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Incremental haemodialysis

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ABSTRACT

Thrice-weekly haemodialysis schedules have become the standard default haemodialysis prescription worldwide. Whereas the measurement of residual renal function is accepted practice for peritoneal dialysis patients and the importance of residual renal function in determining technique success is well established, few centres routinely assess residual renal function in haemodialysis patients. Although intradialytic hypotension and episodes of acute kidney injury may predispose to an earlier loss of residual renal function, a significant proportion of haemodialysis patients maintain some residual function long after dialysis initiation. As such, an incremental approach to the initiation of dialysis with careful monitoring of residual renal function may potentially provide some haemodialysis patients with an improved quality of life and greater preservation of residual renal function whilst fewer dialysis sessions may reduce health care costs. Prospective trials are required to determine the optimum approach to the initiation of haemodialysis for the oliguric patient. Once residual renal function has been lost, then dialysis prescriptions should be re-examined to consider the use of longer or more frequent treatment sessions and switching from low-flux to high-flux dialysis or haemodiafiltration to offset retention of middle sized molecules and protein-bound azotaemic solutes.

Keywords: haemodiafiltration, haemodialysis, hypotension, Kt/*V*, residual renal function

INTRODUCTION

During the past 50 years, haemodialysis (HD) has evolved as a life-extending treatment for patients with end-stage kidney disease. However, in spite of many advances, the optimum dialysis dose is still unclear. In the early 1980s, the concept of Kt/V_{urea}—dialyser urea clearance normalized to its volume of distribution—emerged as a marker of adequacy [1]. Subsequently, the HEMO study investigated clinical outcomes in HD patients randomized to two different doses of Kt/V_{urea} and helped to define an equilibrated Kt/V_{urea} (eKt/V) of 1.2 as an acceptable target for thrice-weekly dialysis schedules [2]. The equivalent suggested dose for peritoneal dialysis was a weekly Kt/V_{urea} target of 2.0, but this was envisaged as the sum of peritoneal urea clearance and residual kidney clearance [3]. Targets for HD can be similarly expressed as standard Kt/V [4, 5] to allow dose comparisons between HD regimes of different sessional frequency [6]. However, standard Kt/V_{urea}, as with equilibrated Kt/V_{urea}, does not include the contribution to small solute clearance from residual renal function (RRF). Given the focus on preservation of kidney function in the predialysis setting and for peritoneal dialysis patients, it seems counterintuitive to ignore the contribution of RRF when patients initiate HD. Why should the same dose of dialysis be prescribed for newly incident patients and for long-standing prevalent patients who are likely to have very different levels of RRF? The notion that we should take account of RRF in deciding how much haemodialysis to prescribe is not new. Ahmad and Scribner stated in 1979 that 'residual renal function is a major determinant of dialysis requirements' [7]. Bonomini was the first to apply an 'incremental' approach to dialysis in practice [8]. This concept for both PD and HD was further promoted by Gotch and Nolph in the initial Dialysis Outcome Quality Initiative (NKF-KDOQI) guidelines in 1997 [9] and further described by its Work Group members [10, 11].

Most renal units do not account for the presence of RRF in the HD prescription; however, there has been renewed interest in this concept, with some recent observational studies suggesting that an incremental approach to HD initiation and less frequent dialysis regimes may have benefits including preservation of RRF [12–16], and better patient experience due to less interruption of lifestyle [15]. Providing significant RRF is present, long-term outcomes do not appear to be affected by less-frequent dialysis [17]. With an increasing dialysis population, an incremental approach may also be helpful to reduce

the burden of HD therapy on patients and health care resources. This review will discuss the principles of incremental HD, the possible benefits and how it can be applied in clinical practice.

WHAT IS INCREMENTAL HAEMODIALYSIS?

Incremental dialysis uses the concept of adjusting dialysis dose according to RRF so that the dialysis dose is individualized. The basis is to supply sufficient dialysis to provide supra-minimum removal of uraemic solutes and control of hypervolaemia and then escalating the dose of dialysis as RRF declines. The general principle is to calculate the total amount of urea removal during dialysis and adding this to residual renal urea clearance (KRU) to provide a total composite clearance. For peritoneal dialysis, it is relatively straightforward to combine peritoneal clearance to RRF since both are forms of continuous clearance. Total solute removal can be readily calculated from collections of spent peritoneal dialysis effluent and urine carried out over the same 24-h period.

