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## Twice-Weekly and Incremental Hemodialysis Treatment for Initiation of Kidney Replacement Therapy

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### Abstract

Mortality is highest in the first months of maintenance hemodialysis (HD). In many Western countries, patients who transition to kidney replacement therapy usually begin thrice-weekly HD regardless of their level of residual kidney function (RKF). RKF is a major predictor of survival. RKF may decline more rapidly with more thrice-weekly HD treatments, is associated with a reduced need for dialytic solute clearance, and is an important factor in the prescription of peritoneal dialysis. In this paper we review the concept of incremental HD, in which weekly dialysis dose, in particular HD treatment frequency, is based on a variety of clinical factors such as

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RKF (including urine output >0.5 L/day), volume status, cardiovascular symptoms, body size, potassium and phosphorus levels, nutritional status, hemoglobin, comorbid conditions, hospitalizations, and health related quality of life. These ten clinical criteria may identify which patients might benefit from beginning maintenance HD twice-weekly. Periodic monitoring of these criteria will determine the timing for increasing dialysis dose and frequency. We recognize that twice-weekly HD represents a major paradigm shift for many clinicians and jurisdictions. Therefore, we propose conducting randomized controlled trials of twice-weekly vs. thrice-weekly HD to assess the potential of twice-weekly HD to improve survival and health related quality of life while simultaneously reducing costs, protecting fragile vascular accesses, and optimizing resource use. Such incremental and individualized HD therapy may prove to be the most appropriate approach for transitioning to dialytic therapy.

## Keywords

Transition of care; residual kidney function; incremental dialysis; incremental hemodialysis; end-stage renal disease; kidney replacement therapy; renal replacement therapy

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Currently, there are over 400,000 people who receive maintenance hemodialysis (HD) in the United States. The prevalence of HD patients is increasing, with approximately 100,000 new starts and 80,000 deaths each year.<sup>1</sup> While HD is life-sustaining, maintenance dialysis patients have marked decrements in health-related quality of life (HRQOL) and a seven-fold increase in mortality compared to the general population.<sup>1</sup> Mortality during the first year of conventional thrice-weekly HD is unacceptably high (see Figure 1) even though 45% of patients have an eGFR  $\geq 10$  ml/min/1.73 m<sup>2</sup> when they initiate dialysis therapy.<sup>2</sup> Despite multiple studies, the cause of the exceedingly high mortality in the first year of transition to conventional HD treatment remains unclear.<sup>3, 4</sup> Whereas there are many potential risk factors for this exceptional death rate in the first months of dialysis therapy,<sup>5, 6</sup> the most obvious change is the abrupt transition from non-dialysis dependent CKD to thrice-weekly HD, although no study has examined whether a gradual and incremental transition to HD therapy with less HD frequency would have improved the dismal first year survival rate. The observed high mortality in the first year of HD may also be the result of confounding by indication as a result of clinical deterioration that may prompt the physician to initiate thrice-weekly HD in very sick patients or may be caused by the initiation of HD, including a truly causal effect of thrice-weekly HD treatment. Therefore, the relationship may be complex and similar to the association of high doses of erythropoiesis stimulating agents (ESA) and thromboembolic events and mortality, which encompasses both confounding by indication (as sicker patients with ESA hyporesponsiveness usually need higher ESA doses) and true harm of ESAs, including harm due to relative thrombocytosis.<sup>7</sup>

## Residual Kidney Function

Progressive loss of RKF in incident dialysis patients is associated with increased death risk over time.<sup>8-10</sup> Nevertheless, mortality is the highest in the first several months of dialysis therapy<sup>4</sup> when most patients starting kidney replacement therapy have their highest RKF. The loss of RKF is faster in patients on HD than those receiving peritoneal dialysis (PD).<sup>10, 11</sup> HD may cause episodic ischemic damage to the kidneys, leading to repetitive

bouts of ischemic events similar to acute kidney injury (AKI).<sup>8,9</sup> Notwithstanding the ongoing debate about the causal link between AKI and subsequent CKD<sup>12</sup> and that the use of the term “AKI” may not be appropriate for the mechanism of the faster loss of RKF in HD patients, the cumulative effect of repetitive ischemic events may accelerate the decline in RKF.<sup>8,9</sup> Consistent with this hypothesis, the recent Frequent Hemodialysis Network (FHN) study showed that frequent nocturnal HD may accelerate loss of RKF.<sup>13</sup> Intense dialysis therapy may also remove the stimulus for the hyperfunctioning of the remaining nephrons, which would be consistent with Bricker’s “intact nephron hypothesis”.<sup>14</sup>

