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Effect of ultrafiltration profiling on outcomes among maintenance hemodialysis patients: a pilot randomized crossover trial

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Abstract

Background: More rapid fluid removal during hemodialysis is associated with adverse cardiovascular outcomes and longer dialysis recovery times. The effect of ultrafiltration (UF)

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Authors' contributions: JEF conceived the study and its design; MJT and JHN collected the study data; ALH interpreted the transthoracic echocardiograms; QL and YW performed the statistical analyses; all authors participated in manuscript development by interpreting study data and contributing to manuscript drafts and revisions. All authors read and approved the final manuscript.

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The results of this study were presented in abstract form at the American Society of Nephrology Kidney Week Meeting in Washington, D.C. in November 2019.

Conflicts of interest/Competing interests: In the last 3 years, JEF has received speaking honoraria from American Renal Associates, the American Society of Nephrology, Dialysis Clinic, Inc., the National Kidney Foundation, and multiple universities. JEF is on the medical advisory board of NxStage Medical, Inc. and has received consulting fees from Fresenius Medical Care, North America, and AstraZeneca. In the last 3 years, MMA has received investigator-initiated research funding from the Renal Research Institute, a subsidiary of Fresenius Medical Care, North America, and honoraria from the International Society of Nephrology. The remaining authors have no competing interests.

Ethics approval: This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board (#17–1057).

Consent to participate: Written informed consent was obtained from all participants.

Consent for publication: Not applicable.

Availability of data and material: The datasets generated during the presented study are not immediately publicly available due to University of North Carolina at Chapel Hill data sharing policies. However, the data can be made available to interested parties upon execution of appropriate data use agreements.

Code availability: Available upon request.

profiling, independent of concomitant sodium profiling, on markers of intradialytic hemodynamics and other outcomes has been inadequately studied.

Methods: Four-phase, blinded crossover trial. Participants (UF rates >10 mL/h/kg) were assigned in random order to receive hemodialysis with UF profiling (constantly declining UF rate, intervention) vs. hemodialysis with conventional UF (control). Each 3-week 9-treatment period was followed by a 1-week 3-treatment washout period. Participants crossed into each study arm twice (2 phases/arm); 18 treatments per treatment type. The primary outcomes were intradialytic hypotension, pre- to post-dialysis troponin T change, and change from baseline in left ventricular global longitudinal strain. Other outcomes included intradialytic symptoms and blood volume measured-plasma refill (post-dialysis volume status measure), among others. Each participant served as their own control.

Results: On average, the 34 randomized patients (mean age 56 years, 24% female, mean dialysis vintage 6.3 years) had UF rates >10 mL/h/kg in 56% of treatments during the screening period. All but 2 patients completed the 15-week study (prolonged hospitalization, kidney transplant). There was no significant difference in intradialytic hypotension, troponin T change, or left ventricular strain between hemodialysis with UF profiling and conventional UF. With UF profiling, participants had significantly lower odds of light-headedness and plasma refill compared to hemodialysis with conventional UF.

Conclusions: UF profiling did not reduce the odds of treatment-related cardiac stress but did reduce the odds of light-headedness and post-dialysis hypervolemia.

Trial Registration: [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03301740) identifier: [NCT03301740](https://clinicaltrials.gov/ct2/show/study/NCT03301740) (registered October 4, 2017)

Keywords

hemodialysis; cardiovascular; ultrafiltration; hypotension; clinical trial; echocardiogram; blood pressure; symptoms

INTRODUCTION

Individuals receiving maintenance hemodialysis have exceedingly high rates of cardiovascular complications with such events accounting for nearly 50% of all deaths.[1] Prior observational research has demonstrated associations between aspects of the hemodialysis treatment and cardiovascular morbidity and mortality. Higher rates of fluid removal (ultrafiltration, UF), driven by larger interdialytic weight gains and/or shorter treatment times, are associated with higher rates of hospitalizations, mortality, and intermediate outcomes such as intradialytic hypotension and longer post-dialysis recovery times.[2–6] Intradialytic functional imaging studies of the heart, liver, brain, and kidneys have shown hemodialysis-induced end-organ ischemia with more aggressive UF,[7–12] providing a potential mechanistic explanation for the observed UF rate and outcome associations.

Reducing UF rate-related intradialytic complications has the potential to improve both cardiovascular and patient-reported outcomes, but, to date, safe and effective strategies that do not require lengthening the dialysis treatment have not been identified. Clinical trials of

blood volume monitor-guided UF, controlled manually and by biofeedback, (vs. constant UF rates) have yielded mixed results regarding prevention of hypotension.[13–19] Sodium profiling, the practice of varying intradialytic dialysate sodium concentration to maximize oncotic pressure, has been shown to promote hemodynamic stability.[20] However, such benefit often comes at the expense of sodium loading and its untoward consequences of enhanced thirst, extracellular volume expansion, and hypertension.[20–22] As such, sodium profiling is typically avoided unless sodium balance can be achieved and post-dialysis hyponatremia avoided. Alternatively, UF profiling, the practice of varying UF rates to maximize fluid removal during periods of greatest intravascular fullness and oncotic pressure, does not alter sodium balance. Existing data suggest that UF profiling may improve hemodynamics and reduce symptoms,[23] but data are sparse, and no prior studies have investigated the impact of UF profiling on markers of cardiac ischemia such as troponin and intradialytic myocardial stunning.[23–25]

To begin addressing this evidence gap, we conducted a randomized crossover trial investigating whether hemodialysis with UF profiling (constantly declining UF rate) reduces markers of hemodialysis-related cardiovascular stress and patient-reported symptoms compared to hemodialysis with a constant UF rate.

METHODS

Overview

We performed a randomized, single blind, crossover trial of hemodialysis with UF profiling (constantly declining UF rate, intervention) vs. hemodialysis with a constant UF rate (control) among individuals receiving outpatient maintenance hemodialysis. We recruited participants from two dialysis clinics affiliated with the University of North Carolina at Chapel Hill. Recruitment occurred in March and July 2018, and the study was completed in December 2018. The study protocol was approved by the University of North Carolina at Chapel Hill Institutional Review Board (#17–1057), and all study procedures were conducted in accordance with the Helsinki Declaration (registered on [clinicaltrials.gov: NCT03301740](https://clinicaltrials.gov/ct2/show/study/NCT03301740)). We reported our findings consistent with the Consolidated Standards of Reporting Trials 2010 statement: extension to randomized crossover trials.[26]

Study population

All adults receiving maintenance hemodialysis at the participating clinics were screened for eligibility. Individuals aged 18 to 85 years-old with UF rates >10 mL/h/kg in >30% of treatments during the 4-week screening period who had received in-center hemodialysis for at least 90 days were eligible to participate. Exclusion criteria included unstable angina; New York Heart Association class IV heart failure; >1 hospitalization, bloodstream infection, or non-adherence to hemodialysis (>2 unexplained absences) during the screening period; and anticipated kidney transplant or modality change within 6 months (Supplemental Table S1).

Study design

The detailed study design has been previously reported.[27] In brief, we performed a 4-phase crossover trial in which participants were successively alternated between fluid removal strategies with intervening washout periods (Figure 1). Treatment order (i.e. starting with UF profiling vs. conventional UF) was randomized. Patient eligibility was assessed in a 4-week screening period, followed by a 6-week baseline period (laboratory testing, medication review, history and physical). Then, participants were randomized to hemodialysis with UF profiling vs. hemodialysis with a constant UF rate for a 9-treatment phase, followed by a 3-treatment washout period. Participants then crossed over to the other study arm for a 9-treatment phase and 3-treatment washout period. The same sequence was then repeated such that each patient underwent 2 phases of UF-profiled hemodialysis (18 treatments total), 2 phases of hemodialysis with conventional UF (18 treatments total), and 3 washout periods (9 treatments total). Randomization of the treatment sequence (i.e. beginning study treatments with UF profiling vs. conventional UF) was performed by computer-generated random numbers. Study participants, investigators, cardiac sonographers, and analysts were blind to study treatment type. Dialysis clinic personnel and treating nephrologists were not blinded.

Ultrafiltration interventions and washout treatments

The study intervention was hemodialysis with UF profiling (profile 2 on the Fresenius 2008T machine), fluid removal with a constantly down-sloping pattern in which UF begins at a rate 40% higher than the baseline rate and ends at 60% of the baseline rate. The control was hemodialysis with conventional UF, fluid removal with a constant rate. Study washout treatments were the same as control (standard hemodialysis prescription with a constant UF rate).

Hemodialysis prescription

All participants were dialyzed on Fresenius 2008T machines with high-flux dialyzers, a dialysate temperature of 37°C, and a dialysate sodium concentration of 137 mmol/L (the clinic-standardized dialysate sodium concentration in both participating clinics). Hemodialysis treatment parameters such as dialysate composition (except for sodium concentration, which was fixed), estimated dry weight, and treatment time were those prescribed by the treating nephrologist. Intradialytic hemodynamic instability was managed per routine clinical protocols with UF rate reduction, UF termination, saline administration, etc. In cases of UF termination, upon return of hemodynamic stability, UF profile 2 was resumed for participants in the UF-profiled arm, and UF at a constant rate was resumed for participants in the conventional UF arm.

Study outcomes

The primary study outcomes were intradialytic hypotension (nadir systolic blood pressure (BP) <90 mmHg), two related troponin T metrics (pre- to post-dialysis troponin T change (ng/mL) and pre- to post-dialysis troponin T rise $\geq 10\%$), and change from baseline in left ventricular global longitudinal strain (GLS, %). We selected these outcomes because they are surrogates for hemodialysis treatment-related cardiac stress. Left ventricular GLS is a

transthoracic echocardiography (TTE) parameter that expresses myocardial deformation as a percentage and is a measure of systolic function (normal range: -16 to -22% with less negative numbers reflecting greater systolic function impairment) (Supplemental Figure S1). [28] GLS is less load-dependent than other measures of left ventricular systolic function and is sensitive to small changes in contractility. Secondary outcomes included nadir intradialytic systolic BP (mmHg), systolic BP change (mmHg), failed target weight achievement (post-dialysis weight >1 kg above or below estimated dry weight), change from baseline in left ventricular GLS $\geq 2.5\%$, change from baseline in early mitral inflow velocity/mitral annular early diastolic velocity (E/e' , a Doppler echocardiography index of left ventricular diastolic function and filling pressure), patient acceptance (willingness to adopt UF type), patient-reported intradialytic symptoms (cramping, nausea, vomiting, light-headedness, palpitations, chest pain, shortness of breath, thirst, headache, itching, restless legs, and tingling measured with 5-point severity Likert scales), and patient-reported time to recovery (hours), among others. The exploratory outcome was blood volume monitor-measured plasma refill (hematocrit fall by $\geq 0.5\%$ from the termination of UF to the end of treatment), [29] a post-dialysis volume status measure.

