Increasing haemodialytic clearances as residual renal function declines: an incremental approach

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Abstract

Many patients with chronic kidney disease start thrice weekly haemodialysis, aiming for a haemodialysis sessional dialyzer urea clearance target, irrespective of whether they have residual renal function. Whereas increasing sessional dialyzer urea clearance above a target of 1.2 has not been shown to improve patient survival, preservation of residual renal function improves patient self-reported outcomes and survival. Observational studies have suggested that initiating haemodialysis with twice weekly schedules leads to greater preservation of residual renal function. This has led to the concept of an incremental approach to initiating haemodialysis, steadily increasing the amount of weekly dialyzer clearance as residual renal function decreases. As such incremental dialysis practice requires regular assessment of residual renal function to prevent inadequate delivery of dialysis treatment. Once residual renal function is lost, then the dialysis schedule, and modality needs to be adjusted to try to increase middle sized solute clearance and protein bound toxins.

Introduction

Haemodialysis (HD) is currently the most accepted life-saving treatment for patients with end stage renal disease (ESRD) worldwide (1). Based on an initial trial which recruited a relatively small number of patients, urea clearance adjusted for the volume of urea distribution (Kt/Vurea) has become the basis for the delivery of HD dialyzer clearance for patients (2). Patients receiving thrice weekly HD sessions achieving a single pool Kt/Vurea of <0.9 were more likely to be withdrawn from the National Co-operative Dialysis Study (NCDS) study, and as such a minimum sessional target of >1.0 was suggested, which was later increased to 1.2. However, a further study, the HEMO study failed to demonstrate a survival advantage for a higher sessional dialyzer Kt/Vurea target (3, 4). As these studies had recruited prevalent rather than incident patients, none had included measurements of residual renal function (RRF).This has led to a clinical practice of starting most incident HD patients on a thrice-weekly HD schedule, aiming for a sessional urea clearance of ≥1.2, irrespective of RRF.

Whether this dialyzer urea clearance target can be generalized to every HD patient irrespective of age, race, body size and composition, nutritional intake, physical activity, dialysis modality and RRF remains questionable. As the original NCDS trial recruited patients with little or no additional co-morbidity (5), and the HEMO study included few patients weighing more than 100 kg (3). Since an increase in sessional dialyzer urea clearance per se did not appear to increase patient survival, attention turned to the clearance of middle-sized molecules. However, a randomised control trial of high-flux dialysis failed to demonstrate improved patient survival (MPO) (6). More recently on-line HDF, which allows much greater convective exchange, has been introduced into clinical practice. Although there is controversy, as to whether on-line HDF does increase patient survival, as several of the individual trials failed to demonstrate an advantage, although retrospective analysis of the pooled individual data was reported to show an overall survival benefit (7), especially when adjusted for body size (8).

Despite increasing convective clearances, on-line HDF only effectively clears water-soluble solutes. Accumulating data now suggests that protein bound solutes have a role in causing cardiac and

endothelial pathology (9). Many of these protein-bound solutes are naturally excreted by the renal tubular organic acid transporters. Thus, the concentrations of these toxins are much lower in HD patients with RRF. Recent observational studies have suggested that patients initiating dialysis with less frequent dialysis schedules than the thrice-weekly traditional approach have greater preservation of RRF (10). This has led to a resurgence into an incremental approach to initiating dialysis. However, this approach also the requires regular measurement of RRF, and adjusting the amount of dialyzer clearance as RRF falls, and then when RRF has been lost to consider on-line HDF, or more frequent and longer HD schedules to improve azotaemic toxin clearance.

Is there a downside to applying a fixed dialyzer urea clearance to all patients?

