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Let us give twice-weekly hemodialysis a chance: revisiting the taboo

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The thrice-weekly hemodialysis (HD) regimen is considered the ‘standard of care’ for both initiation and maintenance of this therapy. Historically, however, HD started with two treatment sessions per week in the 1960s and 70s, but by the early 1980s the HD frequency had increased to thrice-weekly [1]. This development was partly enhanced by the 7-day nature of a week providing two alternating every-other-day shifts of Monday-Wednesday-Friday versus Tuesday-Thursday-Saturday, leaving Sunday as the universal off-day for both patients and dialysis staff to recuperate. Thrice-weekly HD has established itself as the default format without any randomized controlled trial to examine whether less frequent HD treatments including twice-weekly HD would be inadequate or harmful [2]. Clinical practice guidelines generally advise against a less than thrice-weekly HD schedule, which is considered as inferior. These guidelines do not recommend incremental transition from less to more frequent HD over time, while ironically according to most peritoneal dialysis (PD) guidelines PD dose is to be adjusted upwards parallel to decline in residual kidney function, the preservation of which is a high priority target in PD [2, 3].

Although chronic kidney disease (CKD) patients with worsening kidney function are told that it is in their best interest to switch their life style from non-dialysis dependent status to full-blown thrice-weekly HD, the twice-weekly HD regimen has continued to be practiced, although often as the unwanted or inferior modality that would happen in ‘non-compliant’ dialysis patients who would not agree with the thrice-weekly schedule, or under certain suboptimal circumstances including financial constraints or resource scarceness. To most European and American nephrologists, twice-weekly HD treatment is considered substandard, to be out of the question and a taboo.

Over the past 30 years, major trials of HD adequacy (Kt/V), modality (nocturnal, home or in-center) and frequency (daily

HD) have been anchored to thrice-weekly HD regimens as the gold standard, including the HEMO Study which failed to prove survival advantages of higher HD dose [4]. Interestingly, a recent randomized controlled trial suggested that more frequent (more than thrice-weekly, such as daily) HD may provide patient outcome benefits [5]. What is important to note is that the challenge of preserving the residual kidney function or urine output in HD patients has never been taken as seriously, in contrast to PD discussions where efforts to maintain residual kidney function are the core component of the dialysis therapy. It has remained widely unknown whether twice-weekly HD regimen can preserve residual kidney function longer, especially upon transition to renal replacement therapy and, if so, whether the longer lasting urine output would confer significant survival benefits to such HD patients as it does to their PD counterparts. This question has recently become more relevant when a recent controlled trial showed that more frequent (daily) HD was associated with faster loss of residual kidney function than thrice-weekly HD regimen [6]; hence, the logical inference is that twice-weekly HD may preserve residual kidney function longer than the thrice-weekly regimen. There are additional pertinent questions including patient-related outcomes such as the possibility that twice-weekly HD leads to a higher level of patient satisfaction and better health-related quality of life. Moreover, the twice-weekly HD schedule may offer a more efficient way of resources utilization, given the possibility to dialyze three twice-weekly patients (Monday-Thursday, Tuesday-Friday and Wednesday-Saturday) in lieu of two thrice-weekly patients while using the same finances, space and staff. All in all, there are reasons to believe that twice-weekly HD may offer certain advantages—or at least may not be inferior—to thrice-weekly HD schedule. The ultimate question is whether the twice-weekly regimen would lead to better or worse survival.

In this issue of *Nephrology Dialysis Transplantation*, a contemporary comparison was undertaken between the dialysis

practice pattern in China and several other countries that have participated in the *Dialysis Outcomes and Practice Patterns Study* (DOPPS) in order to juxtapose the utilization of twice-weekly HD schedule in China versus other countries [7]. The investigators found that in a representative sample of 1379 Chinese HD patients in 45 dialysis centers of the three largest cities in China (Beijing, Shanghai and Guangzhou) 26% of the patients received twice-weekly HD treatment, whereas this proportion was <5% in 11 054 patients from all other DOPPS countries during the 2009–11 period. Further examination of the characteristics of the twice-weekly patients in China showed that they were more likely to be women and to have shorter dialysis vintage. These findings suggest that less frequent HD is offered more likely to newer (incident) patients with more recent transition to renal replacement therapy [7]. The observed lower socioeconomic status with less health insurance coverage among Chinese patients with a twice-weekly HD regimen implies the potential role of financial constraints in the choice of HD frequency. Interestingly, there were less diabetic and hypertensive patients among the twice-weekly patients, which may indicate that the infrequent HD is offered more to healthier patients. While the standardized Kt/V was lower in China (2.01) than other countries (2.12–2.27), among Chinese dialysis patients twice-weekly HD was associated with longer treatment times but lower standardized Kt/V. Of note, however, the reported health-related quality of life scores were similar between twice- and thrice-weekly HD patients suggesting that patients were equally happy (or unhappy) with both HD regimens [7].