Since residual urea clearance (KRU) occurs continuously and urea removal during haemodialysis occurs intermittently, KRU cannot be simply added to dialyser urea clearance to calculate total Kt/V_{urea} [18], making it technically more complex to include RRF in HD adequacy calculations. Most centres do not routinely measure RRF in HD patients, and thrice-weekly HD regimes are the standard of care offered to patients initiating haemodialysis. Many current clinical practice guidelines do not recommend incremental transition of haemodialysis dose as RRF declines, unlike that practiced in peritoneal dialysis [2, 5, 19].

For HD, several methods have been proposed to add dialyser urea clearance to KRU but none are universally accepted [20]. The general principle is to convert intermittent dialyser urea clearance to an equivalent continuous clearance and adding it to continuous RRF or to convert RRF to an equivalent intermittent clearance akin to dialysis allowing the two intermittent clearances to be added together. Whichever method is employed, since well-established targets for HD dose are readily available in the form Kt/V_{urea} [2, 5, 21, 22], it is necessary to ensure that total Kt/V_{urea} (combined dialyser and KRU) in incremental HD exceeds this minimum. We will briefly describe some suggested methods of calculating urea clearance in incremental HD, but it must be remembered that dialysis urea clearance is not truly equivalent to native residual renal clearance.

ADDING HAEMODIALYSIS AND KRU

Converting RRF to equivalent intermittent clearance

A simple method is to convert KRU to an equivalent intermittent clearance analogous to dialyser clearance (K_d) followed by simple addition of urea clearance by both the dialyser and the native kidneys to obtain total Kt/V_{urea}.

$$\text{Total } \frac{\text{Kt}}{V_{urea}} = \frac{(K_d \cdot T_d)}{V_{urea}} + \frac{(\text{KRU} \cdot f)}{V_{urea}}, \quad (1)$$

where T_d is the dialysis treatment time (min), V_{urea} is the volume of distribution of urea (mL) and f is a factor used to convert KRU into an intermittent equivalent to allow comparison of more frequent dialysis regimens. The f factor takes into account the greater effect of continuous urea clearance provided by the native kidney compared with that achieved with intermittent dialysis clearance. Different values for f are used depending on the frequency of dialysis sessions [5, 20].

Converting dialysis clearance to equivalent continuous clearance

An alternative method is to convert intermittent haemodialysis clearance (K_d) into an equivalent continuous clearance and then adding it to residual renal clearance (KRU) [23, 24]. This principle has been advocated by European and American guidelines, though they advise different methods of calculation. The European Best Practice Guidelines (EBPG) recommend the Casino and Lopez method [4, 23] whereas the National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-KDOQI) recommend Gotch's method of calculating standard Kt/V together with a number of different methods to account for RRF when prescribing dialysis dose [5, 6].

EBPG: The Casino–Lopez method

Casino and Lopez computed kinetic estimates of combined dialyser and residual kidney urea clearance (normalized to volume), which they termed 'equivalent renal urea clearance' (EKR_c) [23]. The EKR_c is computed as a ratio of urea generation (G, mg/min) to time-averaged urea concentration (TAC, mg/mL) normalized to the volume for an average man (40 L) to allow comparison amongst different sized patients. The EKR_c can be applied to different dialysis regimes and schedules [24]. Using their nomogram, the minimum adequate EKR_c to achieve an eKt/V of 1.2 was ~13 mL/min [4]. The relationship between EKR_c (mL/min), eKt/V and residual kidney urea clearance normalized for urea distribution volume (KRU_c) is given by (mL/min):

$$\text{EKR}_c = 1 + 10 \times \frac{\text{eKt}}{\text{V}} + \text{KRU}_c \quad (2)$$

Rearranging Equation (2) allows the minimum dialytic dose required to achieve an EKR_c of 13 mL/min in the presence of KRU_c (mL/min) varying from 0 to 5 mL/min to be derived as follows:

$$\frac{\text{eKt}}{V} = \frac{[12 - \text{KRU}_c]}{10} \quad (3)$$

Equation (3) applies to thrice-weekly sessions only. Different formulas are required for other dialysis frequencies [4].