Higher RKF in dialysis patients has been associated with improved HRQOL, a decrease in pro-inflammatory mediators, and improved survival.<sup>15</sup> The rate of loss of RKF over time may correlate with mortality risk.<sup>16</sup> Higher RKF may be related to greater survival through different mechanisms, including better fluid and salt removal, more effective phosphorus excretion, better middle molecule clearance, more endogenous vitamin D and erythropoietin production, reduced left ventricular hypertrophy, and less inflammation.<sup>8–11, 17</sup> Indeed a survival advantage of diuretic therapy in dialysis patients may be related to RKF.<sup>18</sup>

Consistent observations suggest that RKF declines more rapidly in patients on HD than PD. In a recent study, 617 of 734 (84%) HD patients reported good urine output at baseline, but only 28% had acceptable RKF after one year.<sup>15</sup> Preserved RKF was independently associated with lower mortality (HR, 0.70; 95% CI, 0.52–0.93) and better HRQOL, lower C-reactive protein (p=0.02) and IL-6 (p=0.03) levels and, 12,000 U/wk lower erythropoietin doses (p<0.001).<sup>15</sup> Incremental dialysis has been used successfully in the initiation of PD. Therefore, it seems prudent to revisit the topic of incremental HD and plan a randomized controlled trial to explore the hypothesis that transitioning to kidney replacement therapy with incremental HD may preserve RKF longer and decrease mortality during the first year of HD. Several investigators, including Termorshuizen et al.,<sup>19</sup> Bargman et al.<sup>20</sup> and Szeto et al.<sup>21</sup> have reported that among patients with substantial RKF, dialysis dose did not have a significant impact on outcomes.

## Relationship of Twice-Weekly HD to Outcomes

In the United States, twice-weekly HD with longer duration of each treatment<sup>22</sup> was replaced by thrice-weekly HD as the standard of care some 30 years ago.<sup>23</sup> Unfortunately, however, no clinical trials have compared twice-weekly vs thrice-weekly HD. Currently, in some countries, including India and China, over half of HD patients receive 2 treatments per week. Some patients are dialyzed even less frequently, e.g. once weekly to even once a month. This practice pattern may largely reflect limited resources and financial constraints. Nevertheless it may be associated with improved outcomes in some patients.<sup>11, 24</sup> In a seven-year observational study in Taiwan,<sup>11</sup> patients dialyzed twice (n= 23) versus thrice (n=51) weekly had a slower decline of RKF, as indicated by higher urine output and better creatinine clearance. Patients dialyzed twice weekly also had lower levels of serum beta-2-microglobulin, fewer intra-dialytic hypotensive episodes, and fewer hospitalizations.<sup>11</sup>

Hanson et al.<sup>25</sup> reported that among 15,067 adult HD patients, the 570 patients who were receiving twice-weekly HD were more likely to be older, White, and women and to have

shorter dialysis vintage (<1 year), higher serum albumin, lower serum creatinine, lower BMI, and higher eGFR upon transition to maintenance dialysis therapy.<sup>25</sup> Interestingly, twice-weekly HD patients had a 24% *lower adjusted mortality* (RR=0.76, p=0.02), although among incident patients the survival advantage of infrequent HD was not significant when adjusted for RKF (RR=0.85, p=0.31).<sup>25</sup> Notably, outcomes were no worse with the more convenient, less intrusive, and less costly schedule. The observed survival advantage among patients receiving twice-weekly HD may have reflected higher baseline RKF and longer preservation of RKF. Unfortunately, however, data on RKF were not collected in this study.<sup>25</sup> Therefore, a carefully planned and adequately powered randomized controlled trial is needed to determine if the apparent survival advantage of infrequent HD is mediated, at least in part, from higher baseline RKF or improved preservation of RKF.

