

Bulletin de la Dialyse à Domicile

Questioning one-size-fits-all hemodialysis prescription: balancing dialysis prescription and residual kidney function

(Remise en cause de la prescription d'hémodialyse standard :
adaptation de la prescription de dialyse à la fonction rénale résiduelle)

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Summary

Recent awareness of the viability and benefits of incremental hemodialysis is an opportunity to review clinical practices and improve the process of dialysis induction. Incremental dialysis is a standard approach in peritoneal dialysis prescription, with a focus on the quality parameter of nephroprotection. The same should apply in hemodialysis, with individualization of the prescribed extracorporeal technique: frequency, duration and intensity, in either home or center hemodialysis, are prescription variables to adjust according to the patient's residual renal function, medical condition and psycho-social priorities. Considering that fluid balance and smooth ultrafiltration critically impact patient survival, incremental dialysis schedules need to be carefully tailored and grounded in routine residual kidney function measurement. This paper raises concerns about both the benefits of incremental dialysis and its putative detrimental effects, these being mainly dependent on the quality of the hemodialysis prescription and external economic constraints. As a comparator, incremental peritoneal dialysis is a scientifically based model to pursue, whichever the modality, based on updated concepts of patient-centered prescription and adequacy in dialytic renal replacement therapies.

Keywords : incremental dialysis, hemodialysis, peritoneal dialysis, residual renal function

Résumé

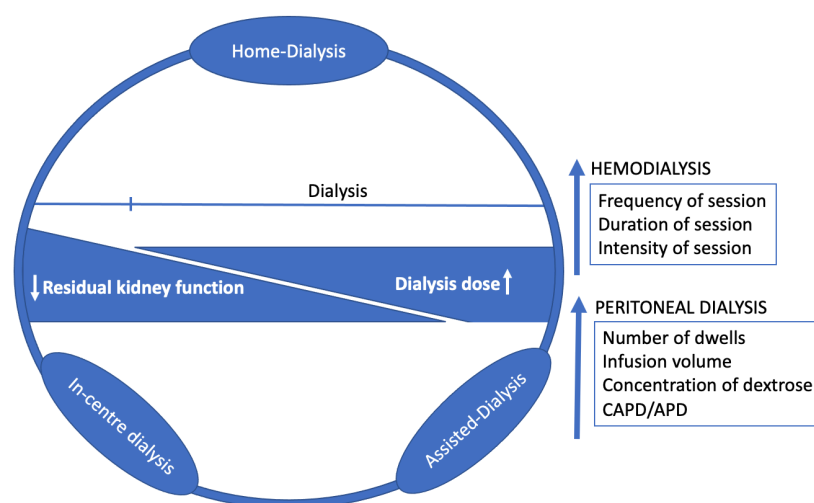
La prise de conscience récente de la viabilité et des avantages de l'hémodialyse incrémentale est l'occasion de revoir les pratiques cliniques et d'améliorer le processus d'initiation de la dialyse. La dialyse incrémentale est une approche standard dans la prescription de la dialyse péritonéale, avec un accent mis sur la qualité de la néphro-protection. Il devrait en être de même pour l'hémodialyse, avec une individualisation de la prescription : la fréquence, la durée et l'intensité, que ce soit en hémodialyse à domicile ou en centre, sont des variables de prescription à ajuster selon la fonction rénale résiduelle du patient, de son état de santé et de ses priorités psychosociales. Étant donné que l'équilibre hydrique et l'ultrafiltration régulière ont un impact critique sur la survie du patient, les programmes de dialyse incrémentale doivent être soigneusement adaptés, sur la base des mesures de routine de la fonction rénale résiduelle. Cet article soulève la question des avantages de la dialyse incrémentale, mais aussi de ses effets néfastes présumés, qui dépendent principalement de la qualité de la prescription de l'hémodialyse et des contraintes économiques externes. En comparaison, la dialyse péritonéale incrémentale est un modèle scientifiquement fondé à poursuivre, quelle que soit la modalité, basé sur des concepts actualisés de prescriptions d'adéquation des thérapies d'épuration extra-rénale centrées sur le patient.

Mots clés : dialyse incrémentale, hémodialyse, dialyse péritonéale, fonction rénale résiduelle

INTRODUCTION

More than 60 years after Clyde Shields' first session of chronic hemodialysis in Seattle, there are still questions about the best way to start treatment. In his foundational paper, BH Scribner had already pointed out the importance of the decline in estimated RKF on creatinine clearance, which led him to increase the frequency of sessions [1].

