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What Is Known and Unknown About Twice-Weekly Hemodialysis

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Key Words

Twice-weekly hemodialysis · Incremental dialysis · Individualized therapy · Residual kidney function · End-stage renal disease · Health-related quality of life

Abstract

Background: The 2006 Kidney Disease Outcomes Quality Initiative guidelines suggest twice-weekly or incremental hemodialysis for patients with substantial residual kidney function (RKF). However, in most affluent nations de novo and abrupt transition to thrice-weekly hemodialysis is routinely prescribed for all dialysis-naïve patients regardless of their RKF. We review historical developments in hemodialysis therapy initiation and revisit twice-weekly hemodialysis as an individualized, incremental treatment especially upon first transitioning to hemodialysis therapy. **Summary:** In the 1960's, hemodialysis treatment was first offered as a life-sustaining treatment in the form of long sessions (≥ 10 hours) administered every 5 to 7 days. Twice- and then thrice-weekly treatment regimens were subsequently developed to prevent uremic symptoms on a long-term basis. The thrice-weekly regimen has since become the 'standard of care' despite a lack of comparative studies. Some clinical studies have shown benefits of high hemodialysis dose by more fre-

quent or longer treatment times mainly among patients with limited or no RKF. Conversely, in selected patients with higher levels of RKF and particularly higher urine volume, incremental or twice-weekly hemodialysis may preserve RKF and vascular access longer without compromising clinical outcomes. Proposed criteria for twice-weekly hemodialysis include urine output >500 ml/day, limited interdialytic weight gain, smaller body size relative to RKF, and favorable nutritional status, quality of life, and comorbidity profile. **Key Messages:** Incremental hemodialysis including twice-weekly regimens may be safe and cost-effective treatment regimens that provide better quality of life for incident dialysis patients who have substantial RKF. These proposed criteria may guide incremental hemodialysis frequency and warrant future randomized controlled trials. © 2015 S. Karger AG, Basel

Introduction

Almost a decade has passed since the 2006 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommended twice-weekly hemodialysis (HD) treatment regimens for patients with substantial residual kidney function (RKF) [1]. However, with regards to HD

Table 1. Proposed criteria for twice-weekly HD

1. Urine output >0.5 liters/day
2. Interdialytic weight gain <2.5 kg (or <5% of dry weight) at intervals of 3–4 days
3. Limited or readily manageable cardiovascular or pulmonary symptoms without clinically significant fluid overload
4. Appropriate body size relative to RKF
5. Infrequent or readily manageable hyperkalemia (K >5.5 mEq/l)
6. Infrequent or readily manageable hyperphosphatemia (P >5.5 mg/dl)
7. Good nutritional status without overt hypercatabolic state
8. Appropriate responsiveness to anemia therapy with Hb >8 g/dl
9. Limited or easily manageable comorbid conditions
10. Satisfactory health-related quality of life

Patients should meet the first criterion (urine output >0.5 liters/day) plus ≥ 5 of the other 9 criteria, followed by monthly reevaluation. Consider transition to thrice-weekly HD regimen if patient's urine output decreases (<0.5 liters/day) or patient's nutritional status or general health condition shows a deteriorating trend over time. These criteria are general rather than specific and should be refined for use in clinical studies and clinical decision making. Adapted from Kalantar-Zadeh [3]. Hb = Hemoglobin; K = potassium; P = phosphorus.

adequacy targets, it is only the 'golden rule' for 1.2 single-pool Kt/V for thrice-weekly regimens that has been remembered in most dialysis-therapy practicing circles. To that end, thrice-weekly HD has continued to be regarded as the standard of care of HD treatment for patients with end-stage renal disease (ESRD) [2]. Whereas thrice-weekly HD appears to be an appropriate treatment for many ESRD patients, they continue to show markedly decreased health-related quality of life (HRQoL) and survival [3]. The cost of HD treatment is inherently high, typically 100–300 USD per treatment in most industrialized nations; hence it places an enormous financial burden on the healthcare system worldwide. Given the cumulative evidence discussed below, we believe that it is time to revisit the so-called taboo of twice-weekly HD, as an important form of individualized and incremental treatment for selected patients with ESRD [4, 5], especially upon their de novo transition to dialysis. Table 1 shows criteria recently developed by international consensus for evaluating the appropriateness of twice-weekly HD (see Kalantar-Zadeh et al. [3] for more details).