Several historical reports and reviews have advocated the use of incremental or infrequent (including twice-weekly) HD upon the first transition to kidney replacement therapy in the United States.<sup>26, 27</sup> Some of these recommendations stem from the 1997 KDOQI Peritoneal Dialysis Adequacy Work Group report published in *AJKD* in 1998 that suggested using incremental PD to maintain the RKF,<sup>28</sup> as well as from the European Best Practice Guidelines Expert Group on Hemodialysis.<sup>29</sup> According to some of the authors of this Perspective, nephrologists caring for US veterans with chronic kidney failure often encounter patients who insist on initiating hemodialysis twice-weekly instead of the routine thrice-weekly protocol. Some nephrologists may not be adverse to this arrangement as long as patients are clearly informed that their choice is not considered the standard of care in the US. Many patients may choose less frequent HD because of reluctance to travel inconvenient distances three times a week, skepticism about their need for more frequent dialysis (or dialysis at all), involvement with infirm family members and children requiring time and attention, or post dialysis fatigue, among other reasons. Also, some patients are elderly or debilitated with cancer and other comorbid conditions, and thus their HRQOL or life expectancy are unlikely to benefit from more frequent dialysis. For such patients, end-of-life concerns and palliative considerations including less frequent HD are more important, and more frequent dialysis could adversely affect their and their family members' quality of life. Some patients have fragile or otherwise tenuous dialysis vascular accesses that would benefit from infrequent puncture and smaller needles, and less frequent, incremental HD could be viewed as a form of breaking-in the access.

While the target for urea reduction ratio (URR) in patients dialyzed twice a week is uncertain, we suggest that a URR of 65% should be achieved with each treatment, or alternatively target equivalent eKt/V of >1.2 adjusted for HD frequency. This, combined clearance of urea and creatinine, can be used to monitor RKF.<sup>30</sup> In 1997, KDOQI articulated in detail how standard dialysis dosing could account for the intensity and frequency of HD and RKF.<sup>28</sup> Many patients who start twice-weekly HD may eventually transition to thrice-weekly HD when urine output declines, interdialytic weight gain increases over time, or hypertension becomes more difficult to control; nevertheless, many patients may continue twice-weekly HD for extended periods and with acceptable outcomes. According to coauthors KKZ and CPK, in some Veterans Affairs medical centers in the United States, until recently, twice-weekly HD was the standard transition to kidney replacement therapy

in many veterans undergoing maintenance hemodialysis treatment. Incident twice-weekly HD patients are likely healthier and have higher RKF than thrice-weekly HD patients. Similarly, twice-weekly HD was the typical initial prescription in the United Kingdom (UK) until the past decade, when the British Renal Association was able to pressure the National Health Services to ensure thrice-weekly HD as the standard of care in the UK.<sup>31</sup> However, it should be reiterated that to date no controlled trial has been conducted to examine superiority or non-inferiority of twice-weekly HD upon transition to kidney replacement therapy.<sup>6</sup>

There are other important reasons to perform twice-weekly HD upon initiating dialysis therapy. First, having two sessions a week means less frequent cannulations of a new arteriovenous fistula or graft, which may prolong its longevity. In addition, incremental HD may offer a compromise and reconciliation between the two camps of early vs. late dialysis initiation<sup>32, 33</sup> in lieu of the traditional approach of initiating thrice-weekly HD. A potential issue, however, is the report of increased mortality on Mondays and Tuesdays after longer interdialytic intervals,<sup>34</sup> which may reflect higher interdialytic weight gains and fluid gains<sup>35</sup> and hyperkalemia.<sup>36–38</sup> With a twice-weekly HD regimen, the patients would be subjected to 3-day and 4-day intervals, assuming patients receive HD on Monday-Wednesday, Tuesday-Friday, or Wednesday-Saturday. Indeed that is why we suggest a threshold of 2.5 L fluid gain, as well as the potassium eligibility cutoffs (see Box 1 and the discussion below).

