ mL}/\text{min}/1.73 \text{ m}^2$, low levels of both dose and dialysis frequency can be used at the start of KRT, which, however, must be frequently assessed and promptly increased to compensate for any reduction in K_{ru} .

The current method of calculating the amount of dialysis required to compensate for RKF reduction is based on the principle according to which the total weekly clearance (dialysis + kidney) must always be at least equal to the level of adequate clearance established for anuric patients on the conventional 3 HD/wk regimen: in practice, at any time, the adequate dialytic clearance is given by the total adequate clearance (dialysis + kidney) minus K_{ru} . In detail, the total weekly clearance is expressed by the so-called equivalent continuous clearance (ECC) of urea, which is a hypothetical continuous clearance capable of removing, in a weekly time period, the same amount of urea jointly removed by both intermittent HD and continuous K_{ru} in a given patient. The above principle has been advocated by both the Kidney Disease Outcomes Quality Initiative (KDOQI) [23] and European Best Practice guidelines [24].

Two versions of ECC exist: standard Kt/V (stdKt/V), i.e., the pre-dialysis averaged concentration (PAC)-based ECC [25], and the equivalent renal clearance (EKR), i.e., the time-averaged concentration (TAC)-based ECC [26]. According to the KDOQI clinical practice guidelines for HD adequacy, the minimum dialysis dose to be administered in anuric patients on the 3 HD/wk regimen is a spKt/V of 1.2, which corresponds to a stdKt/V

of 2.1 volumes/week [23] and to a total EKR of urea (EKRU) of 10 mL/min/35 L of urea distribution volume (V) of the patient [27,28]. Therefore, the weekly amount of dialysis required to achieve an adequate total stdKt/V of 2.1 is $2.1 - K_{ru}/V \times 10,080$, where 10,080 are the minutes of the week. Similarly, the amount of dialysis required to achieve the minimum total EKRU of 10 mL/min/35 L is $10 - KRUN$, where KRUN is the K_{ru} normalized for V and corrected for a typical V of 35 L, i.e., $KRUN = K_{ru}/V \times 35$ [28].

It has been argued that the assumption of a constant EKRU, the so-called “fixed target model” (FTM), implicitly establishes that each mL/min of urea clearance provided by dialysis (Kd) has the same clinical value of 1 mL/min of clearance provided by K_{ru} [27]. However, this is clearly wrong because basic physiology notions tell us that the kidney performs many vital functions that cannot be carried out by dialysis [29]. This error derives from assuming in the clinical setting an equivalence between K_{ru} and Kd, which is only valid from a pharmacokinetic point of view in the UKM [30]. To correct, at least in part, this error, a “variable target model” (VTM) has recently been proposed [27].

In summary, it has been hypothesized that an adequate total EKRU can range from a minimum value, for instance, at the start of HD treatment when KRUN is about 4 mL/min per 35 L, corresponding to a glomerular filtration rate (GFR) of approximately 6 mL/min/1.73 m², to a maximum value of 10 mL/min/35 L, corresponding to the adequate equilibrated eKt/V (eKt/V) of 1.05 or spKt/V of 1.2 on a 3 HD/wk regimen, when $K_{ru} = 0$. It must be underlined that the above threshold GFR value to start HD in the absence of symptoms was suggested by the Canadian clinical practice guidelines [31].

The equation that calculates the minimum adequate EKRU as a function of KRUN is as follows: $EKRU_{Adeq} = 10 - 1.5 \times KRUN$ [28]. It implicitly establishes that each mL/min/35 L of KRUN is worth 2.5 mL/min/35 L of Kd. On this basis, a UKM-based dialysis simulation can be performed to compare the eKt/V needed to achieve adequacy with 1, 2, or 3 HD sessions per week; using the EKRU-based adequacy criterion (with KRUN ranging from 0 to 6 mL/min/35 L) with the eKt/V needed to achieve adequacy in 1, 2, or 3 HD sessions per week; or using the stdKt/V adequacy criterion. Table 1 shows that using the EKRU-based adequacy criterion allows for a lower dialysis frequency and dose than using the stdKt/V-based criterion. This is especially evident in the 1 HD/wk regimen: it would be permitted by EKRU down to $KRUN \geq 2.5$ mL/min/35 L, whereas stdKt/V would only allow the 1 HD/wk regimen for $KRUN > 4$ mL/min/35 L. This explains why in the US, where stdKt/V is currently used, once-weekly HD is not really foreseen, and US authors, when thinking of “incremental HD”, only refer to “twice weekly HD” [21].