Chronic kidney disease (CKD) progression is a gradual process. Nonetheless, dialysis prescription is fundamentally empirical, and incidental dialysis patients' treatment is often the same as that of those who have long periods of kidney replacement therapy (KRT), lacking individualization and adjustment to residual kidney function (RKF). The initiation of KRT is a highly disruptive life event that is made more so by the demanding standard dialysis prescriptions caused by the underappreciation of residual kidney function (RKF). While peritoneal dialysis was always grounded in the benefit of RKF protection, a relevant analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2 clearly showed that residual renal clearance is also an important predictor of survival in hemodialysis patients [2]. Balancing KRT with RKF is the groundwork of incremental dialysis (ID). In this model, dialysis dose, either by hemodialysis (HD) or peritoneal dialysis (PD), is inversely proportional to RKF (as seen in Figure 1). This "tailored" dialysis is theoretically less aggressive than the "one size fits all" classic approach, and may therefore improve quality of life. It has also been associated with RKF preservation, though controversial data on this issue exist, showing that incremental HD may have a neutral or even detrimental effect on RKF preservation [3,4]. The lack of randomized controlled trials (RCT) of this method may be one of the reasons why ID remains a rather uncommon way of prescribing hemodialysis. This paper raises concern about ID's potential benefits as well as its putative detrimental effects, as both are mainly dependent on the quality of the hemodialysis prescription. Results presumably depend mostly on the prescribed rate of ultrafiltration per hemodialysis session, to avoid the threat of ischemic nephrons. As a comparator, incremental dialysis in peritoneal dialysis is the standard and is presented as a scientifically based model to pursue whatever the modality, based on updated concepts of adequacy in dialytic renal replacement therapies.



↑ Figure 1. Incremental dialysis paradigm

DEFINITION

ID is generally considered a prescription that delivers a dialysis dose inferior to the “standard,” but a sine qua non condition is that the lower dialysis dose should be mandatorily outweighed by RKF (Figure 1). Incremental hemodialysis (IHD) is most commonly defined as < 3 HD sessions per week (infrequent HD) or 3 sessions of less than 4 hours [5,6]. However, ID is not synonymous with infrequent or shorter dialysis, as the adjustment of dialysis intensity per session (measured as small solute clearance such as Kt/V urea) is also one way of achieving ID [7,8]. In the hemodialysis field, individualization is seldom done, and the standard of quality remains fixed on the schedule of 3 HD sessions 4 hours each /week, which does not align with the updated concept of adequacy [9].

On the other hand, in peritoneal dialysis, the systematic schedule of 4 exchanges per day with 2L solutions each has long been abandoned and substituted with incremental regimens of continuous ambulatory (for example, 3 exchanges /day, with variable intra-peritoneal volumes) or automated peritoneal dialysis “a la carte,” according to the residual renal function and patient-specific medical conditions and lifestyle options. In peritoneal dialysis, the focus of the prescription is on nephroprotection, as it is known that each mL of renal creatinine clearance is qualitatively more important and has more impact on survival than the same amount of peritoneal creatinine clearance. Dialysis prescription therefore targets supplementary doses of small solutes and fluid removal on top of residual renal function, still taking into account that standard measures of KT/V urea neglect the clinical relevance of the removal of other toxins, such as phosphate and sodium [10,11].

Therefore, incremental dialysis is in fact an individualized prescription, with adjustments in the frequency, duration, and intensity of sessions according to patient renal reserve and psycho-social demands. The question is which targets it aims to achieve and in what way those targets are conditioned by modulating such prescription variables. Prioritization of targets by clinicians and negotiation of patients’ priorities is the unsolved challenge, but the authors argue that HD should progress and mimic the quality achievements of incremental PD prescription.

Use of incremental dialysis regimens

The world prevalence of incremental hemodialysis (IHD) is unknown. In the USA, infrequent HD is used in as much as 6% of HD patients. Interestingly, an American prospective cohort of 20,000 incident dialysis patients showed that the prevalence of ID (twice-weekly hemodialysis) was 2%, although half of patients had enough RKF to allow ID [12-15]. On the other hand, as a result of economic constraints, some countries have a high prevalence of infrequent hemodialysis. But the prescription of less frequent hemodialysis regardless of RKF cannot be misclassified as ID because it lacks the pivotal balance of RKF and RRT. Consequently, the potential ID harms identified in some studies must be analyzed carefully [16].