Data collection

Baseline data, including medical history and laboratory values, were obtained from the electronic health record. Hemodialysis treatment data, including intradialytic BPs, pre- and post-dialysis weights, UF volume, and intradialytic interventions were abstracted from the electronic health record. Blood pressure was machine-measured pre- and post-dialysis and every 15 minutes during all treatments. Troponin T was measured before and after hemodialysis during 4 end-of-phase study treatments (2 per study arm) and analyzed using a fifth-generation assay (Mayo Medical Laboratories, Rochester, MN). Echocardiography was performed by two experienced sonographers on a Samsung HM70A cardiac ultrasound machine (Seoul, South Korea) during the baseline period on a non-dialysis day and 30 minutes before the end of 2 study treatments (1 per study arm). The latter timing was selected to capture “peak intradialytic stress.” [7, 8] Baseline left ventricular ejection fraction was determined using the biplane Simpson’s rule from apical 4-chamber and 2-chamber images of the heart. Two-dimensional speckle-tracking echocardiography-derived GLS was used to quantify left ventricular systolic function, and left ventricular diastolic function was characterized as E/e' , measured by pulsed wave and tissue Doppler. Images were analyzed offline by an experienced, blinded cardiologist using TomTec software (TomTec Corporation, Chicago, IL). Plasma refill was measured with a Crit-Line Monitor (Fresenius Medical Care North America, Waltham, MA).

Sample size

We based the sample size on power calculations for the primary study outcomes. We estimated a sample size of 30 participants would provide power of 80% to show a 31% absolute difference in the binary endpoint of intradialytic hypotension occurrence, assuming an event rate of 20%, a ≥ 0.07 ng/mL pre- to post-dialysis troponin T change difference (S.D. 0.1) [30], and a 2.2% difference from baseline in GLS (S.D. 3) [31].

Statistical analyses

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Baseline characteristics are presented as count (%) for categorical variables and mean $\pm$ standard deviation or median [quartile 1, quartile 3] for continuous variables. Each study participant served as their own control. We estimated odds ratios (OR) and 95% confidence intervals (CI) for binary outcomes (e.g. intradialytic hypotension (present vs. absent) and symptoms (none or mild vs. moderate, severe, or very severe)) using repeated measures logistic regression models. We estimated β -coefficients and 95% CIs for non-TTE continuous outcomes (e.g. pre- to post-dialysis troponin T change and nadir systolic BP) using repeated measures linear regression models. For all models, the binary treatment indicator (UF profiling vs. conventional UF) was treated as a fixed effect predictor, and each participant was assigned a random intercept term. We used Wilcoxon signed rank tests to compare the median differences of continuous TTE endpoints (e.g. GLS change) between UF profiling and conventional UF. All analyses were based on the intention-to-treat principle. Results were considered statistically significant if the 95% CI of the OR did not span the value of 1.0, or the 95% CI of the β -coefficient or estimated median difference did not span the value of 0.0.

RESULTS

Cohort formation

A total of 186 individuals were screened, and 139 were excluded (Figure 2). Of the 47 individuals meeting selection criteria, 34 (72%) agreed to participate. During baseline, the mean delivered UF rate was 10.3 ± 3.7 mL/h/kg and, on average, $55 \pm 21\%$ of participant baseline treatments had delivered UF rates >10 mL/h/kg. All 34 individuals who entered the baseline period were randomized, 18 to the arm that received UF profiling first and 16 to the arm that received conventional UF first. In the first treatment sequence (UF profiling, conventional UF, UF profiling, conventional UF), 1 participant dropped out in phase 2 (conventional UF) due to kidney transplant, and 1 participant dropped out in phase 4 (conventional UF) due to a prolonged hospitalization. As the phase 2 dropout did not complete a full phase of each treatment type, this individual was excluded from analyses. For the phase 4 dropout, data from this individual's phases 1 (UF profiling) and 2 (conventional UF) were included. There were no dropouts in the second randomization order (conventional UF, UF profiling, conventional UF, UF profiling). A total of 33 individuals and 1,149 hemodialysis treatments were included in the analyses.

Participant characteristics

Table 1 displays participant baseline characteristics. Participants had an average age of 56 ± 15 years, 8 (24%) were women, 22 (65%) were Black, 11 (32%) were Hispanic, and the most common cause of dialysis-dependent kidney failure was hypertension (12, 35%). Of the 34 randomized participants, 17 (50%) had diabetes, 30 (88%) had hypertension, and the mean baseline left ventricular GLS was $-15.5 \pm 3.3\%$. In regard to hemodialysis treatments, 5 (15%) participants dialyzed via a catheter, the mean delivered treatment time was 220 ± 27 minutes, and $13 \pm 15\%$ of baseline treatments were complicated by intradialytic hypotension. During the final baseline week, 6 (18%) participants reported itching and

restless legs, 5 (15%) cramping and thirst, and 3 (9%) light-headedness. The average recovery time was 4.5 ± 6.5 hours.

Primary outcomes

Table 2 and Supplemental Table S2 display study results. The overall rate of intradialytic hypotension was 14.3% (164 of 1149 treatments). There was no significant difference in intradialytic hypotension between hemodialysis with UF profiling and conventional UF (OR [95% CI]: 1.2 [0.8, 1.7] for UF profiling vs. conventional UF). There was no significant difference in pre- to post-dialysis troponin T change (ng/mL) between the treatment arms (mean [95% CI]: 12.3 [4.4, 20.2] ng/mL for UF profiling and 11.3 [3.4, 19.2] ng/mL for conventional UF) (mixed model β -coefficient [95% CI]: -2.8 [-6.9, 1.4] for UF profiling vs. conventional UF). Similarly, there was no significant difference in pre- to post-dialysis troponin T rise $\geq 10\%$ between UF profiling and conventional UF (OR [95% CI]: 0.5 [0.2, 1.3] for UF profiling vs. conventional UF). Finally, there was no significant change in left ventricular GLS from baseline to peak hemodialysis stress between the study arms (mean [95% CI]: 0.9 [-0.1, 1.8] % for UF profiling and 1.3 [0.1, 2.4] % for conventional UF) (estimated median difference [95% CI]: -0.8 [-2.0, 0.5] for UF profiling vs. conventional UF) (Figure 3).

Secondary and exploratory outcomes

With UF profiling, participants had significantly lower odds of plasma refill (i.e. less post-dialysis hypervolemia) (OR [95% CI]: 0.2 [0.05, 0.9]) and the patient-reported symptom of light-headedness (OR [95% CI]: 0.2 [0.06, 0.9]) compared to conventional UF. With UF profiling, patients also had significantly higher odds of patient-reported itching (2.8 [1.2, 6.6]) compared to conventional UF. There was no significant difference in other secondary and exploratory outcomes between arms. Additionally, 0 participants had serious adverse events during the study, and 5 participants had adverse events (2 with UF profiling and 5 with conventional UF; Supplemental Table S3). Finally, there were a total of 81 fluid boluses (defined as normal saline ≥ 500 mL) administered during study treatments among 25 unique patients. Of the 81 boluses, 39 (48%) occurred during conventional UF and 42 (52%) occurred during UF profiling.

DISCUSSION

In this pilot randomized crossover study, we found that hemodialysis with UF profiling (constantly declining UF rate) did not reduce the rate of hypotension, occurrence of pre- to post-dialysis troponin T rise, or the degree of dialysis-associated left ventricular strain compared to hemodialysis with conventional UF. Ultrafiltration profiling did result in lower odds of post-dialysis plasma refill and intradialytic light-headedness compared to conventional UF. Taken together, the plasma refill and light-headedness findings may suggest a role for UF profiling in improving post-dialysis volume status, but these findings are modest and should be interpreted with caution given the lack of objective measures of volume status.

There have been relatively few prior investigations of UF profiling independent of sodium profiling as a strategy to mitigate hemodialysis-induced hemodynamic stress. A recent randomized crossover trial of blood volume-monitoring-guided UF biofeedback (machine-adjusted UF rate in response to real-time relative blood volume) found no difference in the rate of symptomatic hypotension, cardiac troponins, or dialysis recovery time between the intervention and standard UF.[14] However, such biofeedback-based approaches are dependent on the accuracy of relative blood volume monitoring and are not widely available. Prior trials of automated UF profiling, a setting on most hemodialysis machines, and hemodynamics yielded mixed results and were of limited sample sizes (8–53 patients) and conducted over a decade ago.[23–25] Moreover, none of these studies examined the effect of UF profiling on other cardiac ischemic markers such as troponin T and intradialytic myocardial stunning.

In our pilot trial, we found no difference in markers of cardiac ischemia (nadir intradialytic systolic BP, troponin T, and left ventricular strain) between hemodialysis treatments with UF profiling and those with conventional UF. While the GLS change (%) was not significantly different between UF paradigms, there was a trend toward lesser strain with UF profiling. Similarly, the OR for troponin T rise was potent (0.5) but the 95% CI crossed 1.0 (0.2, 1.3), suggestive of an association obscured by lack of power. One explanation for these findings may relate to our selection of a relatively low UF rate threshold for study inclusion (>10 mL/h/kg). Participants' mean baseline UF rate was near this threshold, 10.3 ± 3.7 mL/h/kg. While observational data have shown significant associations between UF rates ≥ 10 mL/h/kg and higher mortality risk, such associations were relatively modest compared to those observed with UF rates >13 mL/h/kg,[2] the threshold specified in dialysis care quality programs.[32] Additionally, we performed intradialytic TTEs 30 minutes prior to the end of two study hemodialysis treatments (one each with UF profiling and conventional UF), coincident with peak intradialytic stress timing as demonstrated in prior studies.[7, 8] It is plausible that the timing of peak intradialytic stress from UF profiling may coincide with the maximum UF rate and thus occur earlier in treatment. It is also possible that we missed an effect by evaluating only 2 treatments. Finally, we studied UF profile 2 on the Fresenius 2008T machine, a profile that begins with a UF rate 40% higher than the baseline UF rate. For a 70 kg person with a 3.25-hour treatment and 3 kg interdialytic weight gain, the initial UF rate would exceed 18 mL/h/kg. While the timing of this profile's maximum UF rate use is coincident with peak intravascular hydration and oncotic pressure, this high of a UF rate may be disadvantageous. Study of UF profiles that utilize lower peak UF rates and/or different patterns of fluid removal are areas for future inquiry.