The reason for the discrepancy between stdKt/V and EKRU is that stdKt/V does not sufficiently emphasize the clinical relevance of RKF, particularly at the start of dialysis, when RKF is usually relatively elevated. In this regard, it can be noted that the adequate value of stdKt/V of 2.1 in a patient starting maintenance dialysis, with, for example, $V = 35$ L, implies that $K_{ru} \times 10,080/35,000 = 2.1$. Then, the K_{ru} threshold for starting dialysis is $2.1 \times 35,000/10,080 = 7.3$ mL/min. This K_{ru} value corresponds to a GFR value of approximately 11 mL/min/1.73 m², a GFR value much higher than that suggested, among others, by the Canadian guidelines for starting dialysis, at least in patients without severe clinical complications [31].

Table 1. Comparison of eKt/V values needed to achieve adequacy with 1, 2, or 3 HD sessions per week, using the EKRU-based criterion with the stdKt/V-based criterion, with KRUN values ranging from 0 to 6 mL/min/35 L.

KRUN mL/min/35 L	Adequate EKRU	1 HD/wk eKt/V	2 HD/wk eKt/V	3 HD/wk eKt/V	Adequate stdKt/V	1 HD/wk eKt/V	2 HD/wk eKt/V	3 HD/wk eKt/V
0.0	10.00	>2.0	1.75	1.05	2.1	>2.0	>2.0	1.05
1.0	8.50	>2.0	1.21	0.76	2.1	>2.0	1.76	0.86
2.0	7.00	1.95	0.79	0.50	2.1	>2.0	1.28	0.67
3.0	5.50	0.79	0.37	0.26	2.1	>2.0	0.88	0.49
4.0	4.00	*	*	*	2.1	1.72	0.58	0.33
5.0					2.1	0.79	0.36	0.17
6.0					2.1	0.31	0.23	0.02

Note: The second column shows the adequate total EKRU value (according to VTM) as a function of the normalized RKF (KRUN) given in the first column. The third, fourth, and fifth columns show the eKt/V values to be delivered on once-, twice-, and thrice-weekly HD, respectively, to achieve adequate EKRU. Analogously, the seventh, eighth, and ninth columns show the eKt/V to be delivered on once-, twice-, and thrice-weekly HD, respectively, to achieve the constant adequate stdKt/V value of 2.1 volumes/week, accounting for the actual KRUN. One can see that assuming, for instance, a reasonable eKt/V of 1.2 per session, EKRU-based criteria allow 1 HD/wk with KRUN around or greater than 3.0 mL/min/35 L and 2 HD/wk with KRUN \geq 1.0 mL/min/35 L. On the contrary, the stdKt/V-based criterion can allow 1 HD/wk with KRUN around or greater than 5.0 mL/min/35 L and 2 HD/wk with KRUN \geq 2.0 mL/min/35 L. * No need for dialysis, according to the adequacy criterion of total EKRU, ranging from 4 to 10 mL/min/35 L, KRUN alone being equal to or greater than 4 mL/min/35 L.

5. Review of the Literature

Three systematic reviews and meta-analyses have been recently published [32–34]. Table 2 summarizes their key results [32–34]. The first one included 22 observational studies, 15 in HD and 7 in peritoneal dialysis (PD) (Table 2). The other two systematic reviews and meta-analyses focused only on incremental HD [33,34] (Table 2). In the first one [33] 26 studies were analyzed, 24 cohort studies and 2 RCTs [35,36]. Notably, the first of the two RCTs was a feasibility study and concluded that a large and definitive trial comparing the outcomes of the incremental (2 HD/wk) vs. the standard approach is feasible, safe, and requires lower financial costs in patients with sufficient RKF [35]. An unexpected result of both RCTs was the absence of signals in favor of better preservation of RKF by incremental HD compared to the conventional regimen, in contrast to the findings of many observational studies. However, as the authors acknowledged, “this may reflect a lack of power” [35]. The systematic review and meta-analysis by Takkavatakarn et al. included 36 studies: of them, 32 were observational and 4 were RCTs [34] (Table 2).