In the field of peritoneal dialysis, the prescription of incremental dialysis has largely been advocated based on scientific evidence that considers routine residual renal function measurement, residual and peritoneal small solute clearance, and fluid balance. Such an assessment also includes the individual patient’s labor activities and social priorities. This policy has largely been uninfluenced by economic barriers and has long been the “standard” prescription in PD. Additional

investment in biocompatible peritoneal solutions has been made, with evidence that neutral pH, low-GDP PD solution improves residual renal function and urine volume preservation [17-20].

Theoretical advantages: residual renal function protection/vascular access protection/ patient reported outcomes/costs

As we learned from the work of Bricker, in the CKD setting, the surviving nephrons slowly adapt by increasing their excretory rates to compensate for the damaged ones, and this change is promoted by several stimuli like volume overload [21]. Intermittent hemodialysis can cause ischemic damage to the kidneys, leading to a faster decline in RKF, and, by overcorrecting volume expansion, may reverse the adapting phenomenon. This hypothesis is known as the “intact nephron hypothesis in reverse” [22]. Some authors advocate that less frequent hemodialysis prevents residual nephron deterioration, which manifests as RKF preservation. This consideration is supported by several cohort data in which RKF was better preserved in incremental than in conventional hemodialysis [14]. The data showed faster RKF decline in 6-times-per-week nocturnal HD versus 3-times-per-week nocturnal HD, in-center thrice-weekly HD versus PD therapy, and thrice-weekly HD treatment versus twice-weekly HD [23-34]. Additionally, Lin et al. found that patients who were converted from thrice-weekly dialysis to twice-weekly dialysis had slower RKF decline than the group of patients that remained in thrice-weekly dialysis. The first group also had fewer episodes of hospitalization [24]. Conversely, a recent cohort study of 8,000 patients showed a survival benefit associated with longer hemodialysis sessions in patients 65 years or older [35].

From the authors' point of view, these observations should be carefully questioned, because the higher ultrafiltration rate inherent in fewer or shorter treatments could promote more intense ischemic damage to the kidney, and consequently RKF decline and the associated detrimental effects [36,37]. Fluid balance and rate of ultrafiltration are key issues that are not adequately addressed in these studies, adding potential bias to the results, because extremes of dehydration and vascular congestion both threaten residual kidney function.

As previously stated, RKF is linked with several benefits for dialysis patients, such as better fluid management and less cardiovascular structural and functional disease (reduced left ventricular hypertrophy and ventricular systolic dysfunction) [38]. Moreover, RKF is associated with lower levels of inflammatory parameters, lower risk of atherosclerosis, lower abdominal aortic calcification, better nutritional status, and easier anemia and mineral-bone disease management [34,38-42]. Remarkably, even a small RKF is valuable and responsible for larger/middle molecular weight molecule and protein-bound toxin clearance [43].

Data from Frequent Hemodialysis Network and Dialysis Outcomes and Practice trials suggest that fewer arteriovenous access cannulations may extend fistula or graft patency [44,45]. Longer access survival has both clinical and economic advantages associated with less frequent interventions. Two separate trials randomized HD patients in different groups (3-times-per-week in-center HD; 6-times-per-week in-center HD; 3-times-per-week home nocturnal HD), and researchers found that the patients assigned to more frequent treatments had increased risk of vascular access complications (hazard ratio, 1.76; 95% confidence interval [CI], 1.11-2.79; P=0.017) [46].

In addition to ID possibly being a less time-consuming treatment, it has been alleged to promote

better patient satisfaction and health-related quality of life. However, several studies have failed to prove this assumption. A Korean study showed no statistically significant differences in depression burden and quality of life between ID (2-times-per-week) and 3-times-per-week HD patients [4,8]. ID benefits extend to reduced costs because fewer and shorter treatments mean fewer transportation fees, a need for fewer dialysis stations, less use of consumables and need for fewer healthcare professionals.

In PD, there is no doubt that incremental regimens, by reducing the number of CAPD exchanges and tailoring intraperitoneal volume according to body surface area and clearance needs, definitively promote better patient perception of quality of life, producing both clinical and economic gains. On the other hand, in hemodialysis, one should question whether ID is designed to reduce costs and session burdens or to tailor prescriptions according to biologic needs [47].