In 1960, dialysis adequacy was largely determined by controlling clinical symptoms such as malignant hypertension and peripheral neuropathy (11). However, with the introduction of more reliable vascular access, regular thrice- weekly HD treatments became established as standard clinical practice, based on clinical observations reporting increased patient stamina, reduced neuropathy and improved blood pressure control. Following the NCDS report, the concept of urea clearance, adjusted for volume of urea distribution was introduced (2). As such, the dialysis dose is quantified by a urea kinetic model, based on pharmacokinetic principles. Whilst the dosage and frequency of a maintenance dose for a drug is calculated by the rate at which the drug is cleared from its volume of distribution through metabolic and clearance pathways, urea kinetics are somewhat more complex. Whereas drugs come in fixed doses, urea generation depends upon dietary protein intake, particularly meat intake, muscle mass and physical activity and catabolic rate. In keeping with differences in urea generation, the mechanistic analysis of the NCDS reported no benefit for increasing the dialysis dose in patients with a protein catabolic rate (PCR) of less than 0.8 (2). Although for the HD patient dialyzer urea clearance accounts for the majority of urea clearance, there will be varying contributions from RRF and gastrointestinal losses. To allow comparison between patients, dialyzer urea clearance was adjusted to the volume of urea distribution, derived from equations based on anthropomorphic measurements. These equations were based on healthy, predominantly Northern Europeans, and excluded the morbidly obese. The introduction of bioimpedance techniques have shown that total body water measured by bioimpedance differs from that estimated by anthropomorphic measurements, due to changes with age, gender, ethnicity and co-morbidity (12). As such using a single target Kt/Vurea for both HD and peritoneal dialysis patients leads to delivery of a lower effective dialysis clearance to women, small men, patients with a lower body mass index, and those who physically active with little or no-comorbidity (13). On the other hand, as the eGFR of patients initiating HD has steadily increased over recent years, particularly in the US, then a thrice-weekly HD schedule targeting a sessional dialyzer urea clearance of ≥1.4 for a patient with an eGFR of ≥10 mL/min is not required. More HD is not without its consequences, as intra-dialytic hypotension remains the most common complication of outpatient HD sessions, and repeated episodes of systemic hypotension and renal hypo-perfusion potentially increase the risk of acute kidney injury and premature loss of RRF.

Why try and preserve residual renal function (RRF)?

RRF is recognised as a major determinant of morbidity, mortality and quality of life for both HD and PD patients (14). Patients with RRF benefit from less strict dietary and fluid restriction. Preservation of RRF can potentially reduce sodium and water retention, resulting in improved blood pressure control, lower pulse wave velocity, and reduction in left ventricular hypertrophy (15). In addition, RRF increases middle molecule and protein-bound solute clearances. A recently reported β2-microglobulin (β2M) kinetic study showed that any benefit of extracorporeal β2M clearance, whether by high flux HD, on-line HDF, more frequent short daily or and long daily HD, was markedly

reduced if RRF was still present (16). In addition, both the more frequent haemodialysis network (FHN) trials did not show convincing evidence for greater middle molecule or protein bound solute clearances for those receiving more frequent dialysis schedules (17), and also some of the on-line HDF trials equally failed to demonstrate an advantage for middle molecule (18) and protein bound toxin clearances (19). The apparent failure of more frequent and longer HD sessions and on-line HDF to increase middle molecule clearances can be explained by including patients with RRF, so that any potential benefits of more frequent and longer HD sessions were offset by an increased loss of RRF with the more frequent and longer HD sessions (20).

Can too much haemodialysis be detrimental?

Three observational studies reported better preservation of RRF by initiating HD twice-weekly compared to standard thrice-weekly HD (21, 22). The prospective FHN nocturnal trial reported greater loss of RRF in those patients who dialysed six times per week compared to those dialyzing thrice-weekly. In the daily FHN trial, although there was a trend for more rapid loss of RRF with six times a week dialysis schedules, this was not statistically significant, but this may have been due to patient recruitment including patients with no RRF at baseline (20). More frequent dialysis reduces time-average solute concentrations and extracellular volume, which normally promote urine output (23). Reduction in extracellular volume may potentially predispose to episodes of acute kidney injury, and so cause more rapid loss of RRF. Moreover, more frequent exposure to the extracorporeal circuit leads to activation of leukocytes and platelets and this inflammatory response may contribute to more rapid loss of RRF. As more frequent dialysis increases the number of access cannulations, then this potentially risks greater infection and non-infection related access complications. The FHN daily trial reported an increased hazard ratio of 1.76 for the time to first access repair, access loss and access related hospitalization in the more frequent dialysis group, with graft thrombectomy and revision being the commonest vascular access repairs (24). The FHN nocturnal trial reported a similar trend, although differences were not statistically significant. Repeated trauma by access cannulation and in combination with turbulent blood flow can induce local inflammation with release of cytokines and growth factors, which stimulate neointimal hyperplasia and clot formation, resulting in access stenosis and thrombosis (25). An Australian study also reported greater access complications, particularly infection for those patients treated with extended-hours HD, which significantly predicted death and technical failure (26).