Historical Changes in HD Frequency

Historically and upon conception and establishment of HD therapy, duration and frequency of HD treatment was determined to prevent uremic symptoms, such as lethargy, pruritus, nausea, vomiting, volume overload, and peripheral neuropathy. In the early 1960's, ESRD patients were prescribed one long HD session (20–24 hours in duration) every 5 to 7 days [6]. Given the inadequate treatment of uremia with such sporadic HD treatments

and the exceptional severity of kidney failure among those patients who had little to no remaining residual kidney function (RKF), the frequency of HD treatments was gradually increased over time, concurrent with improvement in HD techniques and systems. By the late 1960's, the twice-weekly schedule was employed in many programs (fig. 1), but a high prevalence of uremic neuropathy was still observed [7]. During congressional discussions surrounding the Medicare ESRD Program legislation in 1973, the thrice-weekly schedule was thought to provide a more beneficial HD regimen and was considered 'the best compromise' to deliver HD treatment to as many patients as possible with the limited resources available [6]. Prior to this, HD was literally a life-sustaining intervention in only selected ESRD patients, and very few diabetic or elderly patients were accepted for treatment.

Since then, there has been rapid and innovative progress in HD techniques, equipment, and practices, including fully computerized HD machines, better biocompatibility and performance of dialysis membranes, higher purity of dialysate, and more frequent creation and greater longevity of arteriovenous fistulas. These advances have made HD treatments more streamlined, efficient, and less costly, allowing for an expansion of patients who are eligible for HD treatment, including those who are elderly and/or have multiple comorbidities requiring earlier transition to dialysis while still having substantial RKF. Indeed, in 2012, more than 40% of ESRD patients who started HD were diabetic, and more than 50% were aged ≥ 65 years in both the US and Japan [8, 9]. Treatment time to achieve targeted solute clearance was also decreased over time [10]. International data has shown that over the period of 1999 to 2011,