### Box 1

#### Proposed criteria for twice weekly hemodialysis

##### Treatment Criteria for 2x/wk HD

- 1 Good RKF with a urine output >0.5 L/day
- 2 Limited fluid retention between 2 consecutive HD treatments with a fluid gain <2.5 kg (or less than 5% of the ideal dry weight) without HD for 3 to 4 days
- 3 Limited or readily manageable cardiovascular or pulmonary symptoms without clinically significant fluid overload<sup>\*\*\*</sup>
- 4 Suitable body size relative to RKF; patients with larger body size may be suitable for 2x/wk HD if not hypercatabolic
- 5 Hyperkalemia (K, >5.5 mEq/L) is infrequent or readily manageable
- 6 Hyperphosphatemia (P, >5.5 mg/dL) is infrequent or readily manageable
- 7 Good nutritional status without florid hypercatabolic state
- 8 Lack of profound anemia (Hb >8 g/dL) and appropriate responsiveness to anemia therapy
- 9 Infrequent hospitalization and easily manageable comorbid conditions
- 10 Satisfactory health-related quality of life

##### Implementation Strategies

- 1 In order to initiate and maintain 2x/wk HD, the patient should meet the first criterion (urine output >0.5 L/day) plus most (5 out of 9) of the other criteria.
- 2 Examine these criteria every month in all 2x/wk HD patients and compare outcome between 2x/wk and 3x/wk HD to assure outcome non-inferiority for continuation of 2x/wk HD
- 3 Consider transition from 2x/wk to 3x/wk HD regimen if patient's urine output drops (<0.5 L/day) or if patient's nutritional status or general health condition shows a deteriorating trend over time

The proposed criteria are general rather than specific and should be refined for use in clinical trials and clinical decision making.

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Lack of systolic dysfunction (EF, >40%) and no major coronary intervention over the previous 3 months

Abbreviations: K: Potassium, P: phosphorus, Hb: hemoglobin; 2x/wk, twice-weekly; HD, hemodialysis; RKF, residual kidney function; EF, ejection fraction; 3x/wk, thrice-weekly

## Decision Support for Incremental HD

We suggest developing and implementing a clinically relevant decision support for incremental HD upon transition to kidney replacement therapy. Our proposed approach is based upon 10 clinical criteria that, if proven useful, can guide initial HD dose and frequency as well as the timing of changes in the dialysis prescription (Box 1). The proposed criteria are meant to be inclusive rather than specific and should be refined for use in future controlled trials and clinical decision making. These metrics should be reexamined periodically, e.g. weekly, monthly, or quarterly, and entered into a paper-based or computerized protocol to determine the dose and frequency of HD treatment. The RKF, including urine volume >0.5 L/day, is perhaps the most important determinant of HD frequency. We do not imply that our suggestion of >0.5 L/day of urine output being the core requirement for the twice-weekly HD should replace the KDOQI suggestion of 2 ml/min/1.73 m<sup>2</sup> BSA urea clearance;<sup>28</sup> however, our goal here is to advance pragmatic criteria that can be more consistently pursued under all conditions especially given the simplicity of measuring urine output as compared to the known challenges of accurately calculating urea or creatinine clearance. In India and China, twice-weekly HD therapy is practiced widely with little to no systematically defined selection and maintenance criteria; hence, Chinese and Indian programs can use our suggested criteria listed in Box 1 until the results of comparative effectiveness studies or controlled trials are available.

## Why to Examine Incremental and Twice-Weekly HD

Although physiologic considerations suggest that patients starting HD with significant RKF should require lower dialysis doses than anuric patients, it is common and routine practice in the US and most Western countries to prescribe the same dialysis dose and frequency in both groups of patients. This practice may stem from beliefs that: (1) it will be difficult to make patients adhere to the inevitable increase in dialysis time and/or frequency; (2) RKF declines rapidly and is not generally monitored, and the overlooked loss of RKF will result in inadequate HD; and (3) more frequent HD than is required can only benefit patients. A close examination of these considerations suggests that the uniform dosing approach may not be optimal for a variety of reasons. Although twice-weekly HD is not recognized as the standard of care in most countries, it is commonly practiced in many regions of the world and under circumstances where financial constraints and resource scarceness appear to prevail. Occasionally even in the US patients may choose twice-weekly HD for convenience and perceived superior quality of life and end-of-life constellation.