Infection remains the leading cause of death and hospitalization for HD patients. Not only access-related, HD patients are more susceptible to other forms of infection including respiratory tract infections, due to a combination of increased extravascular lung water, closer exposure to other patients and an altered immune system. HD patients not only have reduced responses to vaccinations, but the increased background pro-inflammatory state, characterised by increased IL-1, IL-6 and TNF-α (27, 28) and complement on one hand and downregulated IL-2 synthesis (29), ICAM-1 and TCR1/CD3 receptor expression on T helper cells (30), and dysregulation of the Th1 and Th2 balance on the other, then impairs the response to pathogens (31). Data from matched daily home and thrice-weekly in-centre cohorts reported a significant greater risk of first infection-related admission for the daily group (32).

Dialysis is unable to selectively regulate solute clearances. As such, more dialysis may potentially lead to vitamin and other deficiencies. Hypophosphatemia is recognised complication of intensive dialysis. As expected, those patients dialysing more frequently in the nocturnal FHN trial required the addition of phosphorus into the dialysate to prevent hypophosphatemia (33).

More dialysis increases the time spent on dialysis, which may increase travelling times to and from dialysis, time to set up and clear away, so reducing quality of life. In addition, loss of RRF imposes greater dietary and fluid restrictions. Neither the daily nor the nocturnal FHN trials were able to demonstrate that more frequent dialysis improved quality of patient life. On the other hand, observational studies have reported better patient reported quality of life for those patients initiating HD with a twice-weekly schedule compared to thrice weekly (34, 35). A propensity matched study also reported better quality of life and less self-reported depression in patients initially dialysing twice weekly and then increasing dialysis frequency as RRF was lost, although by 12 months differences were no longer significant (36). Moreover, more frequent dialysis impacts on not only the patient, but also places increased stress on the spouse, partner or family.

Should all patients start on twice-weekly haemodialysis schedules?

On the contrary, inadequate dialysis is potentially harmful for patients with insufficient RRF. The report from NCDS recommended against a sessional Kt/Vurea below 0.9 for thrice-weekly HD schedules, as it was associated with increased risk of hospitalization and morbidity (2). Although achieving a target dialyzer urea clearance does not equate with adequate clearance of other azotaemic toxins, inadequate urea clearance will increase uraemic toxin retention, so endangering normal physiologic function, leading to the uraemic syndrome and death. In addition to inadequate uremic solute clearance, if patients do not have sufficient RRF then they will be at risk of of fluid overload with less frequent regimes, and also excessive ultrafiltration requirements both of which may lead to more hospitalization and incurring greater health care costs (37). Although dehydration post-dialysis acutely reduces RRF, maintaining a higher extracellular volume does not only fail to preserve RRF (38), but may accelerate the loss of RRF and risks the consequences of extracellular volume expansion. Although current data suggests favourable RRF preservation with an incremental regime, there is no directed relationship between RRF and better patient survival (36, 39). A recent cohort study from the US reported higher mortality in patients starting dialysis less than thrice weekly with a baseline urea clearance ≤ 3 ml/min/1.73m^2 or urine volume ≤ 600 ml/day (10). As such twice-weekly HD schedules may not provide sufficient azotaemic solute control for such patients. In addition, more physically active patients with greater dietary protein intake will require greater clearances, compared to older more sedentary frail patients, and again may not be suitable for less frequent dialysis schedules (40). Additionally, close monitoring of RRF, total urea clearance and hydration status are mandatory for less frequent regimes. Further prospective studies are required to determine whether there are generalizable cut points to determine which patients should be offered less frequent HD schedules, and as RRF declines when HD schedules should best be increased.

What is incremental haemodialysis?

An incremental dialysis approach to initiating HD is to consider RRF, and aim to achieve a composite total urea clearance target. As such, the amount of dialyzer clearance is increased to compensate for losses of RRF. It is important to note that incremental dialysis does not only apply to initiating HD, but also includes the management of prevalent patients who have lost RRF or have extracellular water excess, so increasing dialysis frequency, duration and considering HDF.

The main objective of starting with incremental dialysis is to preserve RRF. However, it should always be remembered that small solute clearance is only one aspect of patient management, and consideration to sodium balance, extracellular water retention, blood pressure control, bone and mineral disorders and acid-base control is also required. Therefore, any dialysis regime should be adjusted to the needs of the individual patient. When patients have substantial RRF, then a less

frequent, shorter session duration, smaller surface area dialyzer, slower blood or dialysate pump speeds and smaller needle size should be considered. On the other hand, when RRF has been lost, then introducing higher convective volume exchanges with on-line HDF, using a superflux dialyzer, or adding an adsorptive membrane or manipulating diet (39, 41) are potential options to increase solute clearances.