While findings from our primary outcomes were negative, we did observe significantly lower odds of blood volume measured-plasma refill and patient-reported intradialytic light-headedness with UF profiling compared to conventional UF, suggesting that UF profiling may improve post-dialysis extracellular volume status. However, there was no difference in post-dialysis target weight achievement. Blood volume-measured plasma refill is an indirect measure of extracellular volume status, and our lack of objective measures prevents unqualified conclusions about the effect of UF profiling on post-dialysis volume status or other volume-related outcomes. Additional study of UF profiling to mitigate post-dialysis hypervolemia may be warranted.

Strengths of our trial include blinding of investigators and use of standard hemodialysis treatment prescriptions (with the exception of UF paradigm) and clinical protocols, rendering trial conditions similar to those of routine practice. Limitations beyond the aforementioned UF rate threshold selection criteria, intradialytic TTE timing, and lack of objective volume status measures, bear acknowledgement. We considered delivered UF rate (vs. prescribed UF rate) for participant selection. *Delivered* UF rates reflect the speed of fluid removal that occurred in a dialysis treatment whereas *prescribed* UF rates reflect the intended speed of fluid removal based on observed interdialytic weight gain, prescribed treatment time, and prescribed target weight. In cases of hemodynamic instability, delivered UF rates are often lower than prescribed UF rates due to intradialytic interventions such as UF termination or fluid administration. As such, delivered UF rates may not adequately capture UF rate-induced physiologic stress. Second, our findings should not be generalized to patients who fall outside of our study selection criteria, such as incident hemodialysis patients and patients with advanced heart and liver disease. Related, compared to the broader U.S. in-center hemodialysis population,[1] there was relative under-representation of women and individuals of White race and over-representation of individuals of Black race and Hispanic ethnicity in our study. Third, we used a UF rate threshold of 10 mL/h/kg for study inclusion rather than a higher threshold (e.g. 13 mL/h/kg) based on observational data showing an association between UF rates >10 (vs. ≤10) mL/h/kg and higher mortality,[2] and contemporary UF rate trends in the U.S.[33] It is plausible that UF profiling may have different effects on hemodynamics when higher UF rate thresholds are used. Fourth, dialysis clinic personnel and treating nephrologists were aware of the study arm assignment. Therefore, we cannot exclude the possibility that treatment decisions (i.e. UF volume adjustment) were influenced by study arm. Importantly, patients, investigators, cardiac sonographers, and data analysts were blinded. Fifth, this was a small pilot study and may have been underpowered as evidenced by potent ORs that were non-significant (e.g. GLS and Troponin T rise). Finally, we considered numerous secondary and exploratory outcomes and cannot rule out the possibility of type I error.

Our study findings do not support hemodialysis with UF profiling (constantly declining UF rate) as a routine strategy to mitigate risk from higher UF rates. However, we did not find evidence of UF profiling-related harm, and the strategy was well-accepted by participants. As such, UF profiling remains a reasonable volume management strategy to consider, particularly among individuals at high risk for intradialytic myocardial injury or with evidence of post-dialysis hypervolemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

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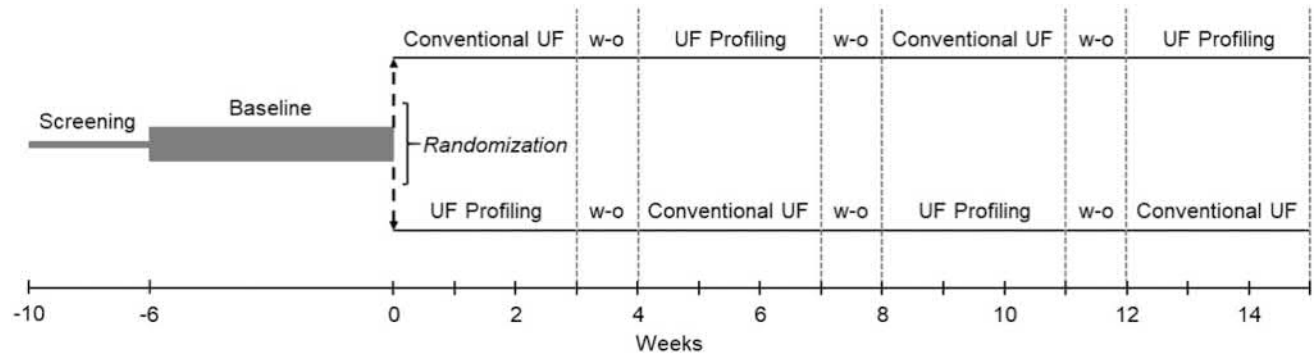


Figure 1.

Study design.

Study eligibility was determined in a 4-week screening period which was followed by a 6-week baseline data collection period. Participants were then randomized to either hemodialysis with profiled UF or hemodialysis with conventional UF for their first 9-treatment study period, followed by a 3-treatment washout period. Participants then crossed over to the other study arm for a 9-treatment phase and 3-treatment washout period. The same sequence was then repeated such that each patient underwent 2 phases of hemodialysis with UF profiling (18 treatments total), 2 phases of hemodialysis with conventional UF (18 treatments total), and 3 washout periods (9 treatments total).

Abbreviations: UF, ultrafiltration; w-o, washout.

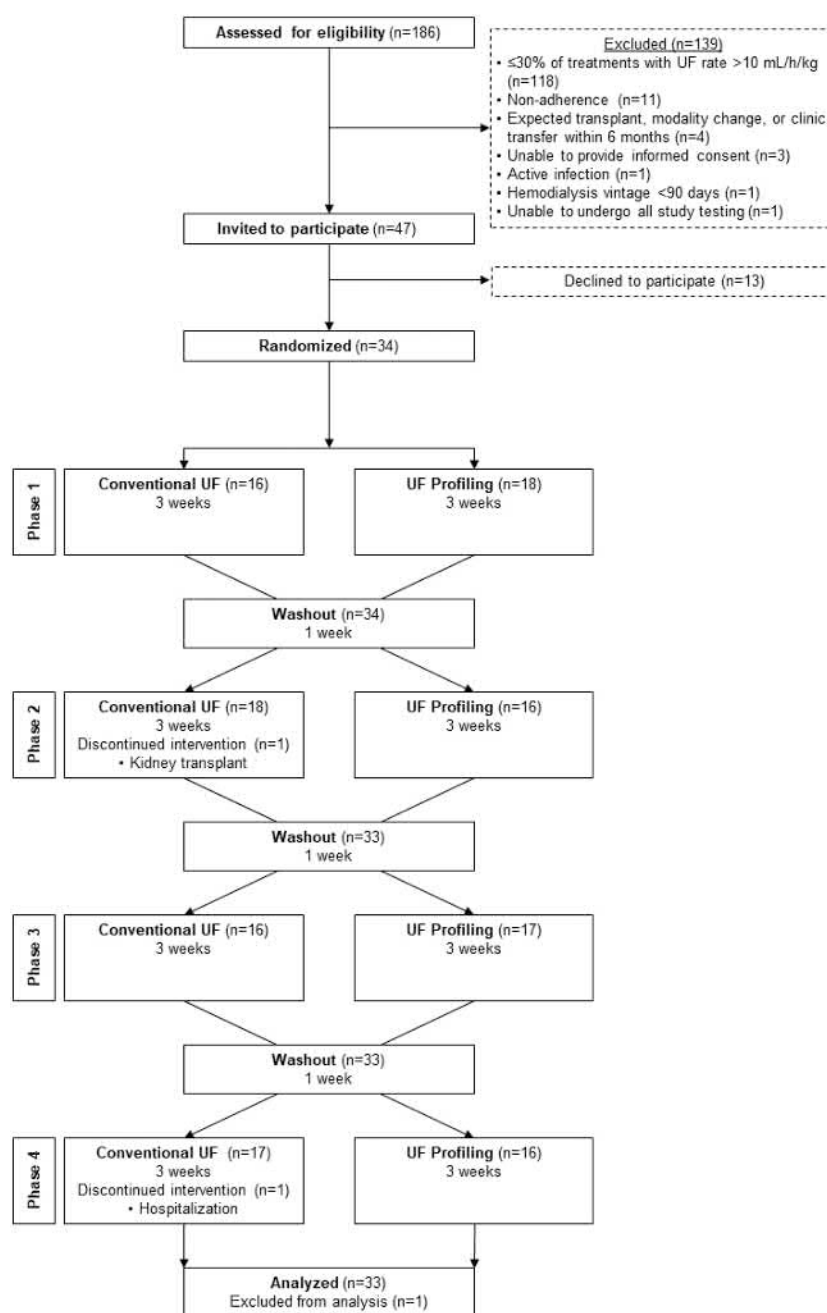


Figure 2.
Participant flow diagram.
Abbreviations: UF, ultrafiltration.