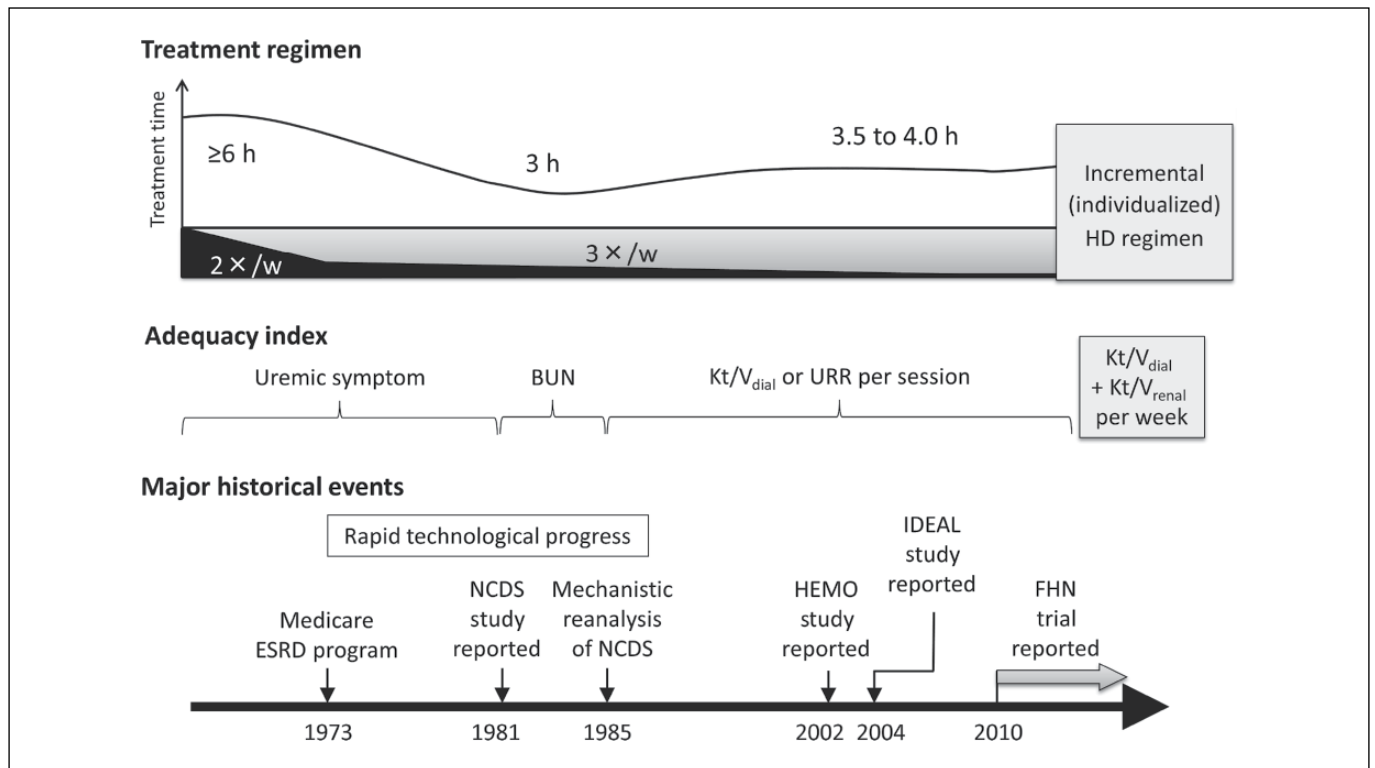


Fig. 1. History of treatment regimens and the major events that affected clinical practice in maintenance hemodialysis. Figure adapted from Lacson and Brunelli [10]. BUN = Blood urea nitrogen; URR = urea reduction ratio.

mean treatment time was approximately 220 and 240 minutes in the US and Japan, respectively [11]. These changes along with the thrice-weekly HD schedule enabled dialysis facilities to provide two alternating every-other-day schedules (Monday-Wednesday-Friday or Tuesday-Thursday-Saturday) across ≥ 3 shifts per day, leaving Sunday as the universal 'day-off' for both patients and dialysis staff [3]. Nevertheless, in some countries such as the UK, there are dialysis centers that also offer Sunday schedules [12].

Conflicting Results from Clinical Trials Evaluating HD Adequacy: Effect Modification by Residual Kidney Function

As HD treatment became established and widely available, the goals of caring for ESRD patients shifted from a focus upon increasing short-term survival towards improving long-term outcomes. There was strong belief that greater solute clearance should lead to better survival. This notion was further strengthened by the 1981 Na-

tional Cooperative Dialysis Study (NCDS) which showed that maintaining lower time-averaged blood urea nitrogen concentrations decreases treatment withdrawals and hospitalizations [13]. Although the HEMO Study failed to prove this concept by using higher HD dose or high-flux membranes [14], the Frequent Hemodialysis Network (FHN) Daily Trial reported somewhat favorable effects of 6-times-per-week in-center HD largely upon changes in left ventricular mass and physical health composite score, as compared with conventional thrice-weekly HD [15]. The FHN Nocturnal Trial showed similar trends [16], but the extended follow-up study found higher mortality in patients randomly assigned to frequent nocturnal HD [17].