KDOQI recommendations

The KDOQI 2006 guidelines propose several methods to account for RRF when calculating dialysis dose. The simplest

method allows single-pool Kt/V to be reduced by 20% or so in those with a KRU of >2 mL/min/1.73 m^2 [18]. The guideline recommends limiting the allowed reduction at this level of RRF. Hence, patients with a KRU of 3–5 mL/min/1.73 m^2 are required to achieve the same dialysis Kt/V as those with a KRU of 2 mL/min/1.73 m^2. As an alternative, dialyser clearance may be converted to a continuous equivalent clearance ('standard Kt/V' (stdK), proposed by Gotch [6], based on normalizing generation (G) to average weekly pre-dialysis urea. This is similar to the EKR$_c$ of Casino and Lopez except that average weekly pre-dialysis urea replaces TAC urea [5, 6, 18]. Minimum single-pool Kt/V targets for different treatment times and schedules in the presence of significant RRF are published in the KDOQI guidelines [5].

UREA CLEARANCE AS A MARKER OF RRF AND DIALYSIS ADEQUACY: LIMITATIONS

Although both American and European guidelines provide suggestions to quantify RRF and haemodialysis dose with urea clearance, using urea clearance as a marker of dialysis adequacy has its limitations [25–27]. Urea was thought to be an ideal marker of adequacy because it is an end-product of protein catabolism, abundant in plasma, has a low molecular weight, distributes evenly throughout total body water and can be easily measured. However, urea is not considered a 'toxic' solute but more as a surrogate for other undetermined low-molecular-weight azotaemic toxins [28]. There is increasing evidence that other molecules including protein-bound solutes (e.g. p-cresol sulphate and indoxyl sulphate) and middle molecules (e.g. β2-microglobulin) are important predictors of cardiovascular disease and/or mortality [29]. The kinetic profiles of these solutes are significantly different from those of urea. For instance, Sirich *et al.* [30] were able to modify clearance of p-cresol sulphate and indoxyl sulphate without affecting Kt/V_{urea}, therefore relying on clearance of a single solute (urea) as marker of dialysis adequacy has its flaws. Notably, the HEMO study showed that patients did not benefit from receiving a higher Kt/V urea dose [22]. Quantifying RRF using urea clearance and adding this to dialyser Kt/V_{urea} also has its limitations. First, urinary clearance of urea (and creatinine) may not reflect GFR equally amongst all individuals since tubular secretion may differ depending on the aetiology of the underlying kidney disease and co-existence of other clinical states such as cardiac failure [31], and changes in body composition, in particular muscle mass [32], and physical activity may influence urea and creatinine generation rates. Second, the model assumption of equivalence between renal urea clearance and dialysis urea clearance is only valid in mathematical or pharmacokinetic terms and not in clinical terms since 1 mL/min of native renal urea clearance is more beneficial to the patient than 1 mL/min of an equivalent continuous clearance provided by the dialyser [17], as the native kidney has many more biological functions than simply urea excretion. Accounting for RRF in those with KRU, significantly above 2 mL/min may lead to reduction of dialysis Kt/V targets well below conventional recommended targets [5]. Thus, there is no universally accepted method of incorporating KRU into dialysis adequacy calculations since different authors have declared their own preferences [1, 23]. However, whichever method is employed, urea clearance targets should still be met since Kt/V_{urea} is the only marker that has been thoroughly examined in interventional trials [1, 22]. Given the limitations with urea clearance and adding KRU to dialyser clearances as described earlier, attention should also be paid to other parameters such as nutritional state, volume status, middle molecule removal, anaemia, bone mineral metabolism, control of metabolic acidosis and inflammation—all of which contribute to overall well-being in HD patients [27].

PREVALENCE OF INCREMENTAL HD

The exact prevalence of incremental forms of HD is unknown since these data are not collected by any renal registry in a standardized manner. Most units though do not measure RRF routinely in HD patients and do not adopt a formal incremental approach. Infrequent or twice-weekly regimes are employed in ∼2.7–6.1% of US HD patients and appear to be used mainly in the elderly Caucasian female population with higher residual GFR [33]. In countries with financial constraints, patients with significant RRF are often initiated on twice-weekly dialysis regimes if considered appropriate by the treating physician, but this 'incremental' approach does not appear to have a rigorous underpinning [12, 15, 33–35].

MEASUREMENT OF RRF

Due to the progressive decline of RRF with time [36] and the inter-patient variability in rate of decline [37], it is important to monitor RRF regularly when taking an incremental approach, preferably monthly, whilst urine output is maintained. Less rigorous monitoring risks under-dialysis.