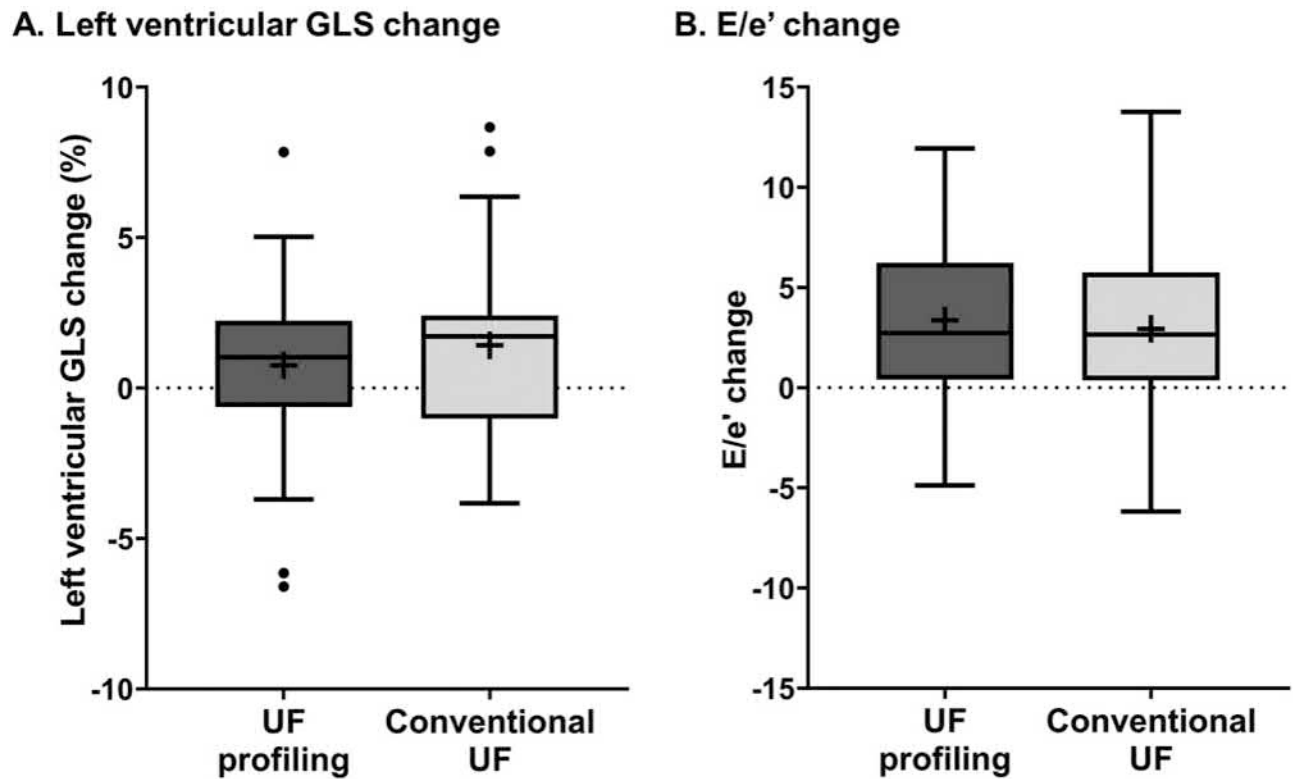


Figure 3.

Change in left ventricular systolic and diastolic function from baseline to peak intradialytic stress with UF profiling vs. conventional UF.

Comparison of change in left ventricular GLS (%) and E/e' from baseline to peak intradialytic stress with hemodialysis with UF profiling compared to hemodialysis with conventional UF. A greater positive change from 0 for left ventricular GLS indicates greater left ventricular systolic function impairment with dialysis. A greater positive change from 0 for E/e' indicates greater left ventricular diastolic function impairment with dialysis. Baseline TTEs were performed on a non-dialysis day. Intradialytic TTEs were performed 30 minutes before the end of hemodialysis during a hemodialysis treatment following the 72-hour break.

Abbreviations: E/e', early mitral inflow velocity/mitral annular early diastolic velocity; GLS, global longitudinal strain; LV, left ventricular; UF, ultrafiltration.

Table 1.Baseline patient characteristics (N=34).^a

Characteristic	Value
Age (years)	56 ± 15
Female	8 (24)
Black race	22 (65)
Hispanic	11 (32)
Dialysis vintage (years)	6.3 ± 5.0; 5.6 [2.0, 9.2]
Hospitalizations (%) ^b	2 (6)
History of kidney transplant	2 (6)
ESKD cause	
Diabetes	9 (27)
Hypertension	12 (35)
Glomerular disease	4 (11)
Other	9 (27)
Comorbid medical conditions	
Diabetes	17 (50)
Congestive heart failure	14 (41)
Coronary artery disease	11 (32)
Hypertension	30 (88)
Cancer	3 (9)
TTE characteristics ^c	
LV global longitudinal strain (%) ^c	-15.5 ± 3.3; -15.9 [-17.6, -12.3] n=32 ^d
LV ejection fraction (%)	52.8 ± 6.9; 53.0 [49.1, 57.0] n=32 ^d
E/e'	11.6 ± 4.6; 10.2 [8.8, 14.8] n=32 ^d
Blood pressure medications	
Beta blocker	23 (68)
Calcium channel blocker	15 (44)
RAAS inhibitor	16 (47)
Diuretic	8 (24)
Other anti-hypertensive medication	7 (21)
Midodrine	2 (6)
Vascular access type	
Fistula	24 (70)
Graft	5 (15)
Catheter	5 (15)
Hemodialysis treatment	
Delivered treatment time (minutes)	220 ± 27

Characteristic	Value
Pre-HD systolic BP (mmHg)	150 ± 27
Prescribed target weight (kilograms)	69 ± 14
UF volume (liters)	2.7 ± 1.8
Intradialytic hypotension (%) ^e	13 ± 15
Delivered UF rate (mL/h/kg)	10.3 ± 3.7
Symptoms ^f	
Cramping	5 (15)
Nausea or upset stomach	1 (3)
Vomiting	0
Dizziness or light-headedness	3 (9)
Racing heart or heart palpitations	1 (3)
Chest pain	0
Shortness of breath	1 (3)
Thirst or dry mouth	5 (15)
Headache	2 (6)
Itching	6 (18)
Restless legs or difficulty keeping legs still	6 (18)
Tingling or feeling of pins and needles	2 (6)
Time to recovery after hemodialysis (hours)	4.5 ± 6.5

^aValues presented as n (%), mean ± standard deviation, and median [quartile 1, quartile 3].

^bPercentage of patients with a hospitalization during the baseline period. No patients had more than 1 hospitalization during this period.

^cLV global longitudinal strain is a measure of left ventricular systolic function. Normal range is −16 to −19% with less negative numbers reflecting greater impairment.[28]

^dTwo baseline TTEs were of poor quality due to technical difficulty obtaining the examinations.

^ePercentage of baseline treatments with a nadir systolic BP <90 mmHg.

^f(+) symptom defined as patient-reported symptom to the level of moderate, severe or very severe.

Abbreviations: BP, blood pressure; E/e', early mitral inflow velocity/mitral annular early diastolic velocity; ESKD, end-stage kidney disease; HD, hemodialysis; LV, left ventricular; RAAS, renin angiotensin-aldosterone system; TTE, transthoracic echocardiography; UF, ultrafiltration.

Table 2.

Comparison of binary study outcomes for UF profiling and conventional UF treatment conditions.

Outcome	Definition	Odds ratio (95% CI)
<i>BP and cardiovascular outcomes</i>		
Intradialytic hypotension ^a	Nadir systolic BP <90 mmHg	1.2 (0.8, 1.7)
Troponin T rise ^a	[(Post-HD - pre-HD troponin T) / pre-HD troponin T] ≥10%	0.5 (0.2, 1.3)
Left ventricular GLS change	(Peak intradialytic stress GLS - baseline GLS) ≥2.5%	0.8 (0.1, 4.4)
<i>Volume-related outcomes</i>		
Plasma refill ^b	Hematocrit decrease by ≥0.5%	0.2 (0.1, 0.9)
Target weight achievement	Post-HD weight <1 kg above or below prescribed target weight	1.0 (0.7, 1.3)
<i>Symptom outcomes</i>		
Cramping	Cramping during last 3 HD treatments ≥moderate severity	0.9 (0.4, 2.1)
Nausea	Nausea or upset stomach during last 3 HD treatments ≥moderate severity	0.7 (0.2, 2.2)
Vomiting	Vomiting or throwing up during last 3 HD treatments ≥moderate severity	1.0 (0.1, 16.0)
Light-headedness	Dizziness or light-headedness during last 3 HD treatments ≥moderate severity	0.2 (0.1, 0.9)
Racing heart	Racing heart or heart palpitations during last 3 HD treatments ≥moderate severity	3.1 (0.3, 32.4)
Chest pain	Chest pain during last 3 HD treatments ≥moderate severity	1.0 (0.2, 6.0)
Shortness of breath	Shortness of breath during last 3 HD treatments ≥moderate severity	1.3 (0.3, 6.5)
Thirst	Thirst or dry mouth during last 3 HD treatments ≥moderate severity	0.6 (0.3, 1.2)
Headache	Headache during last 3 HD treatments ≥moderate severity	0.9 (0.4, 2.3)
Itching	Itching during last 3 HD treatments ≥moderate severity	2.8 (1.2, 6.6)
Restless legs	Restless legs or difficulty keeping legs still during last 3 HD treatments ≥moderate severity	1.2 (0.5, 2.6)
Tingling	Tingling or feeling of pins and needles during last 3 HD treatments ≥moderate severity	0.6 (0.2, 2.4)
Time to recovery after HD	Response to question, "How long did it take you to recover after your last 3 HD treatments?" >12 hours	1.1 (0.7, 1.8)
<i>Other</i>		
Patient acceptance	Affirmative response to question, "If recommended by your kidney doctor, would you be willing to adopt the HD prescription you have received for the last 9 treatments?"	NR ^c

^aPrimary study outcome. All other listed outcomes were secondary or exploratory outcomes.^bPlasma refill was measured by Crit-Line Monitors (Fresenius Medical Care North America, Waltham, MA). In treatments with plasma refill measurements, the UF time was set to 10 minutes shorter than the prescribed treatment run-time, and hematocrit values were measured at the time of UF termination and at the end of treatment. Plasma refill was deemed present if the hematocrit decreased by ≥0.5% from the termination of UF to the end of treatment.^cLow event rate (non-acceptance=3 vs. acceptance=131) precludes accurate estimation of odds ratio (95% CI).**Abbreviations:** BP, blood pressure; CI, confidence interval; GLS, global longitudinal strain; HD, hemodialysis; NR, not reported; UF, ultrafiltration.



Organ Stunning On Hemodialysis: What Is It And What Can You Do?