Although these results may seem conflicting, the beneficial effects of high HD dose or frequency in some of these studies are likely observed in patients with little or no RKF. The NCDS trial limited participants to those who had creatinine clearances < 3 ml/min [13], but in contemporary practice, patients are typically transitioned to HD when kidney function is above this threshold. A subgroup analysis of the HEMO study suggested that pa-

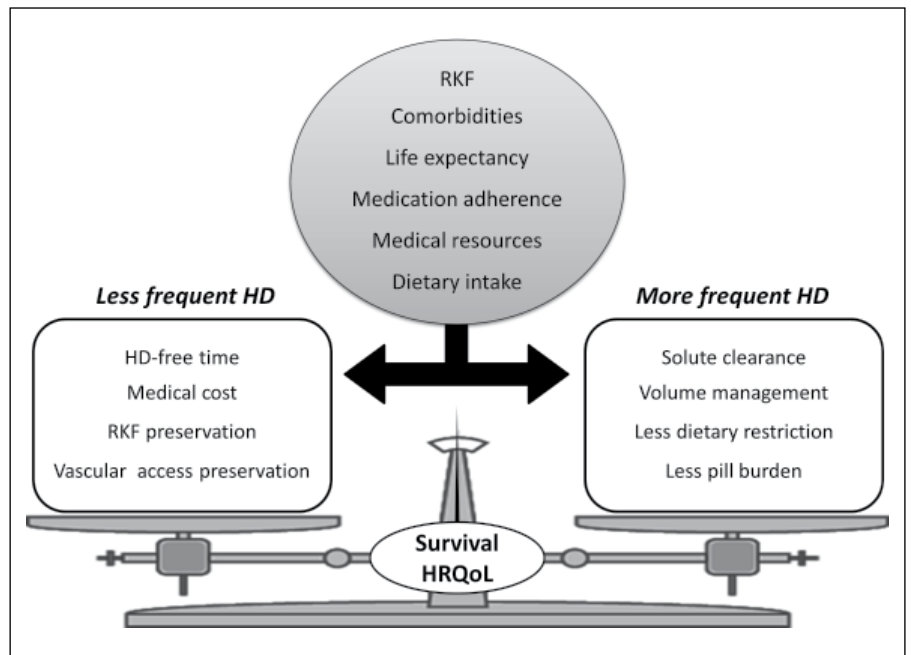


Fig. 2. Benefits from a less or more frequent HD schedule and their potential effect modifiers.

tients with longer dialysis vintage (≥ 3.7 years), most of whom were presumed to have little RKF, may benefit from receipt of the high-flux dialysis membrane [14]. In the FHN Daily Trial, 84% of patients had dialysis vintage ≥ 2 years, and 66% were anuric [15]. In contrast, in the FHN Nocturnal Trial where higher mortality was observed in the frequent nocturnal HD group, patients had a comparatively lower median dialysis vintage of approximately 1 year, and 47% of patients had urine volume >500 ml/day [17]. It is important to note that in the latter study, patients who received more frequent HD had significantly faster loss of their RKF [18]. This unfavorable outcome has been highlighted in commentaries by Daugirdas et al. [18], Kalantar-Zadeh et al. [3, 4], Rhee et al. [2], and Wong et al. [5]. The Initiating Dialysis Early and Late (IDEAL) study also showed similar results, such that earlier initiation of HD did not improve survival nor major clinical outcomes [19], suggesting that HD treatment offers little benefit to patients with substantial RKF.

Therefore, the expected benefit of HD treatment should be weighed against potential adverse effects on a case-by-case basis as discussed below (fig. 2). The balance between the benefits and harms of HD treatment may be influenced by several factors such as life expectancy, dietary intake (i.e., protein, sodium, potassium, and phosphorus), medication adherence, access to medical resources, and, most importantly, RKF.