The gold-standard estimate of GFR is measurement of urinary clearance of inulin [38]. This requires the continuous infusion of inulin so is impractical for routine clinical use. Alternative exogenous markers such as ^{125}I-iothalamate and ^{51}Cr-ethylenediaminetetra-acetic acid (^{51}Cr-EDTA) [38] show good correlation with inulin clearance; however, both constitute a long-term radiation exposure risk and there can be significant tubular secretion (^{125}I-iothalamate) [39], extra-renal elimination and tubular reabsorption (^{51}Cr-EDTA) [39, 40], limiting their applicability for use in this context. The potential for allergic reactions and nephrotoxicity, together with significant extra-renal clearance at low GFR, add to the practical difficulties of using iohexol [41]. Cost is also a limiting factor for all of these methods.

Hence, the default method of measuring RRF in this setting utilizes an interdialytic urine collection to calculate urea and creatinine clearances. In the absence of a mid-collection point blood sample, the mean of the post- and pre-dialysis samples is conveniently used to reflect the mean inter-dialytic blood level. Ideally, urine collection should

span the whole interdialytic period rather than just 24 h since urine volume and GFR can vary significantly during the inter-dialytic period [42]. However, in clinical practice, there is often a trade-off between the ideal and what patients find acceptable and their compliance. As such many centres opt for a 24-h urine collection, as this is less inconvenient for the patient. The timing of such collections in relation to a dialysis session then becomes important, particularly for patients with less-frequent dialysis schedules, as clearance will vary with time from the previous dialysis session and volume status. Patients and dialysis staff must be motivated, involved and educated on the importance of regular urine collections for the assessment of RRF for an incremental approach to HD to work [11]; otherwise, RRF will not be measured accurately risking under-dialysis.

Although KRU is used to represent RRF in incremental dialysis, the mean of urea and creatinine clearances provide a better estimate of GFR as measured by inulin clearance in HD patients [43]. Urea clearance slightly underestimates GFR due to tubular reabsorption whereas creatinine clearance overestimates GFR due to tubular secretion. Attempts to inhibit creatinine secretion with cimetidine to improve GFR estimation in HD patients have not been successful [43]. It also has to be accepted that colourimetric creatinine assays may potentially introduce a measurement error [44]. As such other markers of filtration have been advocated such as pre-dialysis plasma levels of cystatin C [45–47], β2-microglobulin [46] and β-trace protein [46, 48] although it is unclear whether any of these markers will prove sufficiently accurate in the range of RRF in dialysis patients to support a formal incremental approach. Further research into alternative inexpensive and easily measured filtration markers that are accurate enough to estimate RRF without the need for urine collections is necessary given the current limitations with using urea clearance. Until such times, then regular monitoring of RRF by urine collections is required to ensure that RRF is being maintained and that dialysis schedules do not require adjustment.

RESIDUAL RENAL FUNCTION AND MIDDLE MOLECULE CLEARANCE

There is increasing evidence to suggest that clearance of other uraemic solutes particularly middle molecules such as β2-microglobulin is highly dependent on RRF. This extends even to very low levels of RRF: patients with urea clearance of <0.5 mL/min have significantly higher serum β2-microglobulin levels than those with values between 0.5 and 1 mL/min [49]. Furthermore, RRF is the most significant determinant of β2-microglobulin levels, even in patients treated with convective modalities such as haemodiafiltration [50, 51]. The same may apply to other middle molecules such as Cystatin C [52] and protein-bound solutes such as p-cresol, which are poorly removed by HD and haemodiafiltration (HDF) [53, 54]. Residual renal tubular function may represent important removal pathways for these and other compounds [55].

BENEFITS OF RRF

The presence of small amounts of RRF is strongly associated with improved outcomes in both PD and HD populations [17, 56]. Although there is some evidence to suggest that RRF declines more rapidly in HD patients [57], this does not appear to be inevitable [29, 41]. Around 50% of HD patients retain significant KRU (>1 mL/min/1.73 m^2) 3 years post-initiation [17]. The benefits of retaining RRF appear to be greater than one would expect from simply enhanced small solute clearance. RRF is associated with lower levels of β2-microglobulin [58], improved anaemia control [59], blood pressure [60], nutritional status [61] and bone mineral metabolism [62]. Volume control is also better due to its significant contribution to fluid and sodium removal [63]. A multivariate survival analysis of patients on incremental HD from our centre suggested that 1 mL/min of residual renal urea clearance resulted in greater survival benefit that 1 mL/min of HD urea clearance, possibly due to greater removal of middle molecules by native kidneys and improved volume control [17]. This observational evidence suggests that it is important to make efforts to preserve RRF in HD patients. It should be recognized though that observational data can be confounded, as stable patients are likely to remain on less frequent and shorter hour schedules, whereas those with progressive loss of RRF and volume overload will be quickly transferred to more frequent dialysis schedules, and factors such as primary renal disease and comorbidities may influence the rate of loss of RRF [37].