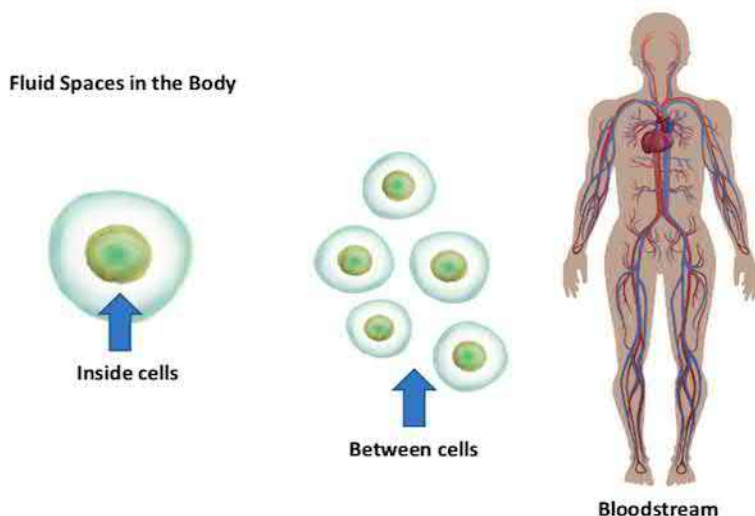
Organ Stunning on Hemodialysis: What Is It and What Can You Do?

You may not have heard of organ stunning. In fact, the concept is still pretty new, even for health care teams. But, you probably *have* heard that knowledge is power, which is true! Learning what stunning is—and how you can avoid it—can help you feel better and live longer on dialysis. If your clinic now tells you water can only be removed at a certain rate, *this is why*.

Organ Stunning Basics

Dialysis filters wastes—and water—out of your blood when your kidneys can't do their job. But, if hemodialysis (HD) does not remove water *gently*, it can “stun” your organs. In our bodies, water is in one of three “spaces:”

1. Most water is **inside our cells**.
2. A lot of water is **between our cells** in what we call the “interstitial” space. (CNN just reported this space as a “new” organ.¹ But, the kidney field has known about it for decades!)
3. The *least* body water is in our **blood**—just 8% or so. But, our blood holds the *only* water we can directly reach with dialysis.

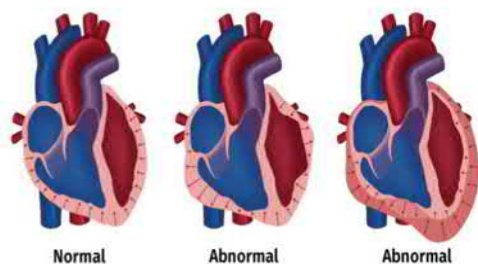


When your feet or hands swell up, your eyes are puffy, or it's hard to breathe, *that water is not yet in your blood*. It is inside or between your cells. Pulling this water out takes *time*, as it must pass through cell membranes to shift from one space to the next. Once water is in your blood, it can be removed. But, if water is removed too quickly—or too much is removed:

1. **Your blood becomes thick,**² so it is harder for your heart to pump.
2. **Your blood pressure drops.**³ You may have painful muscle cramps, feel dizzy, see “stars,” etc. You may get sick to your stomach. Your ears may ring, or you may have a headache or chest pain. This is *intradialytic* (during dialysis) *hypotension* (low blood pressure), or IDH.
3. **Your heart gets less blood**⁴—so it is *starved for oxygen*.

Tissue damage that occurs when your heart is starved for oxygen is called “stunning.” The muscles in your heart work together to beat, relax, beat. When they are stunned, their work is scrambled.⁵ Some muscles contract while

others relax. Changes to how the heart muscles work can last for months after *each* bout of stunning. The damage is like having a small heart attack. You may even have chest pain. In fact, *troponin T*—a substance found in the blood after a heart attack—is also found in those whose hearts have been stunned by dialysis.⁶

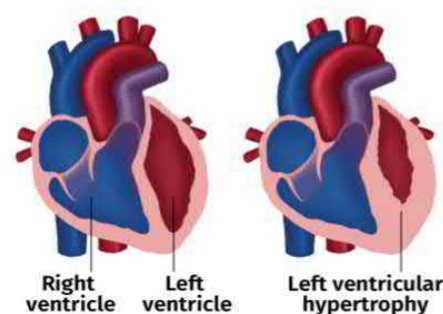


Over time, stunning can cause heart failure.⁷ Our bodies repair damage through *fibrosis*—using fibers to patch wounds. Fibrosis takes up space in the heart that should hold blood. This reduces the *ejection fraction* (EJ)—how much blood the heart can push out with each beat. A low EJ can keep someone off of the kidney transplant list. And, the patch fibers do not work like muscle. So, they make the left ventricle (the heart’s main pumping chamber) large and flabby—and weak. This is *left ventricular hypertrophy* (LVH).

LVH predicts sudden cardiac death.⁸ Sudden

death is *not* the same as a heart attack, which occurs when the heart does not get enough blood. Instead, it is an *electrical* failure. The heart just...stops. Sudden cardiac death is a leading cause of death on dialysis—and is 50% more likely on the Monday or Tuesday after the 2-day no treatment weekend⁹—when heart rhythms are most changed.¹⁰

Other organs are stunned, too. Researchers have done HD on people *inside PET scanners* to see what can happen in real time. Along with the heart damage, what they found was:



- The white matter of the **brain** can be stunned. This may be the reason for some of the cognitive problems people have on dialysis. As HD goes on, the brain gets less blood—so, less oxygen.¹¹ Damage occurs to the white matter of the brain.¹²
- The **gut** can be stunned—and then leak toxins into the blood.¹³ This can cause nausea, lead to inflammation, and may be a factor in heart disease.¹⁴
- Any **kidney function** you still have can be stunned. This may be why people who do standard in-center HD lose their function faster than those who do PD.

How to Know if Your Treatments are Stunning Your Organs

There are a few clues you can watch for:

1. **Your heart rate speeds up during HD.** This may be the first sign you see, but harm is already starting to occur.
2. **Your blood pressure drops during HD** and you have symptoms—cramps, etc. This is a late sign.
3. **It takes you hours to feel normal again after an HD treatment.** The sooner you feel well after HD, the less risk there is of stunning. *If it takes you more than 7 hours—or into the next day—to feel well, there is a good chance that you have been stunned.* This is an even later sign—and a very dangerous one.



How to Prevent Organ Stunning

Removing the right amount of water—*gently*—is key to preventing organ stunning. How much is the “right” amount for you? While there is equipment to measure body water, most U.S. clinics do not yet use it. (It’s called a *body composition monitor*.) Instead, “target weight,”—weight without excess water—is a bit of a guess.¹⁵ With too much water, you can swell

up like a balloon, or drown in your own fluids. With too little, your organs can be stunned. Here are some target weight factors to think about:

- **If you still make a lot of urine, your care team needs to know how much.** You don't want HD to pull water that isn't there. So, ask for a toilet hat and use it to *measure* your output for 24 hours on a day when you'll be home. Your care team may have you do this every 2 months or so while you still make urine.
- **Weigh yourself in a consistent way.** At home, weigh yourself without clothes, at the same time each day, after you move your bowels. For in-center HD, wear the same kind of clothes at each treatment (e.g., jeans and a sweatshirt). Take off extra layers and shoes. Empty your pockets. A scale can't tell *your* weight vs. your car keys or wallet.
- **Know when you have gained or lost "real" (muscle or fat) weight that is not water.** A stomach bug or grief may cost you real pounds. A new exercise plan or a doughnut stop after each treatment may help you gain muscle or fat. Tell your care team.
- **Your blood pressure should be in the normal range.** If it crashes, your target weight may be set too low for you. If it rises too high, not enough water is being removed.
- **You should *not* have symptoms during or after an HD treatment.** Cramping or feeling sick to your stomach may be common—but are NEVER "normal," and should not happen.
- **The rate of water removal (ultrafiltration) during HD matters.** When your clinic limits how much water you can pull and how quickly, this is why. They are trying to save your life. The free calculator at www.homedialysis.org/ufr-calculator can help you see if your rate is in a safe range that won't stun your organs. If it is in the red, ask for longer treatments or an extra treatment to remove the water.
- **How much water you remove matters, too.** If you are on a fluid limit for HD, follow it closely. Eat less salt and sugar to curb thirst. But, if you gain too much water weight, pulling water at the right rate won't help. You will end treatment waterlogged and risk swelling, trouble breathing, heart failure, and death.



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Ultrafiltration Rate Calculator



Are you in the green? Pulling water out of your blood at dialysis is "ultrafiltration" (UF). A safe UF rate (UFR) for HD is gentle—and you may feel well after a treatment. Put in your fluid goal, weight, and treatment time to find out.

I want to take off this much fluid:

 Liters

My weight before treatment:

 Kilograms

My treatments are this long:

 Hours

My doctor says I have heart problems:

☐ Yes



Fill in the fields on the left to see your ultrafiltration rate.

What is Dialysis?

Dialysis Museum

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Paying for Treatment

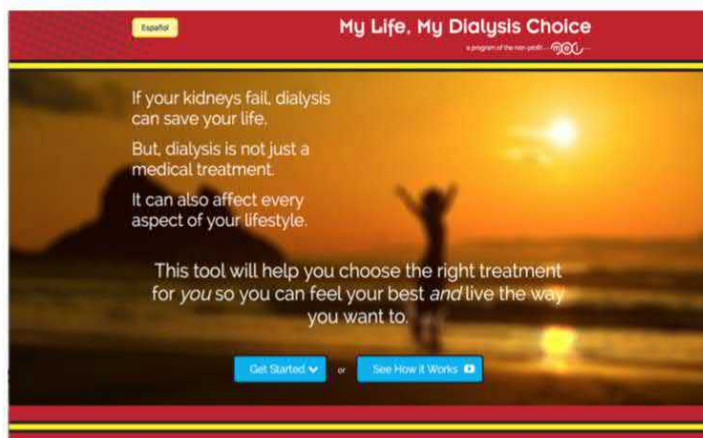
Tools & Links

Glossary

Developed by MEI with input from members of the Renal Unit, Barwon Health, Geelong, Australia

If you do in-center HD, ask your doctor about cooler dialysate. Studies find that cool *dialysate* (the fluid that water and wastes flow into during dialysis) protects you from stunning. If you have had an IV, you know how it can make you feel freezing on the inside. An IV bag may be room temperature—about 70°—while your body is close to 98°. Dialysate does not have to be *that* cold. Just ½°C below your core body temperature is enough.¹⁶ So, if you are at 98.6°F (37°C), it can protect your organs to have the dialysate set to 36.5°C—which is just 97.7°F.