Potential Benefits of Twice-Weekly HD

We argue that twice-weekly HD in the current era is not a suboptimal treatment regimen for patients with substantial RKF as compared with conventional thrice-weekly HD. Using the equation for standard Kt/V_{urea} by Daugirdas et al. [20], urea clearances in thrice-weekly HD versus twice-weekly HD treatment regimens with 1.2 single-pool Kt/V and 210-minute treatment times are equivalent to 9.3 ml/min versus 6.15 ml/min, respectively. This differential in urea clearance is similar to the minimum threshold RKF level of 3.0 ml/min at which twice-weekly HD is recommended by the KDOQI guidelines [1]. This major differential in clearance bears substantial clinical significance, and it is doubtful that other interventions (such as increasing HD dose per session, enhancing dietary management, and use of drugs including erythropoiesis-stimulating agents, phosphate binders, and calcimimetics) offer the same degree of benefit as preservation of RKF. Given that over 100,000 patients initiate HD annually in the US, among whom 45% have estimated glomerular filtration rates ≥ 10 ml/min/1.73 m² upon dialysis initiation [8], appropriate implementation of twice-weekly HD may have a favorable impact upon ESRD patient outcomes as well as considerable economic advantages. Currently available evidence for less frequent HD is summarized in table 2.

Table 2. Summary of studies examining the association between infrequent hemodialysis and clinical outcomes

Study Author (Journal, Year)	Cohort description	Exposure (vs. thrice-weekly HD)	Results
Mortality			
Hanson et al. [27] (Am J Nephrol 1999)	Incident HD (n = 4,888) Prevalent HD (n = 10,179)	Twice-weekly HD	Lower adjusted mortality risk in both incident and prevalent HD patients. This association was attenuated after adjustment for RKF at HD initiation (available only in incident patients).
Lin et al. [28] (Blood Purif 2012)	Incident HD (n = 639) Prevalent HD (n = 673)	Twice-weekly HD	Similar adjusted mortality risk overall as well as subgroups of incident and prevalent patients (RKF data not available).
Stankuviene et al. [39] (Medicina 2010)	Incident HD (n = 2,428)	Once- and twice-weekly HD	Higher adjusted mortality (RKF data not available)
Elamin and Abu-Aisha [40] (Arab J Nephrol Transplant 2012)	Prevalent HD (n = 2,012)	Twice-weekly HD	Higher 1-year crude mortality (85% vs. 89%)
Fernández-Lucas et al. [23] (Nephrologia 2012)	Incident HD (n = 95)	Incremental HD	Greater crude survival
Residual renal function			
Lin et al. [22] (Nephrology 2009)	Prevalent HD (n = 74)	Twice-weekly HD	Greater RKF preservation (without adjustment)
Fernández-Lucas et al. [23] (Nephrologia 2012)	Incident HD (n = 95)	Twice-weekly HD	Greater RKF preservation (without adjustment)
Caria et al. [38] (BMC Nephrology 2014)	Incident HD (n = 68)	Once-weekly HD with low protein diet	Greater RKF preservation (without adjustment)
Zhang et al. [24] (Am J Nephrol 2014)	Incident HD (n = 85)	Twice-weekly HD	Greater RKF preservation (without adjustment) Odds ratio for faster RKF loss was 7.2 after adjustment for sex, urea reduction rate, and intradialytic hypotension episode.
Nutritional parameters			
Supasynndh et al. [41] (J Med Assoc Thai 2009)	Prevalent HD (n = 142)	Twice-weekly HD	Similar nutritional laboratory parameters and protein intake, but greater energy intake
Lin et al. [22] (Nephrology 2009)	Prevalent HD (n = 74)	Twice-weekly HD	Similar nutritional laboratory parameters
Updated from Rhee et al. [2].			