Apart from standard clinical evaluation, initiating patients on less frequent HD schedules requires regular monitoring of RRF and prompt intervention to adjust dialyzer clearance as RRF declines, are the key to success. In clinical practice, RRF is assessed by 24-hour urine urea or combined urea and creatinine clearance, which only represent glomerular function, and neglect renal tubular function which is important for middle molecule and protein-bound solute clearance. As such, adjusting dialyzer urea clearance solely based on urinary small solute clearance alone might not be the most appropriate clinical target. Moreover, 24-hour or inter-dialytic urine collections increase costs, and increase workload on dialysis centre staff, and are a burden to patients. Equally, not all patients are capable of collecting urine. Thu, there has been renewed interest in trying to develop serum-based RRF assessments. Two equations have been recently proposed, using serum biomarkers including β2M, β-trace protein (βTP) and cystatin C (42, 43) and have been validated as a pragmatic technique for estimating RRF and developing this approach will allow more dialysis centres offer an incremental dialysis approach.

Incremental regimes and alternative approaches to preserve RRF

A reduction in weekly dialysis time can be achieved by either shortening session times or reducing frequency. Despite an apparent equal weekly dialysis time, e.g. 2 hours thrice-weekly versus 3 -hours twice-weekly dialysis, these schedules result in different clearances. Shorter session times but more frequent dialysis reduce the time average concentration of small molecules, including urea and potassium as these small solutes are readily cleared during the first hour of the dialysis session. Likewise, acidosis is also initially corrected by the movement of bicarbonate from the dialysate. In addition, the shorter inter-dialytic interval limits accumulation of solutes and fluid retention, as such, intra-dialytic electrolyte and osmotic changes are less and with lower ultrafiltration rates, may consequently allow greater hemodynamic stability during dialysis. Avoiding intra-dialytic hypotension and cardiac arrhythmias are associated with preservation of RRF (44), fewer cardiovascular events (45) and mortality (46). Another potential advantage of shorter dialysis session length is that recovery time may be faster, which is positively related to quality of life and inversely related to hospitalization and mortality (47). However, most azotaemic solutes are intracellular, such as phosphate, are cleared slowly, as are protein-bound solutes, both of which so tend to be retained with short dialysis schedules. Patients with high inter-dialytic weight gains are not suitable for short dialysis sessions, as they would require higher ultrafiltration rates, so increasing the risk of intra-dialytic hypotension, loss of RRF and mortality (48). Longer dialysis session times, but less frequent schedules are more effective for compartmental solute clearances, longer ultrafiltration time, less exposure to the extracorporeal circuit, fewer access cannulations, lower health care costs and more dialysis- free days. However, this approach may cause some patients to become symptomatic due to the greater intra-dialytic solute drop and longer recovery times, higher inter-dialytic weight gains with increased risk of inter-dialytic hypotension. Other incremental approaches such as using small-gauge fistula or graft needles along with slower blood pump speeds are likely to increase access survival (49), while slower dialysate pump speeds, using less dialysate or using smaller surface area dialyzers may reduce health care costs.

As the amount of dialysis required depends upon azotaemic solute generation, one group proposed the combination of a low-protein diet and once-weekly dialysis, and reported better preservation of

RRF and nutritional status (39). RRF increases the clearance of inflammatory cytokines and other mediators, which potentially may have helped to prevent malnutrition (50). However, longer-term studies are required to determine whether patients would adhere to the diet, and short term benefits could be sustained. Aside from dialysis adequacy, a longer inter-dialytic gap potentially risks greater fluid and sodium gains, with several studies reporting increased hospital admissions due to pulmonary oedema in thrice-weekly HD patients following the longer inter-dialytic interval (51). As such, infrequent HD schedules should be avoided for patients with high inter-dialytic weight gains and those with cardiac failure.