Choose a treatment option that will not cause stunning. PD¹⁷ and daily or nocturnal HD¹⁸ do *not* stun organs. All of these treatments remove water much more gently than standard in-center HD. You can learn more about which option might fit your life with the [My Life, My Dialysis Choice](#) tool online.



Or, learn more about each treatment at <https://www.homedialysis.org/home-dialysis-basics>.

Home Dialysis Basics

There are different options for doing dialysis at home. One of them might be a good fit for your lifestyle and needs right now.

Types Of Home Dialysis

Peritoneal Dialysis • Easy to do • No needles • Gentle on your heart • Take it along when you travel	Daily Home Hemodialysis (HD) • Fit treatments around your life • Fewer food and drink limits • Take it along when you travel • More dialysis than standard HD • Have friends visit during dialysis
Nocturnal Home HD • This is the most dialysis of any option • Better energy, sleep and intimacy • Few food and drink limits • May live longer than with standard HD	Nocturnal In-Center HD • Twice as much dialysis as standard HD • Keep your days free • You may feel better and live longer • No partner needed • No machine at home
Standard Home HD • More dialysis than standard In-Center HD • Feel more in control than in a center • Set your own schedule • Have friends visit during dialysis	See A Comparison Chart • See pluses and minuses • Six treatment options compared • Learn what might fit YOU best • Download the chart as a PDF

Conclusion

Knowing what organ stunning is—and taking steps to prevent it—can help you live better in the short *and* long run.

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CHANGES IN INTRAOCULAR PRESSURE DURING HEMODIALYSIS AND THE ROLE OF ULTRAFILTRATION RATEMerita Proji¹, Saimir Seferi¹, Bulica Eglantina¹, Erjola Likaj¹, Myftar Barbullushi¹¹*UHC Mother Tereza, Tirana, Albania*

INTRODUCTION: Ocular problems have been reported to exist in patients with end-stage renal disease (ESRD). Changes in intraocular pressure (IOP) are an eye problem among hemodialysis patients, about which there is controversy in the literature. Elevated intraocular pressure (IOP) is reported as a risk factors for glaucoma development and progression. Most studies have shown an increase or no changes in IOP during hemodialysis, but some describe a decrease in IOP during session. This study aimed to evaluate the effects of a one session of hemodialysis on IOP and its relationship with ultrafiltration rate.

METHODS: This cross-sectional study was carried out on 67 patients, 35% females, (134 eyes) who were under conventional intermittent hemodialysis for at least 3 months. Patients under glaucoma treatment, with corneal abnormalities, history of corneal surgery, allergy to topical anesthetic agents, or a current eye infection were excluded. Measurements were made at 2 time points, using a pneumotonometer with the patient in a seated position: approximately 15 minutes before starting hemodialysis (T1), and approximately 15 minutes after ending hemodialysis (T2). Blood pressures were also measured at these times. Echocardiographic studies were performed prior to and 30–60 min following the dialysis session. Mean inferior vena cava diameter (IVCD) was expressed as (IVCD in inspiration + IVCD in expiration)/2. IVCD was adjusted for body surface area (BSA).

RESULTS: Mean age of the patients was 53.2 +/- 11.5 years. Laterality of the eyes (right or left) had no significant effect on the predialysis and post dialysis IOP values. Significant increase in intraocular pressure and decrease in plasma osmolarity, SBP, IVCD was found post dialysis session ($p < 0.012$, $p < 0.034$, $p < 0.39$, $p < 0.45$ respectively). Changes in the intraocular pressure correlated with ultrafiltration rate ($r = -0.5$, $p < 0.01$) and difference in vena cava diameter ($r = 0.4$, $p < 0.01$). However, there is no significant correlation between changes in IOP and that in plasma osmolarity ($r = -0.2$, $p > 0.2$).

CONCLUSIONS: In conclusion, our results indicate a relationship between hemodialysis, ultrafiltration rate and intraocular pressure in ESRD patients. Higher ultrafiltration rate may predict increase risk for glaucoma in hemodialysis patients so ophthalmic scheduled examination may be in regular protocol of hemodialysis.

EFFECT OF THE HEMODIALYSIS PRESCRIPTION ON PATIENT MORBIDITY

Report from the National Cooperative Dialysis Study*

E. G. LOWRIE, M.D., N. M. LAIRD, PH.D., T. F. PARKER, M.D., AND J. A. SARGENT, PH.D.

Abstract This report summarizes morbidity in 151 patients in a cooperative trial designed to evaluate the clinical effects of different dialysis prescriptions. Four treatment groups were divided along two dimensions: dialysis treatment time (long or short), and blood urea nitrogen (BUN) concentration averaged with respect to time (TAC_{urea}) (high or low). Dietary protein was not restricted. There was no difference in mortality between the groups. Withdrawal of patients from the high-BUN groups for medical reasons was significantly greater than withdrawal from the low-

BUN groups. Hospitalization was also greater in the high-BUN groups, but dialysis treatment time had no significant effects.

The data indicate that the occurrence of morbid events is affected by the dialysis prescription. Increased morbidity appears to accompany prescriptions associated with a relatively high BUN. Conversely, morbidity may be decreased by prescriptions associated with more efficient removal of urea if the dietary intake of protein and other nutrients is adequate. (N Engl J Med. 1981; 305:1176-81.)

PHYSICIANS who prescribe hemodialysis therapy have long been confronted by the difficult problem of how to determine an appropriate "dose" of dialysis for individual patients. In clinical practice, most patients in a dialysis program undergo treatment for similar lengths of time and with dialyzers that have similar performance characteristics. The needs of individual patients are often not considered or, if they are considered, are judged more by clinical impression than by quantitative measures to guide therapy. Any difference between treatment regimens is usually influenced more by different needs for removal of fluid than by different metabolic needs; individual requirements for solute removal are often ignored.

The National Cooperative Dialysis Study (NCDS) was initiated because of the perceived need to develop a quantifiable definition of adequate long-term dialysis treatment within the domain of current clinical therapies. The study was designed to evaluate two concentrations of blood urea nitrogen (BUN: about 50 and about 100 mg per deciliter [20 and 40 mmol per liter]) at two different treatment durations (TIME: about three hours and about 4½ hours) with a thrice-weekly treatment schedule. There were four treatment groups representing all combinations of BUN and TIME. It should be noted that the target BUN concentration was the value averaged over a dialysis cycle,¹ so that BUN might typically oscillate between

120 mg per deciliter (40 mmol per liter) (before dialysis) and 80 mg per deciliter (30 mmol per liter) (after dialysis) in the high-BUN groups and between 70 and 30 mg per deciliter (20 and 10 mmol per liter) in the low-BUN groups.

The dependent variables consisted of major organ-system indexes, psychosocial data, and measures of general morbidity, such as death, hospitalizations, and withdrawal from the study. Although most of the data were analyzed at the end of the study, morbidity analysis was ongoing to ensure that patients would not be subjected to a continuing and potentially preventable risk. In March 1980 there were sufficient data to demonstrate significantly higher morbidity in the high-BUN groups, and the NCDS Patient Safety Committee — whose members were not involved in the day-to-day management of the study — recommended that these groups be discontinued. This report describes those data.

METHODS

General

Urea nitrogen averaged with respect to time (TAC_{urea})¹ and the length of the dialysis treatment were used as the primary independent variables. TAC_{urea} is an integrated parameter computed as the mean BUN during a full dialysis cycle and was considered more appropriate for controlling therapy than an arbitrary pretreatment value. Nonetheless, the two target TAC_{urea} values of 100 mg per deciliter and 50 mg per deciliter correspond clinically to midweek (second dialysis on a thrice-weekly schedule) pre-dialysis values of 120 ± 10 mg per deciliter (range) and 70 ± 10 mg per deciliter, respectively. The dietary prescription included a daily protein intake of 0.8 to 1.4 g per kilogram of body weight.

The test therapies were divided on two dimensions: BUN concentration and dialysis treatment time. The four possible combinations were designated as follows: Group I — standard therapy with relatively long dialysis times (4½ to five hours) and a relatively low urea nitrogen concentration ($TAC_{urea} = 50$ mg per deciliter); Group II — a long dialysis time while permitting urea nitrogen to rise ($TAC_{urea} = 100$ mg per deciliter); Group III — a shortened dialysis time (3 ± 0.5 hours) while maintaining a low urea nitrogen concentration; and Group IV — a reduced dialysis time while permitting urea nitrogen to rise.

The desired BUN concentrations were achieved by manipulating dialyzer urea clearance at the prescribed treatment times. Clearance was manipulated, in turn, by combining four operating variables²: the membrane and surface area of the artificial kidney, the rate of blood flow to the dialyzing membrane, the flow rate of

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the dialysate, and the relative directions of blood and dialysate flow (countercurrent, co-current, or completely mixed dialysate). The clearance required to achieve the desired BUN for individual patients was computed with a mathematical model of urea nitrogen metabolism.³⁻⁷ This model, based on material balance of nitrogen, permits calculation of the net rate of urea generation between dialysis treatments and estimation of the corresponding net rate of protein catabolism.^{4,6,7}

Patients

All patients were between the ages of 18 and 70 years, inclusive; they all received treatment in a dialysis center, and their residual creatinine clearance was no more than 3 ml per minute.⁸ Patients were excluded if they were known to have cancer, diabetes mellitus, uncontrolled hypertension, reversible renal failure, systemic disease such as lupus erythematosus, or unstable cerebral or coronary vascular disease. Patients with clinically important pulmonary disease or hepatic dysfunction were also excluded. One hundred fifty-one patients from eight centers were randomized into one of the four experimental groups during the initial 22 months of the study and are the subject of this report.

Protocol

Each center selected dialyzers from one manufacturer. In practice, there was one manufacturer whose dialyzers use regenerated cellulose membranes (C-DAK series from Cordis Dow providing 1.3 m², 1.8 m², or 2.5 m²) and one whose units use Cuprophane membranes (CF series from Travenol Laboratories providing 1.2 m², 1.5 m², or 2.3 m²). This prospective dialyzer selection was based on the practical range of urea clearance for each device and the range of clearance that would be required for control in patients in each of the groups. The dialyzer was selected for each patient before he or she was assigned to a treatment group.