EFFECT OF DIFFERENT HAEMODIALYSIS STRATEGIES ON RRF

Biocompatible haemodialysis

The use of biocompatible polysulfone dialyser membranes [64, 65] and ultrapure dialysis fluid has been reported in observational studies to be associated with slower decline in RRF and lower markers of inflammation [66]. We, on the other hand, found no difference in the rate of decline in RRF in haemodialysis patients using polysulfone membranes and ultrapure dialysis water compared with CAPD patients, despite an older and more co-morbid HD cohort [36]

Dialysis initiation and probing for dry weight

The rate of decline in RRF appears to be the greatest during the first 3 months of commencing HD and is significantly associated with episodes of intra-dialytic hypotension [67]. Intra-dialytic hypotension and excessive ultrafiltration induces myocardial stunning [68] and is generally agreed to be a significant contributing factor to RRF loss [69]. More frequent HD and prolonged HD schedules now have strong advocates [70, 71], whereas an increasing minority are voicing reconsideration of a less frequent approach to dialysis initiation [72]. How do these different approaches impact on RRF in HD?

The standard approach of ‘drying-out’ patients until symptomatic hypotension is reached may be harmful [69]. The relationship between extracellular volume and BP is not

linear [73]. Due to the lag phenomenon—the time between normalization of extracellular volume and decrease in blood pressure—progressively increasing ultrafiltration in an attempt to control BP by the unwary may lead to increased episodes of intra-dialytic hypotension, particularly if all patients are initiated onto 'full-dose' thrice-weekly regimes with no consideration of native RRF. Although the Tassin group [74] and a recent randomized controlled trial showed that increasing ultrafiltration improved blood pressure control, continuous probing for the optimum dry weight by systematic increments in ultrafiltration [75] may lead to an increased incidence of intradialytic hypotension. This approach may lead to rapid decline in RRF especially following initiation, as has been previously reported [76]. Conversely, keeping patients in a state of hypervolaemia does not preserve RRF [77] and contributes to increased mortality [78]. Observational studies from peritoneal dialysis patients show that RRF is important in reducing the risk of hypervolaemia [79, 80]. Thus, probing for dry weight should be attempted, but with care to avoid the deleterious effects of dialysis-induced hypotension. Measurement of RRF can be a useful tool to aid clinical assessment of fluid balance and prescription of dry weight, particularly for those prone to haemodynamic instability who are less able to tolerate small volume shifts beyond their dry weight (Figure 1).

The difficulties in accurately determining volume status in dialysis patients have led to increased use of bioimpedance to aid clinical assessment of fluid status [81–83]. There is some evidence to suggest reduced left ventricular mass, better blood pressure control and reduced arterial stiffness when bioimpedance has been used to guide ultrafiltration requirements [81, 82]. A small randomized controlled trial also reported short-term mortality benefits [82]. However, since bioimpedance cannot distinguish extracellular water in plasma from the extravascular compartments, in patients with muscle wasting, weight reduction guided by bioimpedance could lead to more rapid loss in RRF, as demonstrated in a recent randomized trial [82]. Despite this, bioimpedance may still be helpful in clinical practice by identifying relatively hypovolaemic patients so that prescribing excessive ultrafiltration can be avoided.

Frequent dialysis regimes

Although frequent HD regimes are reported to be beneficial [71, 84, 85], a *post hoc* analysis of the Frequent Hemodialysis Network trials has suggested that frequent nocturnal regimes may accelerate loss of RRF compared with thrice-weekly dialysis [86], possibly related to a greater tendency to hypotension and/or increased inflammation associated with prolonged extracorporeal exposure. It is noteworthy in those undergoing frequent nocturnal dialysis in this study, there was no short term survival benefit [87]. A number of methodological issues though suggest caution in the interpretation of these findings [88].