Intra-dialytic hypotension is a major risk factor for loss of RRF (22), and high ultrafiltration rates are associated with a greater risk of hypotension. Although there are many patient factors which predispose to intra-dialytic hypotension including impaired cardiac systolic and diastolic function and autonomic neuropathy, preventing excessive fluid removal by setting an appropriate post-dialysis target weight is vitally important. In most centres, post-dialysis target weight is determined by clinical examination, and review of blood pressure and pre-and post-dialysis weights, and intra-dialytic symptoms. More recent bioimpedance devices have been used to aid clinical assessment of volume status. However, studies have shown that using bioimpedance is prone to deplete intravascular volume, and as such reduce rather than preserve RRF (52, 53). Intra-dialytic hypotension can be reduced by simple cooling of the dialysate, with a recent meta-analysis reporting a 70% reduction in the rate of intra-dialytic hypotension and a 12 mmHg increase in mean arterial pressure compared with standard dialysis (54). However not all patients can tolerate cooling. Stepwise dialysate sodium profiling can improve vascular refilling and has been reported to reduce Intra-dialytic hypotension (55). Although this may be effective in the short term, it risks sodium loading and increased inter-dialytic weight gains in the longer term. Other studies have reported that changing the ultrafiltration profile scan decreased hypotensive episodes (56). Several studies have observed a reduced incidence of intra-dialytic hypotension with high volume on-line HDF. This may be due to the additional cooling effect of HDF (57), but this greater hemodynamic stability has been reported to better preserve RRF (58). Acetate in the dialysate can potentially induce peripheral vasodilatation, cardiac dysfunction, and an inflammatory response predisposing to intra-dialytic hypotension. Although most dialysates now solution contain 3-5 mEq/L of acetate, this has been suggested to have a clinical effect when infused as part of a large volume replacement fluid (59). Implementation of acetate-free HDF potentially reduces the risk of intra-dialytic hypotension (60) after the long inter-dialytic interval, although this technique typically leads to a greater positive sodium balance, and has not been shown to provide greater cardiovascular stability compared to high volume on-line HDF (61).

Considerations of incremental dialysis

HD is not limited to providing uremic toxin clearance, but is also important in maintaining sodium balance and hydration status. Inadequate fluid and sodium removal increase the risk of volume overload, hypertension, and ventricular hypertrophy (62). Less frequent dialysis has been associated with more episodes of admission due to heart failure, fluid overload and pulmonary oedema, so increasing health care costs (37). Moreover, maintaining overhydration status does not help preserve RRF (38, 52), and possibly increase risk of loss of RRF as more rapid ultrafiltration may be required, resulting in more frequent and more profound hypotensive episodes. The main challenges of applying incremental dialysis are careful review with close monitoring of uraemic toxin clearance, fluid and electrolyte balance along with prompt modification of dialysis prescriptions. However, the concept of dialysis customization may increase dialysis staff workload, as urine collections and more assessments are required.. On the other hand, less frequent dialysis schedules for some patients,

then allow others to dialyse more frequently, and by varying dialysis session times helps avoid staff pressures to start and end all patient treatments at the same time. Depending upon the health care system, incremental dialysis may or may not reduce dialysis centre reimbursement.

Although offering incremental dialysis potentially offers patients a better quality of life and preservation of RRF, the assumption is that dialytic clearance is appropriately increased as RRF is lost. Whereas practising incremental dialysis without adjusting dialytic clearance potentially leads to greater morbidity and mortality (10,42). Appropriate patient selection, for instance baseline urea clearance > 3 ml/min/1.73m^2 or urine volume > 600 ml/day (10,), should be the first step to consider whether patients may be suitable for incremental dialysis. before applying this regime to prevent further complications (table 1).

Dialysis prescription for patients without RRF

When RRF declines, the primary concern is the adequacy of azotaemic toxin clearance. Clinical guidelines advise a minimum urea clearance target. However, the sessional spKt/Vurea only represents small solute clearance, and does not provide information about the clearance of slow-to-equilibrate solutes such as phosphate, middle molecules and protein-bound toxins. As these solutes move more slowly between compartments, their clearance is time limited. Ideally the development of portable or wearable or implantable haemodialysis devices would allow for prolonged treatment times mimicking the native kidney would offer efficient clearance (63). Such devices would potentially not only improve blood pressure control, solute removal and fluid and electrolyte balance, but would allow greater physical activity, liberalize of dietary intake and increase quality of life.