The NCDS protocol is described in detail elsewhere.^{9,10} All patients gave a medical history after providing appropriate informed consent. Their status before the study was evaluated by collecting base-line data while they remained on their pre-study dialysis regimen. Patients then entered the study, and data were collected for no less than three months while they were maintained on standard therapy, as defined by Group I. Patients in whom standard therapy produced successful control were then randomly assigned to one of the four treatment protocols. The randomization was performed by the Lead Center according to a schedule determined before the study began. In order to test the randomization procedure patients were evaluated according to group with respect to potential medical risks, including age, history of heart disease, hypertension, peripheral vascular disease, pulmonary disease, and gastrointestinal disease; there were no statistical differences between the groups. Pre-randomization hospitalization was also evaluated, and again, there was no significant difference between groups.

Data on removal of patients from the study protocol were obtained with a study-exit form. Up to four reasons for withdrawal, with comments, were allowed. These included death, withdrawal for medical reasons, transplantation, and "other." The latter category included unspecified patient preference, moved from area, and completion of the protocol. For purposes of this report, a patient was classified as removed for medical reasons if any medical diagnosis was given on the exit form. Data describing hospitalization were taken from the treatment log. Multiple diagnoses were allowed. Diagnoses thought not to be related to uremia were eliminated prospectively.* The large majority of excluded hospitalizations were for vascular access surgery. When more than one diagnosis was listed, the most serious was selected (the choice of most serious was validated by an exterior, blinded, independent review).

*See NAPS document no. 03906 for a one-page list of diagnoses, including those eliminated prospectively. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163. Remit in advance (in U.S. funds only) \$7.75 for photocopies or \$4 for microfiche. Outside the U.S. and Canada add postage of \$4.50 (\$1.50 for microfiche postage).

Statistical Methods

An analysis of variance was used to compare the treatment groups with respect to the independent variables: dialysis time, midweek BUN, and TAC_{urea}. As is usual with a 2-by-2 factorial design, the total between-groups variance was partitioned into the variance due to the overall effect of BUN, the variance due to the overall effect of TIME, and the variance due to the interaction between TIME and BUN. Thus, the results of three F-tests are reported for each variable in Table 1.

Time to withdrawal and time to first hospitalization were analyzed with covariance analysis methods for life-table data.^{11,12} An exit due to death or medical reasons was counted as a "death"; all patients who did not die were considered to have withdrawn alive at their time of exit or on April 1, 1980, whichever came first. First hospitalization or death was counted as "death" in evaluating hospitalization data. Center, base-line medical risk, and hospitalization before randomization were used as covariates in these analyses.

RESULTS

Control Achieved

Table 1 shows the four group means and their standard errors for duration of dialysis treatment, midweek pre-dialysis BUN, and TAC_{urea}. Overall, the objectives for control were achieved, but the two high-BUN groups fell somewhat below target, so that the actual values of TAC_{urea} compared in this study were about 52 and about 89 mg per deciliter (19 and 32 mmol per liter). Nonetheless, good separation between the groups was achieved. Note that the P values for TIME in columns two and three of Table 1 indicate that the two long-TIME groups had slightly lower BUNs than the two short-TIME groups. The difference is only marginally significant.

Patients Removed from Study for Death or Medical Reasons

Figure 1 shows the proportion of patients remaining in each study group as a function of time on protocol dialysis. By nine months, an estimated 11 per cent, 45 per cent, 6 per cent, and 46 per cent of the patients in Groups I, II, III, and IV, respectively, had been removed because of death or medical reasons. The values at one year were 18 per cent, 45 per cent, 6 per cent, and 62 per cent. Statistical analysis of the group withdrawal rates indicates a highly significant BUN effect ($P < 0.0001$) and no significant TIME or interaction effects ($P > 0.5$ for both tests).

Table 1. Control Achieved According to Study Group.*

GROUP AND FACTOR ANALYZED	DURATION OF DIALYSIS (HR:MIN)	MIDWEEK PRE-DIALYSIS BUN	TIME-AVERAGED BUN
I	4:29±0:03	71.2±1.4	51.3±1.1
II	4:31±0:03	104.9±1.7	87.7±1.4
III	3:19±0:03	73.1±1.4	54.1±1.1
IV	3:14±0:03	109.1±1.5	89.6±1.2
TIME	$P < 0.0001$	$P < 0.05$	$P < 0.05$
BUN	$P > 0.1$	$P < 0.0001$	$P < 0.0001$
Interaction	$P > 0.1$	$P > 0.1$	$P > 0.1$

*Data are reported as means ± S.E.M., and BUN is given in milligrams per deciliter (to convert to millimoles per liter, multiply by 0.357). The probabilities indicate the significance of differences between means for the variable with respect to the experimental factor.

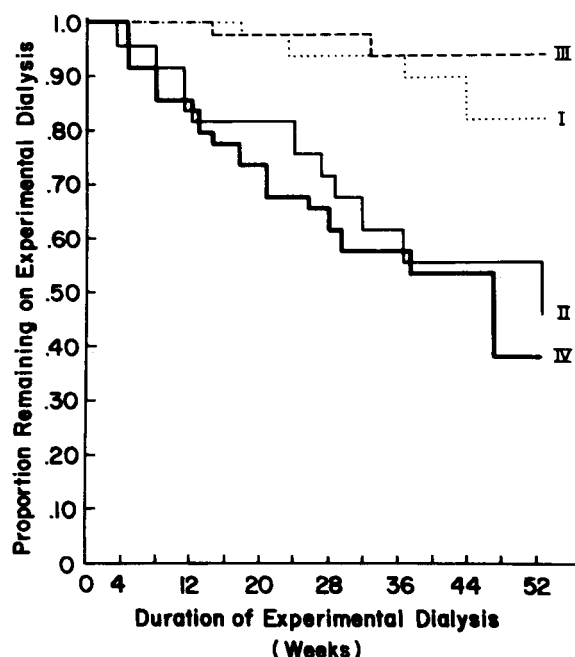


Figure 1. Proportion of Patients Not Withdrawn for Medical Reasons or Death as a Function of Time on Experimental Dialysis in the Four Study Groups.

Loss of patients from the high-BUN groups (II and IV) was greater than loss from the low-BUN groups (I and III). The numbers of patients represented at 24 weeks in Groups I through IV, respectively, were 30, 18, 35, and 23. The corresponding values were 19, 10, 25, and 13 at 36 weeks and six, seven, 13, and five at 52 weeks.

Table 2 shows the numbers of patients randomized and removed for death, medical reasons, or other reasons, and Table 3 shows the primary diagnoses associated with medical removal or death.

Three deaths occurred among randomized patients after their removal from the protocol; one patient had been in Group II, and two had been in Group IV. Thus the total number of deaths after randomization in Groups I through IV were two, one, zero, and three. These differences, controlling for exposure time, were not statistically significant.

Hospitalizations during Experimental Dialysis

Figure 2 shows the proportion of patients remaining non-hospitalized as a function of time on protocol therapy, estimated from a standard life-table analysis. In Group I, 100 per cent, 94 per cent, 86 per cent, and 86 per cent of the patients remained non-hospitalized after three months, six months, nine months, and one year, respectively. The corresponding values were 81 per cent, 70 per cent, 58 per cent, and 46 per cent in Group II; 90 per cent, 79 per cent, 69 per cent, and 69 per cent in Group III; and only 57 per cent, 47 per cent, 31 per cent, and 31 per cent in Group IV.

Differences in time elapsed before the first hospitalization were also analyzed (Table 4). There were

48 first hospitalizations during the 22 months analyzed. The right-hand column in Table 4 (observed/expected) indicates that the two high-BUN groups had excessive hospitalizations — a difference that was highly significant ($P < 0.0001$). Note that the short-TIME groups tended to have more hospitalization than the long-TIME groups when compared within the same level of BUN. For example, within the low-BUN groups less hospitalization was observed if TIME was long (observed/expected, 0.31 vs. 0.54). A similar pattern is observed in the high-BUN groups (observed/expected, 1.62 vs. 3.09). The effect of TIME however, appears quite small in comparison to the effect of BUN.

A percentage of days hospitalized was calculated for each patient in both the control and experimental phase by dividing the number of days hospitalized by the total number of days in the control or the experimental phase. The group averages were 0.67 per cent, 1.98 per cent, 1.86 per cent, and 1.14 per cent during the control phase in patients ultimately assigned to Groups I through IV, respectively. These values declined by 0.11 per cent (to 0.56 per cent) and by 0.46 per cent (to 1.40 per cent) in Groups I and III but rose by 2.81 per cent (to 4.79 per cent) and by 5.35 per cent (to 6.49 per cent) in Groups II and IV. The primary diagnoses associated with these hospitalizations are shown in Table 5. Cardiovascular diseases and miscellaneous medical problems predominate.

DISCUSSION

Throughout the history of hemodialysis therapy for end-stage renal disease, finding a method for prescribing adequate removal of "uremic toxins" has been the goal of many investigations.^{3-7,13-23} The goals of therapy and the methods for achieving these goals have been elusive. Hemodialysis practitioners have never professed to replace normal renal function, with its complex feedback mechanisms and hormonal and metabolic involvement. Rather, the aim has been to remove adequate amounts of accumulated metabolic products and water while balancing certain electrolytes. The question, then, of how to prescribe adequate dialysis is foremost, but questions concerning how one can best determine that the prescription is adequate are also important.

Table 2. Data on Removal from Experimental Protocol as of April 1, 1980.

GROUP	NO. OF PATIENTS RANDOMIZED	NO. OF DEATHS	NO. WITHDRAWN FOR MEDICAL REASONS	NO. WITHDRAWN FOR OTHER REASONS *	NO. NOT WITHDRAWN
I	41	2	2	21	16
II	32	0	11	13	8
III	41	0	2	19	20
IV	37	1	17	13	6
Totals	151	3	32	66	50

*Including all other reasons for removal, such as completed protocol, patient preference, and renal transplantation.

The adequacy of dialysis treatment is inextricably linked to the physical and biochemical nature of uremic toxicity. Historically, there have been attempts to isolate a uremic toxin²⁴ or at least to define clinically the molecular size of the offending substance or substances.^{13-15,18} The results of these investigations have generally been contradictory.²¹ In this study, patient morbidity was used to reflect the adequacy of treatment. The biochemical concept of toxicity was expanded to include a broad category of protein-derived catabolites as represented by their easily measured surrogate — urea.