It may be useful to comment on some interesting findings of a long-term (20 years) observational study performed in a dialysis center in which, by policy, all patients with sizable RKF who chose to be treated by HD started with one or two dialysis sessions a week [37]. In this study, 117 out of a total of 202 patients (57.9%) were able to start with a 1 HD/wk regimen; 46 patients (22.8%) started with a 2 HD/wk regimen, and the remaining 39 patients (19.3%) started with a 3 HD/wk regimen. All patients performed a monthly study of urea kinetics, with urine output collected in the 24 h preceding the study session. The criteria for the increase in frequency were a marked reduction in Kru and/or urine output or the appearance of “uremic” symptoms or signs refractory to medical therapy [37]. Patients starting with a 1 HD/wk regimen were switched to the 2 HD/wk regimen after $11.9 \pm$ SD 14.8 months; they remained on the 2 HD/wk regimen for a further $13.0 \pm$ 20.3 months. Patients who started with the 2 HD/wk regimen remained on this schedule for $16.7 \pm$ 23.2 months. Overall, 25,943 dialysis sessions were performed instead of 47,988 sessions that would have been delivered if the patients had been on a 3 HD/wk regimen (a saving of 22,045 sessions, equal to 45.9% of the sessions). The gross mortality rate of the entire group of 202 patients was 12.6%, comparable to the mean mortality rate of the Italian dialysis population (16.2%) [37]. This observational study, which appears to be similar to the intervention arm of an RCT on incremental HD, showed that nearly 81% of patients could be started on a less frequent treatment that could be maintained for 1 to 2 years, with clinical and financial benefits and no increase in mortality risk [37].

Table 2. Summary of the key results of the three published systematic reviews and meta-analyses [32–34].

Authors (Year/Reference Number)	Number of Studies/Participants	All-Cause Mortality	Hospitalization	Complications of Dialysis Treatment	Time to Full Dose (Months)	RKF Loss	Quality of Life	Cost Effectiveness
Garofalo et al. (2019) [32]	22 observational studies (15 HD, 7 PD) /75,292 participants	Hazard ratio of 1.14 [95% CI 0.85–1.52]	Not available	Arterio-venous fistula complications: no difference in one study; more thromboses in full dose dialysis in another study	12.1 months [95% CI 9.8–14.3], with no significant difference between HD and PD	Lower mean RKF loss in incremental HD [−0.58 mL/min/month, $p = 0.007$]	Not available	Not available
Caton et al. (2022) [33]	24 observational studies and 2 RCTs/101,476 participants	Hazard ratio of 0.99 [95% CI 0.80–1.24]	No difference in observational studies. Lower relative risk= 0.31 [95% CI 0.18–0.54] in incremental HD (in 2 RCTs)	Arterio-venous fistula complications: hazard ratio of 0.26 [95% CI 0.00–0.82] in incremental HD in one observational study. No difference in the feasibility RCT by Vilar et al. [35]. In the same RCT: 1. fluid overload: incidence rate ratio (IRR) of 0.48 [95% CI 0.08–2.95; $p = 0.49$]; 2. iperkalemia: IRR 0.18 [95% CI 0.02–1.60; $p = 0.11$]; 3. significantly lower serum bicarbonate levels in incremental HD	Not available	Significantly lower RKF loss in incremental HD in most observational studies. No difference in the RCT by Vilar et al. [35]	No significant difference in one observational study and in the RCT by Vilar et al. [35]	In four studies, significant savings in incremental HD
Takkavatakarn et al. (2023) [34]	32 observational studies and 4 RCTs/ 138,939 participants	No difference in general. Significant difference in incremental HD with RKF ≥ 2 mL/min or urine output ≥ 500 mL/day. Odds ratio = 0.54 [95% CI 0.37–0.79]	Significantly lower in incremental HD: odds ratio = 0.54 [95% CI 0.32–0.89]	Arterio-venous fistula complications, hyperkalemia, and volume overload are not statistically significantly different between groups	Not available	Significantly lower incremental HD: odds ratio = 0.31 [95% CI 0.25–0.39]	Overall, no significant differences in quality of life between incremental and conventional HD	Not available

Since most of the available data on incremental HD and outcomes are from nonrandomized studies, they are first and foremost subject to confounding by indication (in other words, patients assigned to incremental HD rather than 3 HD/wk are likely to be different in ways that are not measured). Physicians are likely to prescribe incremental HD to patients who, they think, can withstand the less frequent schedule and perhaps enjoy greater overall health [20].