Considering the targets of adequacy in dialysis and leveling the benefits of incremental regimens, it is critical to include the dimensions of patient-reported outcomes, such as pain, fatigue after dialysis sessions, and treatment intrusion in their social and family lives, among other variables, including symptoms. Patients value health-related quality of life (HRQoL) and experience of care the most [9].

Additionally, the role of incremental dialysis in frail patients deserves attention, and the ongoing French study “Qualifragilys” will hopefully add relevant information (<https://clinicaltrials.gov/ct2/show/NCT03782519>).

The barriers and potential harms

The risk of higher mortality when prescribing less-frequent dialysis is one of the major concerns regarding ID. This might be because well tolerated fluid balance is an important target of dialytic support: intermittency and more rapid ultrafiltration rates are significant threats. Nonetheless, data originating from the United States of America and Shanghai renal registries showed no inferiority when survival rates between twice-weekly and thrice-weekly HD patients were compared. Some other studies showed contradictory data; however, the higher all-cause mortality was mostly observed in patients with inadequate criteria or insufficient baseline RKF [13,37,48,49]. In fact, a Korean prospective cohort study compared all-cause mortality and cardiovascular events of patients with a urine output greater than 100 ml/day under twice-weekly versus thrice-weekly HD. Mortality and cardiovascular events were higher in the twice-weekly patients, not surprisingly [37]. The allocation of patients to twice-weekly hemodialysis based on the assumption that a urine output greater than 100 ml/day is enough to support less frequent dialysis is unacceptable. It has been shown that when residual renal urea clearance is below 3 ml/min and urine output below 600 ml, there is an increased mortality risk with IHD [13,50]. Additionally, among other clinical conditions, infrequent HD may be inappropriate for patients with high interdialytic weight gain, even if RKF is supportive for ID [51]. This aspect is critical, and may well explain the reported uptick in mortality and adverse events after hemodialysis start, particularly in older patients, who are more prone to hemodialysis-induced cardiac injury [46,47]. High ultrafiltration rates and the associated intradialytic hypotension and ischemic damage are concerns in congestive patients and in those with high interdialytic weight gain [52,53].

This is a pathway to question dialysis adequacy parameters and argue about the preferred sche-

dule of ID or the respective biologic target: in center HD, is it to reduce the number of sessions in the week while maintaining their 4-hour length, or instead to maintain the standard number of sessions but reduce their length? There is now room to acknowledge that logistic and economic reasons are strongly contributing to the neglect of the opportunity for home hemodialysis, which would allow clinicians to tailor HD “a la carte,” favoring the regimen that best fits a patient’s lifestyle, preferences and biologic needs. A patient with RKF needs higher ultrafiltration benefits from hemofiltration (if fluid removal is the main target, for instance in congestive heart failure), hemodiafiltration (if simultaneous uremic toxins and fluid removal tolerance are needed) and more frequent sessions or nocturnal sessions. A euvolemic patient who has a good hemodynamic profile and who is prone to hyperphosphatemia could benefit from more frequent, shorter sessions (to promote diffusive plasma phosphate removal with high efficiency HD prescription), but mostly from longer sessions to optimize compartment phosphate removal. The kinetics of targeted solute removal deserve investigation beyond KT/V urea [54,55].

Operationalization: evaluation of residual renal function, medical therapies and patient monitoring

Nephrologists are urged to apply scientific evidence that 3 sessions/week of in-center HD at 4 hours per session does not fit all and is not the ultimate quality standard of renal replacement dialytic therapy. It deserves to be mentioned that, as recently documented by the European Kidney Health Alliance, patients with oncologic diseases other than pancreas and lung cancers have improved outcomes and higher 5-year survival than dialysis patients [19]. Neglecting RKF protection leads to debatable dialysis quality. Tailored dialysis regimens, including incremental PD, remain underused, and the outcomes lag behind expectations.

ID is incorporated in clinical practice guidelines in the peritoneal dialysis modality. Thus, incremental PD has opened the way for the growth of IHD [18,56,57]. In fact, IHD is feasible when supported by residual renal function, achieving adjusted outcomes at least similar to those of conventional HD [3,15,58].