Infrequent and incremental dialysis regimes

Repetitive ischaemic insults during the HD session have been proposed as an explanation for rapid decline in RRF in HD patients compared with their PD counterparts [68, 89]. There are suggestions that patients initiated onto twice-weekly regimes may experience better preservation of RRF [13, 16], though the evidence base is weak. Lin *et al.* [12] found that converting prevalent HD patients to twice-weekly dialysis regimes based on urine volumes and other undefined clinical

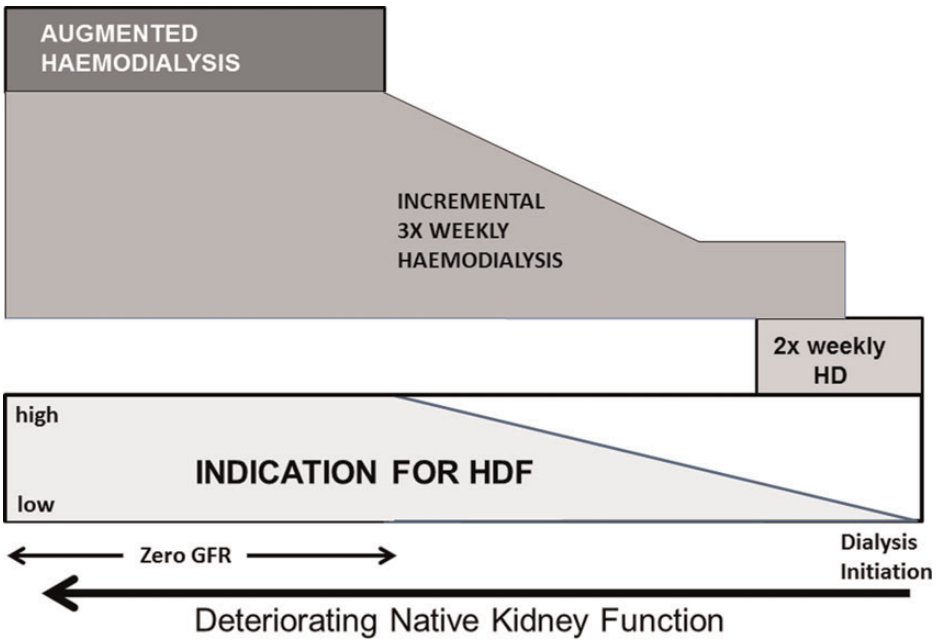

FIGURE 1: Relationship between extracellular volume, haemodynamic instability and deleterious effects of hypervolaemia. Patients with cardiac failure or autonomic neuropathy have less margin for error when being prescribed an optimum dry weight and are more prone to haemodynamic instability (bottom diagram).

conditions led to a slower decline in renal function and lower incidence of intradialytic hypotension compared with those on thrice-weekly regimes. Zhang *et al.* [15] also reported that incident dialysis patients initiated on twice-weekly dialysis regimes had a slower decline in RRF than those started on thrice-weekly schedules. Spanish investigators who adopted an incremental approach reported a slower decline in GFR in patients started on twice-weekly dialysis [16]. Whether infrequent or incremental HD initiation preserves RRF is difficult to confirm due to the absence of prospective controlled trials.

CLINICAL OUTCOMES WITH INCREMENTAL HAEMODIALYSIS

There are no clinical trials that directly compare standard thrice-weekly therapy HD with incremental HD. There are a few observational studies that examined clinical outcomes in those undergoing infrequent or incremental HD (Table 1). We previously reported in 650 incident dialysis patients treated with an incremental high-flux HD programme that despite receiving a lower dialysis dose, patients with significant RRF had a survival advantage and lower erythopoietin requirements [17]. Mortality outcomes from the United States Renal Data System population in 15 067 patients undertaking twice-weekly HD showed that prevalent patients had a lower mortality risk (RR = 0.76, P = 0.02) compared with thrice-weekly patients, although in incident patients, there was no significant difference in mortality risk when adjusted for eGFR at HD initiation (RR = 0.85; P = 0.31) [33]. Similarly, Shanghai Renal Registry data also reported similar survival rates between twice-weekly and thrice-weekly HD patients [15]. In addition to preservation of RRF, Lin *et al.* [12] also reported fewer episodes of hospitalization in twice-weekly HD patients. Nutritional and bone mineral biochemistry status appear to be no worse in infrequent or incremental dialysis regimes [12, 16, 90]. These data should not be interpreted as implying that HD sessional frequency or duration can be safely reduced across the board since in each of these studies RRF was taken into account.

In summary, the available literature suggests that there appears to be no overtly harmful effects to patients by reducing dialysis dose from thrice to twice weekly so long as significant RRF is present. In a world where health care systems are increasingly constrained by financial pressures, an incremental approach to HD to safely allow infrequent schedules may have an economic benefit although there are no data to prove this [13, 91]. More importantly, taking account of RRF to allow dialysis dose to be safely reduced may be of particular benefit to the frail or elderly, many of whom find the frequent trips to the dialysis unit and prolonged dialysis schedules tiring and debilitating. It is evident from the published literature [33, 34, 92] that there appears to be no standardized method of applying incremental HD in practice. Infrequent regimes are currently being used arbitrarily, with no systematic process of deciding which patients require less dialysis and then escalating dialysis dose appropriately as RRF declines over time.