Only four RCTs focused on incremental HD have been published, perhaps indicating the challenges in performing RCTs on this topic [35,36,38,39]. Arguably, further RCTs are needed to demonstrate the safety and clinical efficacy of the incremental approach. Among those ongoing, IHDIP, a Spanish–Italian trial [40], and REAL LIFE, planned by the EuDial Working Group of the European Renal Association (ERA), are worth noting [28]. They were designed to compare incremental HD (1 HD/wk and 2 HD/wk) with the standard 3 HD/wk regimen by using the VTM [27]. Of note, neither trial [28,40] requires the formal prescription of a strict low-protein diet to start and maintain incremental HD, essentially because, even if a low-protein diet could very likely help to preserve RKF, its mandatory prescription would drastically reduce the number of patients who could be offered the incremental approach. In fact, a study focusing on a Combined Diet Dialysis Program concluded that “a low-protein diet combined with weekly hemodialysis can be considered only in motivated and selected ESRD patients” [41]. Furthermore, a more recent study was conducted in 112 highly motivated patients with creatinine clearance < 5.0 mL/min [42]. They received once-weekly HD on a diet of 0.6 g/kg/day of protein adjusted for sufficient energy intake, and less than 6 g/day of salt intake. The study was successful. The conclusions of the authors were as follows: “This treatment cannot be seen as a general maintenance strategy for patients with ESRF, but may represent a favorable option for use with carefully selected, highly motivated patients, with access to continuous support from trained medical staff, especially nutritionists who are experts in prescribing and assisting the maintenance of low-protein, low-salt diets that also provide adequate energy intake” [42]. Here, it must be stressed that the condition sine qua non of the prescription of the once-weekly HD regimen is a very strict monitoring of both RKF [43] and of the clinical status of the patients, with a timely increase in the dose and/or frequency of treatment if needed [28,40]. Clearly, the results of both RCTs will confirm or reject their underlying hypotheses, including, among others, not only the validity of VTM but also the possibility of prescribing the 1 HD/wk regimen in patients with preserved Kru without the prescription of a strict low-protein diet [28,40].

6. Perspectives and Conclusions

The conventional HD start (a 4 h session three times a week) is not appropriate for everyone and is certainly excessive in the presence of substantial RKF. It could be safely replaced by a softer incremental approach guided by UKM, starting with one or two sessions a week. This approach is appealing to both the patient, who can have more dialysis-free time, and the national health systems, which can save financial resources. Furthermore, the uniform prescription of a target stdKt/V of 2.3 with a minimum of 2.1 volumes/week is not appropriate for everyone because it likely overestimates the dialysis requirement in the presence of substantial RKF. Consequently, stdKt/V hinders the implementation of incremental HD in general but, above all, the 1 HD/week regimen because it requires the presence of too-high RKF values. To overcome this problem, it has been suggested that prescribing and assessing the adequacy of incremental HD regimen, at least that of a 1 HD/wk regimen, should not be guided by stdKt/V but rather by the recently introduced version of EKRU, based on the VTM, which establishes variable adequacy levels depending on the RKF, which are much more realistic and compatible with the available clinical data [27,44].

In conclusion, incremental HD allows a tailored prescription of dialysis adequacy [44–46]; patient and staff education is a key aspect of a successful incremental dialysis program; there is growing interest in incremental HD, which was previously a minority program; and

in HD, there are complexities in combining the dialysis dose with RKF, but tools have been developed to facilitate this issue. Observational data suggest RKF may be lost less quickly if dialysis is initiated less frequently than 3 times a week. The literature findings lend support to the safety of incremental HD. Ongoing and future trials will likely generate further evidence of the clinical and healthcare benefits of incremental HD in routine practice. If this is the case, incremental HD could be implemented as a new standard of care in dialysis patients with substantial RKF.

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