The innovative concept of reviving incremental HD including twice-weekly HD upon transition to kidney replacement therapy may lead to an important paradigm shift in our current nephrology practice. It offers a novel approach to the unanswered question of timing

the initiation of maintenance dialysis, as it offers an alternative to the abrupt transition to the usual thrice-weekly HD treatments. Doing so may better preserve RKF<sup>11</sup> and decrease the degree of inflammation. It may also improve patient centered outcomes including health related quality of life, satisfaction,<sup>25</sup> and end-of-life concerns while significantly containing costs and resources. This topic and the associated new approach to “Transition of Care in CKD” is the focus of one of the new special study centers of the United States Renal Data System ([www.USRDS.org](http://www.USRDS.org)) and also is responsive to the novel NIH Roadmap Initiative PROMIS measures of physical function, sleep<sup>39</sup> and fatigue<sup>40</sup> as health-related quality of life outcomes.

We envision a series of randomized controlled trials of incremental versus thrice-weekly HD that characterizes the relationship between dialysis dose and frequency, RKF, and patient-related outcomes. We feel that VA medical center dialysis clinics are excellent sites for these trials. In order to ensure generalizability, future trials should recruit a demographically diverse and representative population sample with respect to race/ethnicity, age, gender, location and cause of chronic kidney failure. These studies should employ state of art methods for assessing RKF, episodes of AKI, and patient centered outcomes.

## Conclusions

The authors appreciate the important challenge of their proposal to the current paradigm of thrice weekly HD treatments upon transitioning to kidney replacement therapy. The long-term goals are to provide personalized and incremental HD to patients at the start of transition to dialysis therapy in order to optimize survival, health-related quality of life, and other pertinent outcomes. The design of future studies should permit a rapid scaling-up of the interventions in larger clinical trials since it takes advantage of resources and personnel that are readily available in many centers including most VA medical centers in the United States. Finally, notwithstanding the potentially favorable aspects of twice-weekly or incremental HD upon transition to kidney replacement therapy, the majority of the authors of this perspective feel that the “PD first”<sup>41</sup> should continue to be highlighted as the preferred mode of transition given consistent data demonstrating an association between preservation of RKF and PD. Moreover, the individualized choice of transition of care to a kidney replacement therapy versus more conservative and palliative options should not be ignored for certain patients with terminal conditions.<sup>5</sup>

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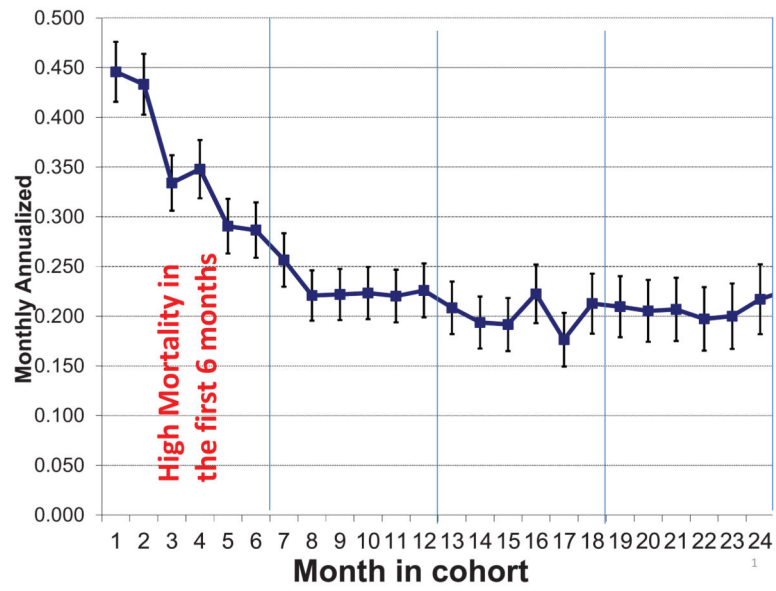
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**Figure 1.** High mortality rate during the first 6 months of hemodialysis therapy. Reproduced Lukowsky et al<sup>4</sup> with permission from S. Karger AG, Basel.