INCREMENTAL HAEMODIALYSIS IN PRACTICE

Optimizing uraemic solute removal

Incremental HD individualizes the dose of the HD prescription to include urea clearance (KRU) provided by RRF as part of dialysis adequacy calculations, accepting the caveat that 1 mL/min of RRF is not equivalent to 1 mL/min of dialyser urea clearance. RRF should be measured at least monthly to ensure that patients who lose RRF are not inadvertently systematically underdialysed by the incremental dialysis algorithm. Dialysis dose should be adjusted according to the change in RRF over time by altering dialysis treatment parameters such as session time, dialyser size, dialysate and blood flow rate. Smaller fistula needles can be used for haemodialysis initiation in those with significant RRF when high blood flow rates are not required. Use of smaller needles is also recommended for new arteriovenous fistulas [93].

The dialysis dose should be targeted towards urea clearance; however, it is important to acknowledge that the use of urea as a surrogate marker to represent all uraemic toxins is controversial as discussed earlier. Other uraemic toxins such as middle molecules (β2-microglobulin), phosphate and p-cresol are also important predictors of mortality in dialysis patients [94, 95] and are more difficult to remove during HD. Therefore, the incremental HD prescription should not be based simply on only meeting urea clearance targets. In patients who lose RRF, middle molecules such as β2-microglobulin start to accumulate rapidly [50]. We suggest that as part of the incremental approach to dialysis treatment, for a patient not already receiving HDF, conversion to this therapy should be undertaken before the onset of anuria to maximize convective removal of middle molecules (Figure 2) [50, 95]. Extending this incremental approach would define a role for augmented dialysis regimes (particularly increasing dialysis frequency or sessional times when RRF is minimal). On this basis—considering the increased mortality reported following the 'long gap' in thrice-weekly dialysis [96]—a larger role for alternate day HD, or preferably HDF, might be considered justified particularly for younger and more active patients. At the other end of the spectrum, there is a role for twice-weekly dialysis for a period following initiation when there is significant RRF (Figure 2). It is important to ensure that the minimum Kt/*V* dose in this setting is increased to 2.0 or so. Conversely, in the frail elderly, frequent HD regimes may be less appropriate, and a greater focus on supportive care and symptom management might lead to de-escalation to palliative HD.

Optimizing volume control

Optimizing volume control in patients should be practiced without inducing hypotension-induced kidney injury, to preserve RRF and importantly to improve patient experience on HD. RRF is an important determinant of ultrafiltration requirement [17]. In patients with significant RRF, dialysis times can be safely reduced without having to resort to excessively high ultrafiltration rates (>10 mL/min)—which have been associated with increased mortality [97, 98]. Exceptions may apply to certain groups of patients such as those with very poor cardiac function (Figure 2), who may benefit from slow ultrafiltration therapies [99], and thus longer or more frequent

Table 1. Summary of clinical outcomes of infrequent or incremental haemodialysis patients

	Study details	No. of patients	(a) Measurement of RRF (b) Effect on RRF	Mortality	Hospitalization	BP and Volume control	Nutrition	Bone metabolism
Hanson *et al.* [33]	Retrospective observational—comparison between twice-weekly and thrice-weekly HD patients	15 067	(a) Estimated GFR (b) Not assessed	Lower mortality in prevalent patients; not significant in incidental cohort				
Lin *et al.* [12]	Prospective observational—comparison between twice-weekly and thrice-weekly HD patients	74	(a) Mean KRU and KRC—interdialytic urine collection (b) Slower decline in RRF in twice-weekly cohort		Fewer hospitalization in twice-weekly cohort	Fewer episodes of intradialytic hypotension in twice-weekly cohort	No difference in albumin	
Vilar *et al.* [17]	Retrospective observational—incident dialysis patients treated with incremental haemodialysis, comparison between patients with urea clearance above and below 1 mL/min	650	(a) KRU-interdialytic urine collection (b) Not assessed	Lower in those with KRU > 1 mL/min		No difference in BP between patients with KRU above or below 1 mL/min	Albumin and nPCR higher in those with urea clearance of >1	No difference in PTH between patients with urea clearance above or below 1 mL/min
Supasyndh *et al.* [90]	Cross-sectional study—comparison between twice-weekly and thrice-weekly HD patients	142	(a) Not measured (b) Not assessed				Similar nutritional status as evaluated by bioimpedance	
Lin *et al.* [34]	Mixture of prospective and observational—comparison between twice-weekly and thrice-weekly HD patients	1288	(a) Not measured (b) Not assessed	Similar mortality risk				
Teruel-Briones *et al.* [16]	Prospective and observational—comparison between twice-weekly, thrice-weekly HD and PD patients	193	(a) Mean KRU and KRC—24-h interdialytic urine collection (b) Slower decline in twice-weekly cohort					
Zhang *et al.* [15]	Retrospective observational—comparison between twice-weekly and thrice-weekly HD patients	85	(a) Mean KRU and KRC—24-h interdialytic urine collection (b) Better RRF preservation in twice-weekly cohort					