Assessment of RKF is pivotal, and the urinary inulin excretion remains gold-standard, but it is an expensive and scarcely available method. Evaluation of RKF by estimated glomerular filtration rate (eGFR) or by urine volume is inappropriate. Urine output does not correlate with solute clearance, especially in ESKD patients, in whom tubular transport gains an especial importance. eGFR has not been validated in dialysis patients [59].

The use of a surrogate marker of uremic toxins to assess RKF and dialysis dose is a common practice in PD. Although PD favors a continuous volume and solute clearance, it is well recognized that 24-hour urine collections have daily variations in volume, urea and creatinine content. Still, real-life studies have validated the routine measurement of the average of creatinine and urea renal clearances to evaluate renal residual function and adjust dialysis prescription.

The discontinuous character of HD adds even greater difficulties in converting RKF to equivalent intermittent clearance or converting dialysis clearance to an equivalent continuous clearance. As most hemodialysis patients attend thrice weekly, urine collections should last 44 hours (the interdialytic period). The longer collection interval adds a potential greater variability due to “missed” samples [60]. Recent investigation raised the possibility of measuring RKF without

urine collection with biomarkers such as cystatin C, beta-2 microglobulin and beta-trace protein, but they need more validation [61].

However, despite the baseline RKF, the clinical indications for KRT remains the same, so ID cannot induce patients into premature dialysis, which would be unacceptable practice.

Adjunctive medical therapies play an important role in ID. Diuretic therapy helps reduce interdialytic weight gain, allowing for reduced ultrafiltration rates, which may protect RKF [62-63]. Potassium binders are useful for keeping potassium levels in an acceptable range in the prolonged interdialytic periods, but they also allow safe incorporation of anti-renin-angiotensin aldosterone agents that can additionally preserve RKF and promote better cardiovascular outcomes [64]. The use of sodium-glucose cotransporter-2 (SGLT2) inhibitors may further protect residual renal function, according to NICE

(<https://www.nice.org.uk/news/article/nice-recommend-dapagliflozin-for-people-with-chronic-kidney-disease>).

In short, a changing approach to dialysis induction is advocated: incremental hemodialysis should not be an alternative to standard HD, as incremental PD is not an alternative to standard PD. There is no standard PD: instead there is tailored PD, as HD should be. If this concept is applied, any patient is candidate for incremental HD, and its planning should start in the pre-dialytic period and highlight the critical role of nephroprotection. Patients should be advised about the inexorable transition to more burdensome and regular dialysis prescriptions if case RRF is lost. The wide range of ID prescriptions, varying from shorter to infrequent or less intense dialysis, makes it impossible to establish a RKF cut-off value for a patient to be safely included in an ID prescription. Integrated patient evaluation is needed to ascertain the criteria for ID. Nonetheless, initial urea clearance > 3 mL/min, urine volume of > 600 mL/day and interdialytic gain < 2,5Kg are generally accepted criteria for infrequent hemodialysis [13,65]. However, infrequent hemodialysis may lag behind the quality concept of incremental dialysis, as clarified in above sections. Clinical practice should incorporate the various regimens of incremental dialysis as a phase of tailored prescription in the same way as the standard care policies in peritoneal dialysis.

CONCLUSIONS

Incremental hemodialysis is an individualized treatment modality strongly linked to the updated paradigm of patient-centered dialysis prescription. As a standard of care in peritoneal dialysis, the RKF associated with IHD in a dialysis dose is a scientifically based option, and its advantages should be thoroughly considered, especially when less than 3 sessions HD/ week are prescribed. The concept of adequacy focused on residual renal function protection, sustained low ultrafiltration rates and harmonization of dialysis modalities may unlock the possibility of widespread home dialysis or assisted dialysis programs. On the other hand, we should not forget that the ID safety pillar is the amount of RKF and its monitoring. RKF decline promptly mandates further and successive dialysis adjustments, or even transition of modalities, whenever appropriate. The implementation of this patient-tailored prescription certainly challenges the standard fixed logistic and economic management of hemodialysis facilities, but it is feasible and desirable as a tool of individualized therapy plans [3,58,66].

DISCLOSURE

The authors declare that they have no conflict of interest in this article.

AUTHORSHIP

JPF : wrote the article. ASR : reviewed and corrected the article.

ETHICAL APPROVAL

This is a systematic review so none.

CORRESPONDENCE

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