Preservation of RKF

RKF in dialysis patients plays important roles in fluid and salt removal, effective phosphorus excretion, middle-molecule clearance, and endogenous vitamin D and erythropoietin production [2–4]. It has also been associated with higher HRQoL, lower inflammation, reduced left ventricular hypertrophy, and better survival. However, RKF decline is faster in patients receiving thrice-weekly HD therapy than in those receiving peritoneal dialysis [21]; whereas HD per se may accelerate RKF decline

by episodic ischemic insults to the kidney, provision of less frequent HD may mitigate this potential risk of HD. Indeed, consistent with the results from the FHN study that showed faster loss of RKF in frequent nocturnal HD compared with conventional thrice-weekly HD [18], several non-controlled clinical studies indicated that twice-weekly HD may preserve RKF [22–24]. In a study of 85 incident HD patients in Shanghai initiated on either a twice-weekly or thrice-weekly HD regimen, a greater proportion of patients receiving twice-weekly HD had

preservation of RKF during the first year of HD initiation [24]. There are complementary studies suggesting that dialysis dose did not have a significant impact on outcomes in patients with certain levels of RKF [25, 26], supporting the notion that twice-weekly HD for such patients may be an appropriate choice.

Survival and HD Frequency

In a retrospective study cohort conducted by the US Renal Data System in the late 1990s, 6.1% and 2.7% of the patients underwent twice-weekly HD treatment regimens in 4,888 incident and 10,179 prevalent HD patients, respectively [27]. Factors associated with twice-weekly HD schedules included older age, female gender, white race, shorter dialysis vintage, higher serum albumin, lower serum creatinine, lower body mass index, and greater baseline RKF at the time of HD initiation. After adjustment for demographics, cause of ESRD, comorbid conditions, and nutritional status, twice-weekly HD regimens showed 21% and 24% lower mortality risk in incident and prevalent HD patients, respectively, versus thrice-weekly HD. This survival differential was attenuated upon adjustment for baseline RKF, which was available only in incident HD patients. There are two additional studies that also reported better survival among patients who received twice-weekly HD without adjustment for RKF [23, 28]. None of these studies have examined the level of RKF where patients could benefit from twice-weekly HD.

Other Potential Benefits

Having twice-weekly HD sessions will also result in less frequent arteriovenous fistula or graft cannulations, which may prolong the longevity of dialysis vascular access [4]. The FHN study has shown that compared with conventional HD, more frequent HD was associated with higher risk of vascular complications including repair, loss, or vascular access related hospitalization; this was thought to more likely be a consequence of increased HD frequency than heightened surveillance [29]. Additionally, by having one less HD treatment a week, patients can spend more time engaging in activities outside of the dialysis unit, which may lead to substantially better quality of life [2–4]. Ironically, certain populations such as patients who are elderly, have advanced cancer, or have other severe comorbid conditions are less likely to benefit from more frequent dialysis, and less frequent HD with conservative management may be considered as a palliative option even when such patients have limited RKF.

Potential Disadvantages of Twice-Weekly HD

Interdialytic Weight Gain and Ultrafiltration

Several studies have identified the long (2-day) interdialytic interval as an independent risk factor for all-cause mortality and cardiovascular hospitalization in patients treated with thrice-weekly HD [30–32], likely due to fluid overload and/or electrolyte derangements. Although the potential complications of the long interval may seem to counteract the benefits of twice-weekly HD, adverse outcomes associated with the long interdialytic interval were not observed among incident HD patients [30], many of whom likely have a higher RKF than prevalent patients and thus maintained better electrolyte and fluid balance. Moreover, it is possible that the higher mortality of the long interdialytic interval relates to excess dialysis and abrupt removal and shifts of fluid and electrolyte (e.g., potassium) [12].