GFR, glomerular filtration rate; KRU, residual urea clearance; KRC, residual creatinine clearance; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; RRF, residual renal function.

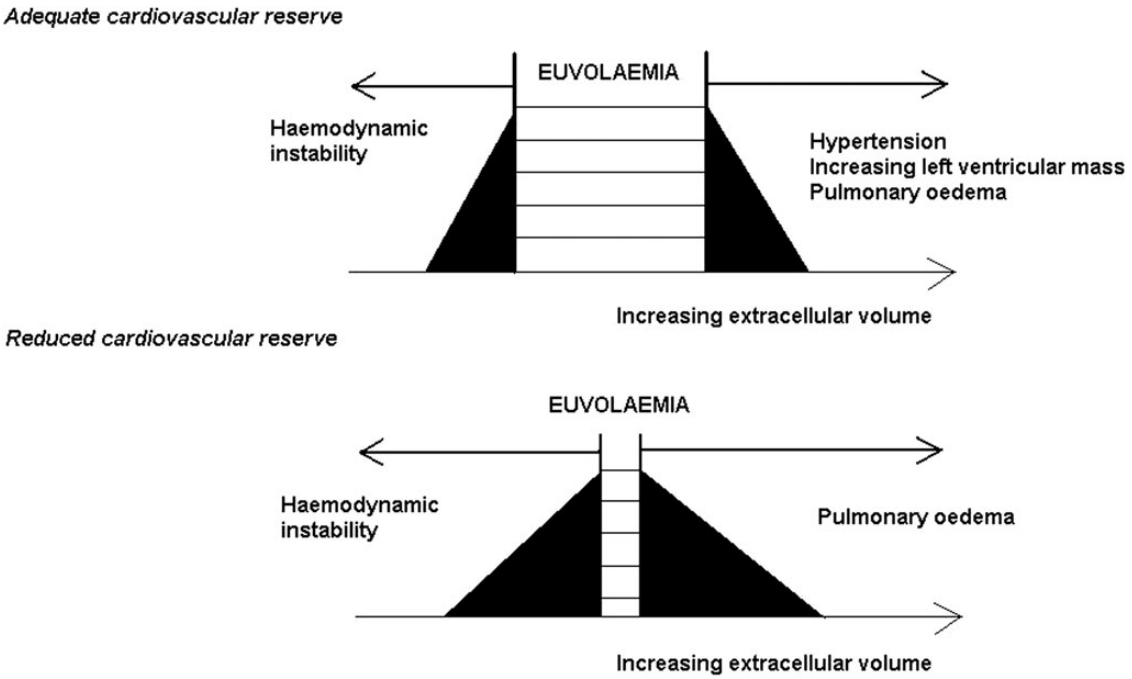

FIGURE 2: Schematic cartoon depicting the application of incremental haemodialysis as patients progressively lose residual kidney function.

treatment sessions. Better fluid management in HD patients may be achieved using individualized volume management algorithms, possibly with diagnostic adjuncts such as bioimpedance [100, 101], and cardiac biomarkers [102, 103]. This may help in identifying patients who might benefit from augmented HD regimes such as alternate daily, daily short hours or nocturnal dialysis.

CONCLUSION

In summary, there is increasing evidence that simply applying a standard thrice-weekly HD dose to all patients with no consideration of RRF is no longer appropriate. We suggest that HD prescription should be tailored towards the needs of the individual, and it should be dynamically adjusted as RRF declines to intensify solute clearance and optimize fluid management. Such measures may improve patient experience and clinical outcomes in HD.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Golper and Mehrotra. The intact nephron hypothesis in reverse: an argument to support incremental dialysis. *Nephrol Dial Transplant* 2015; 30: 1602–1604.)

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