As expected, extending dialysis time results in significant reduction of pre-dialysis, time average concentration and increasing dialyzer clearance of phosphate and β2M (64-66). The weekly treatment time has a more pronounced effect on TAC β2M than frequency alone. Middle molecule clearance has been used to define dialyzer membrane flux, and as such, β2M clearance is greater with high flux dialyzers (67). The HEMO study (3) reported a survival benefit for high-flux HD in prevalent patients with a dialysis vintage in excess of 3.7 years, so presumably those with little or no RRF (68). An alternative approach to improve middle molecule clearance is to add convective transport. HDF results in higher middle molecule clearances than high-flux HD (69-71). Post-dilution HDF is superior to pre-dilution HDF for β2M clearance but not different for protein-bound solute removal (72). On-line HDF provides greater convective volume exchange, with estimates of 0.6 mg/L reduction in serum β2M concentrations for each 10 L of additional weekly convection volume in anuric patients (73). Although some reports have suggested that HDF provided greater protein-bound solute clearance than haemofiltration or high-flux HD, the reductions in pre-dialysis serum concentrations were small and not thought to be sufficient to improve clinical outcomes (72, 74). As studies show increased β2M clearance with on-line HDF and more frequent longer HD schedules, suggesting that these should be the preferred options for HD patients without RRF.

Simply increasing dialysate flow and dialyzer surface area were reported to augment protein-bound solute clearance (75), however overall clearance remained low. A newer generation of highly permeable or “high cut-off” or “superflux” dialyzer which have larger pore sizes, with a molecular weight cut-off point up to 65 kDa, have been developed. Although reporting greater effective clearance of myoglobin (76), free light chains (77) and cytokines (78); any benefit in terms of clearing protein bound toxins has to be traded off against increased albumin losses (78). Advances in membrane technology led to the development of novel dialyzers with enhanced protein-bound solute clearance by adsorption. Some of the hydrophobic membrane polymers such as polysulfone

(PS) and polymethylmethacrylate (PMMA) have affinity to adsorb proteins. Although a PMMA-based protein-leaking membrane showed a significant reduction of pre-dialysis total homocysteine concentration (79), increasing membrane fouling by protein deposition might compromise other solute clearances over time. Experimentally novel mix-matrix membranes (MMM), in which adsorptive particles are incorporated into a macro-porous membrane layer with particle-free membrane layer on the blood-contacting side of the membrane has been developed, and trials have demonstrated the ability remove protein-bound solutes (80,81). In Japan, sorbent cartridges are used to increase β2M removal (80). However, direct contact between blood and sorbents might lead to leukopenia, thrombocytopenia and embolization. An alternative approach is to add the sorbent into the dialysate, and experimental reports have suggested increased protein-bound solute removal (83). An alternative approach has been to try and displace protein bound toxins, by infusing hypertonic saline or docosahexaenoic acid, to disrupt electrostatic binding (84, 85). Although studies have shown this is possible, the additional removal has been marginal, and longer term safety studies are required to ensure that hypertonic saline or docosahexaenoic acid are not returned to the patient.

Conclusion

Incremental dialysis requires a dynamic approach by considering the patient and adjusting the dialysis treatment according to their clinical needs and RRF. However, as clinical circumstances and RRF change over time then this requires adjustments to dialysis treatments to maintain solute clearance targets and extracellular volume control (Figure 1). Applying a single fixed regime to everyone regardless of clinical status and individual requirements is potentially harmful. Among patients with substantial RRF it is important to tailor dialysis and avoid intra-dialytic hypotension to preserve RRF. However, an incremental dialysis approach introduces additional workload as there has to be regular clinical assessments and measuring RRF to avoid compromising other clinical aspects and inadequate dialysis. When patients loose RRF, then although small solute dialysis adequacy has become the main target, these patients need changes to their dialysis prescription to improve middle molecule and protein-bound solute removal, by escalating dialysis session times and considering high volume on-line HDF, or other alternatives.

Figure 1 Incremental dialysis model

Table 1 suggested quality metric for patients treated by incremental haemodialysis

Measurement	Comment
Serum creatinine	1. Monthly pre-dialysis serum creatinine is stable and not increasing
Residual renal function	2. 3 monthly Urine volume 3. 3 monthly Urea clearance 4. 6 monthly β2microglobulin
Hydration status	1. Monthly clinical assessment of inter-dialytic weight gains and target weight 2. Monthly assessment pre-dialysis blood pressure and intra-dialytic hypotension

	3. 3 monthly bioimpedance assessment of extracellular water 4. 3 monthly cardiac natriuretic peptide
Acid-base	1. Monthly pre-dialysis serum bicarbonate
Nutritional status	1. Monthly serum albumin 2. Monthly normalised protein accumulation rate 3. monthly serum urea and phosphate 4. 6 monthly bioimpedance measurement lean body mass and fat mass
Physical status	1. 3 monthly assessment of patient frailty score 2. 3 monthly assessment of Karnovsky score
Quality of life and life expectancy	Should be discussed especially with elderly and terminally ill patients about the effects of dialysis treatments and operational target of dialysis treatment

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