Whereas an important contribution of the study is to embolden dialysis experts and nephrologists to revive the discussion about the potential harms and benefits of twice-weekly HD, a 30-year old taboo in Western nephrology, this paper also highlights the fast rising status of such emerging economies as China and India with their gigantic share of world populations and finances including their evolving leadership on health-related practice pattern. While in China, only a quarter of dialysis population receives twice-weekly HD according to the current study [7], twice-weekly HD regimen may be the routine regimen in half or even larger proportion of the dialysis patients in many other countries including India, Thailand, Vietnam, the Philippines, Indonesia, Bangladesh, Pakistan, etc. [8]. China's staggering development over the past decade is now challenging the economic superiority of the Western world [9]. Nevertheless, this fast rising star is now also suffering from the same side effects of modern lifestyle as Western societies including substantial increases in the rates of metabolic syndrome, obesity, diabetes, hypertension and now CKD [10]. The ongoing struggles of China and India with the challenge of fast transition to the world power status offer unique opportunities to revisit some of the extinguished health care scenarios in Western societies including twice-weekly or even less frequent HD therapy. In doing so, we call for open-mindedness and acceptance of some potentially bitter facts about our own failures in the West including 15–20% mortality rates of dialysis populations in Europe and the USA and even worse mortality during the first year of conventional thrice-weekly HD, annualized to 35–40% in the first 3 to 6 months of HD

[11]. Although there are a number of possible explanations for this exceptionally high death risk in the first year of dialysis therapy [8, 12], the abrupt transition from non-dialysis-dependent CKD to thrice-weekly HD stands out as a potential contributor.

Is it possible that twice-weekly and incremental HD, at least during the first 6 to 12 months of dialysis initiation, save more lives and improve patients quality of life? Can residual kidney function be preserved longer with less frequent HD? Does twice-weekly HD offer a more appropriately conservative therapy and a type of palliative approach for older and sicker patients with terminal conditions or those in Hospice; or ironically is infrequent HD a better regimen for younger and healthier patients with good residual kidney function (e.g. >0.5 L/day of urine output) who desire more dynamic life style? Can twice-weekly HD improve financial challenges and resource constraints from the richest to the poorest regions of the world? What are the criteria to start and to maintain twice-weekly HD? While there are no established guidelines, we believe that in determining the eligibility for twice-weekly HD and guiding through incremental HD decisions, urea kinetic modeling (UKM) should not be used. Instead of relying on UKM, future randomized controlled trials to compare twice versus thrice-weekly HD should rather be based on other clinical metrics including body weight, blood pressure and chemistry panels, and in particular urine output, e.g. > 0.5 L/day [13]. If a monitoring surrogate similar to UKM is desirable, then maybe the combined clearance of urea and creatinine should be utilized with a possible measure of beta-2-microbulin, but probably this would be beyond the scope of the editorial.

Questioning the wisdom of the 30-year-old paradigm of thrice-weekly HD treatments is a major challenge. However, we dare to question the wisdom of 'the one HD regimen is good for all' and propose to examine the role of personalized and incremental HD, ranging from once a week to daily HD. Undoubtedly there is an urgent need to conduct head-to-head randomized controlled trials upon transition from late-stage CKD to kidney replacement therapy [13]. If PD has an incremental and individualized approach [14], so should HD [15].

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CONFLICT OF INTEREST STATEMENT

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(See related article by Bieber *et al.* Two-times weekly hemodialysis in China: frequency, associated patient and treatment characteristics and Quality of Life in the China Dialysis Outcomes and Practice Patterns study. *Nephrol Dial Transplant* 2014; 29: 1770–1777.)

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Intestinal adsorption of uraemic toxins: a new strategy for anaemia management?

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Resistance to erythropoiesis-stimulating agents (ESAs) is an increasing problem influencing the successful management of anaemia in patients with chronic kidney disease (CKD). Hyporesponsiveness to ESAs may occur at the start of the treatment or subsequently and it may be transient or persistent. The importance of this issue is evidenced by the association of hyporesponsiveness with adverse outcomes in both haemodialysis and non-dialysis CKD patients [1–5]. Furthermore, the importance of detecting ESA hyporesponsiveness is also underlined by the fact that in the USA, hyporesponsive patients (those receiving epoetin at a dose >450 IU/week) consumed 52.5% of the total ESAs prescribed [6]. Despite the clinical relevance of ESA hyporesponsiveness, no standardized definition of this phenomenon has been produced. Different criteria have

been proposed for defining initial hyporesponsiveness such as the Hb increase induced by the initial ESA dose [2–4], the ratio between ESA dose and patient Hb level, the so-called resistance index [7, 8], or the prescription of high-ESA dose (>450 U/kg/week IV epoetin or 1.5 µg/kg of SC darbepoetin) [1, 9]. More recently, KDIGO Guidelines classified ESA hyporesponsiveness as ‘initial’ (if there is no increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing) or ‘subsequent’ (if there is need for two increases in ESA doses up to 50% beyond the dose at which the patient had been stable in order to maintain a stable Hb level) [10]. The lack of a universally accepted definition has produced various estimates of prevalence of ESA hyporesponsiveness in haemodialysis patients ranging from 7.3 to 17.6% [11]; similar