There may be misconceptions that larger interdialytic weight gains (IDWG) will be observed with twice-weekly HD schedules compared with thrice-weekly schedules, and that aggressive ultrafiltration may be required to remove excess fluid accumulated during the interdialytic HD interval. Whereas large IDWGs may promote left ventricular hypertrophy and congestive heart failure by increasing afterload and myocardial oxygen demand [33], this should not be the case in patients with substantial RKF who are compliant with restriction of fluid intake. Indeed, it is plausible that more frequent HD may lead to greater IDWGs and cardiac structural abnormalities over time due to faster loss of RKF [18]. Rapid ultrafiltration rates may also contribute to intradialytic hypotension, subclinical cardiac stunning, and myocardial ischemia [34]. Greater IDWG ($\geq 5\%$ of dry weight) and higher ultrafiltration rates (≥ 10 ml/h/kg) are associated with higher risk of mortality [35, 36], and patients with advanced heart disease may require longer or more frequent HD treatments [37]. Aggressive ultrafiltration often causes cramping, dizziness, and fatigue that makes dialysis intolerable. Other potential unfavorable features of twice-weekly HD that bear mention include persistent azotemia and electrolyte disturbances (e.g., hyperkalemia, hypercalcemia, and hyperphosphatemia), but these complications are less likely to occur in patients with substantial RKF who are the optimal candidates for twice-weekly HD [3].

Nutritional Status and Dietary Intake

Whereas thrice-weekly HD patients are recommended to have high dietary protein intake (1.2–1.3 g/kg/day), which is in sharp contradistinction to non-dialysis

CKD patients who are prescribed low protein diets (0.6–0.7 g/kg/day), there is no known dietary recommendation for patients on twice-weekly therapy with substantial RKF. Dietary intake may also appear to affect the fine balance of HD frequency in conflicting ways, as patients with intact appetite usually have good nutritional status, while their serum concentrations of urea nitrogen, potassium, and phosphorus tend to be high.

Caria et al. [38] from Italy has recently suggested that infrequent HD regimens of once-weekly HD, complemented by very low protein, low phosphorus diets supplemented with ketoacids had favorable impact on preserving patients' urine output. We currently propose an averaged dietary protein intake of 0.8–1.0 g/kg/day to most twice-weekly HD with substantial RKF, while on non-dialysis versus dialysis days the dietary protein intake may be comparatively lower versus higher, respectively.

Other Considerations

Incremental transition from twice-weekly to thrice-weekly HD may be eventually considered when increase in dialysis dose fails to compensate for decreased RKF. However, RKF decline rates differ across HD patients, and without regular assessment of patients' RKF and urine output, the appropriate juncture for increasing HD frequency may be overlooked or missed. As this time, there is little evidence as to which patients prescribed twice-weekly HD may continue to benefit from this treatment regimen over time, as opposed to require transition to more frequent HD regimens. It may also be challenging to convince patients who are accustomed to the twice-weekly HD regimen to increase their dialysis time and/or frequency, which may be inevitable if their RKF declines over time. We feel that the criteria set forth by international consensus (see table 1) is an excellent tool to routinely assess the need for such transitions and to communicate with patients when the appropriate time arrives.

Conclusions

Incident dialysis patients with substantial RKF (e.g., KRU >3.0 ml/min/1.73 m² [1]) are likely good candidates for twice-weekly HD, while those with little or no RKF may benefit from conventional thrice-weekly or even more frequent HD, depending on other factors including age, comorbid conditions, and dietary intake. Twice-weekly HD schedules may play an important role

as the first regimen for patients incrementally initiating HD, and also as a palliative approach for conservative management in certain populations in order to optimize HRQoL and resource utilization. However, implementation twice-weekly HD has been hindered by a paucity of evidence of its associated outcomes (benefits and risks). To that end the traditional view of nephrology communities in affluent nations has been that twice-weekly HD is an inferior option and a discussion taboo; however there has very recently been a surge of provocative literature leading to its reconsideration [2–5]. The recently developed consensus criteria for implementing twice-weekly HD is an important development in promoting the concept of individualized incremental HD regimens, and they need to be validated and refined in future research studies.

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Conflicts of Interest

KKZ has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, Aveo, Chugai, DaVita, Fresenius, Genetech, Haymarket Media, Hospira, Kabi, Keryx, NIH, National Kidney Foundation, Relypsa, Resverlogix, Sanofi, Shire, Vifor, and ZS-Pharma.

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