When data concerning removal of patients from the study for medical reasons are analyzed, one finds that significantly more patients left Groups II and IV. This suggests that TAC_{urea} is associated with patient withdrawal more often than TIME is. A wide range of diagnoses were associated with withdrawals from Groups II and IV. The four groups did not differ in death rate during or after the study.

Another method for evaluating morbidity involved determining the need for hospitalization in each of the study groups. Although physicians and patient-care personnel were not “blinded” in this study, precautions were taken to minimize bias against any of the groups based on preconceived notions about the therapies. Study teams were informed about the potential benefits and risks of each therapy, and examples of each were described from clinical practice. It seems unlikely that any potential bias led to hospitalization. Figure 2 shows that 86 per cent, 46 per cent, 69 per cent, and 31 per cent of the patients treated according to Group I through Group IV therapy remained non-hospitalized at the end of one year, and the ob-

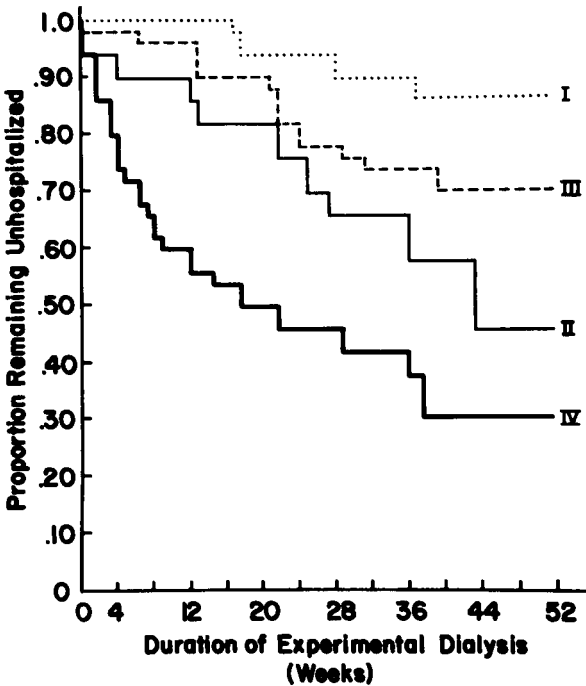


Figure 2. Proportion of Patients Remaining Non-Hospitalized as a Function of Time in the Four Study Groups. The proportion was lower in the high-BUN groups (II and IV) than in the low-BUN groups (I and III).

serva-tion implies a higher relative risk in the high-BUN groups. Finally, the fraction of days hospitalized increased during the protocol dialysis in the high-BUN groups.

Treatment duration appeared to contribute somewhat to morbidity, since Group III had more hospitalization than Group I, and Group IV had more than Group II. Fluid removal is limited by the duration of dialysis treatment. Although there are marginal effects suggesting that short-duration therapy may be inferior to longer-duration therapy, these effects are minor when compared with the effects of TAC_{urea}. Interpreting the contribution of dialysis TIME to morbidity, however, is made more difficult by the observation that TAC_{urea} was slightly higher in the two short-TIME groups than it was in the two longer-TIME groups. Furthermore, we cannot make inferences about the effect of treatment times that exceed the limits of those employed in this study (six hours or two hours). These periods were chosen because a consensus of medical opinion (among physicians involved in the study as well as advisory physicians) had suggested that they represented the upper and lower bounds of clinically acceptable therapy. Finally, TIME may contribute to medical abnormalities not analyzed in this study, and our comments are restricted to morbidity as reported here.

These data suggest that patients dialyzed according to prescriptions resembling those in Group II and Group IV may have a greater risk of hospitalization

Table 3. Primary Diagnoses Associated with Death or Removal before 24 Weeks.

DIAGNOSIS	GROUP			
	I	II	III	IV
	no. of patients			
Anorexia or nausea		4	1	7
Fatigue		1		
Dialysis dementia	1 *			
Hyperkalemia				1
Cardiovascular disease				
Myocardial infarction or cardiac arrest		1		1 *
Resistant congestive heart failure or cardiovascular disease				1
Pericarditis				3
Pleuritis				2
Hypertension				
Neuropathy	1	1		
Convulsive disorder		2		
Worsening anemia	1	1		1
Gastrointestinal bleeding		1		1
Non-gastrointestinal bleeding				
Pancreatitis				1
Severe access infection			1	
Surgical	1 *			
Nonspecified				
Patient preference				
Totals	5	12	2	19

*Died.

Table 4. Analysis of Time until First Hospitalization.

GROUP AND FACTOR ANALYZED *	TOTAL NO. OF PATIENT-WEEKS	NO. OF FIRST HOSPITALIZATIONS	EXPECTED NO. †	OBSERVED NO./EXPECTED NO.
I	1394.5	4	12.95	0.31
II	732.9	11	6.77	1.62
III	1529.3	11	20.37	0.54
IV	698.3	22	7.95	3.09
BUN TIME Interaction			P<<0.0001 P = 0.06 P>0.5	

*The analysis was controlled for hospitalization during control phase, base-line medical risk, and exposure time.

†The expected value represents the number of hospitalizations that would occur in each group if hospitalizations were distributed between groups by chance alone. The expected values are not exactly proportional to exposure time (patient-weeks) because they are adjusted for the covariates listed above.

and medical complications than patients treated by prescriptions similar to those in Groups I and III. Nonetheless, many patients in Group II or Group IV remained non-hospitalized and seemed to tolerate the therapy. Patients receiving these therapies, however, experienced more medical complications as a group.

One cannot infer from these results that one need only maintain BUN at a relatively low level to reduce risk. Dietary intake of protein was not restricted in these patients. Therefore, patients in whom dietary protein is restricted by therapeutic prescription or who reduce protein intake spontaneously, perhaps because of relative underdialysis,²³ are not comparable to the patients described here. In such cases, the concentration of urea nitrogen is reduced by diminished generation of urea. Indeed, undernourished patients may also have a greater medical risk.²⁵

Given an adequate intake of nutrients, the salient differences between the low and the high-BUN prescriptions were due primarily to differences in the efficiency of urea removal. In other words, the dialyzer urea clearances prescribed in Group I and Group III

were substantially higher than those prescribed in Groups II and IV, in order to achieve more efficient urea removal and lower urea nitrogen concentrations at comparable dialysis times.

Physicians may reasonably be concerned about how best to select the most practical combination of dialyzer clearance and dialysis time to reduce the medical risk to a reasonable minimum for a particular patient. These data do not address that issue and such discussions await further analysis. Nonetheless, these results suggest that the clearance-time combination should be selected to maintain BUN in the range in Groups I and II or lower if one confirms that the patient's diet is adequate.

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Table 5. Primary Reasons for All Hospitalizations.

DIAGNOSIS	GROUP			
	I	II	III	IV
	no. of patients			
Congestive heart failure and miscellaneous cardiac disease	1	2	3	5
Myocardial infarction and angina			1	3
Pericarditis			2	1
Hypertension	1			2
Upper-respiratory-tract infection/pneumonia				4
Pancreatitis/gall-bladder disease		2		2
Lower gastrointestinal bleeding				2
Miscellaneous gastrointestinal disorder		3	1	1
Dementia	1			
Seizure		1		
Bone disease		2	1	1
Hyperkalemia				2
Anemia (symptomatic)	1	2	3	1
Miscellaneous bleeding		1		1
Fever of unknown origin/infection		1	2	4
Miscellaneous medical reasons		4	4	4
Nerve compression			1	
Totals	4	18	18	33

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MEDICAL PROGRESS

BIOCHEMICAL GENETICS OF NEUROLOGIC DISEASE

ROGER N. ROSENBERG, M.D.

THERE have been major advances in the biochemical genetics of inherited neurologic disease during the past decade. The molecular basis for the pathogenesis of the sphingolipidoses,¹ the mucopolysaccharidoses,^{2,3} the glycogenoses,⁴ and the hereditary aminoacidopathies⁵ represent the most notable achievements. Additional important new developments include the finding of biochemical defects in several inherited ataxias,⁶⁻⁹ linkage to the HLA complex in patients with multiple sclerosis and myasthenia gravis,¹⁰⁻¹² and the identification of variation in clinical features and corresponding molecular defects due to allelic and nonallelic mutations.^{13,14} Reports on cell-surface-membrane and cytoskeletal defects in several major genetic disorders,¹⁵⁻³² abnormalities in nerve-growth factor,³³⁻³⁵ and familial involvement by slow, latent infectious agents^{36,37} have also provided exciting new observations into the molecular bases of several important diseases. With the knowledge of molecular markers of disease, in utero monitoring of pregnancies at risk and prenatal diagnosis of several lethal disorders have been achieved.³⁸⁻⁴⁰ Several innovative and promising methods of treatment have been introduced.⁴¹⁻⁴⁷ Specific genetic counseling of persons at risk with dominantly inherited disease may become a reality, based on two-dimensional gel-protein patterns,^{7,10} DNA hybridization and polymorphism analyses,⁴⁸ and gene-mapping studies suggesting potential elimination of disease.⁴⁹ It is now clear that the preceding revolution in molecular biology, beginning in 1953 with the description of the structure of DNA by Watson and Crick and continuing through the deciphering of the genetic code by Nirenberg et al. between 1961 and 1966, has entered the arena of molecular neurogenetics. A new genetics based on these technologies is being developed that will explain (it is hoped) most genetic neurologic disease at the molecular level leading to clinical improvement, cure, or prevention of disease. To elucidate properly the progress made in the biochem-

ical genetics of the sphingolipidoses, mucopolysaccharidoses, and glycogenoses within the past decade, this review will describe the associated biochemical defects in relation to each clinical disorder. It has become clear that the autosomal-recessive and X-linked recessive diseases are enzyme-defect disorders, in contrast to the autosomal-dominant disorders, in which the molecular mechanism remains unknown or perhaps is due to structural or receptor-membrane defects. These enzyme defects are described with some care in this review in order to illustrate further the potential presence of allelic and nonallelic mutations involving a given enzyme or biochemical pathway in a given clinical syndrome, to show the degree of possible genetic heterogeneity.¹³ Genetic variation in recessively and dominantly inherited diseases is emerging as an important factor. A series of different mutations involving the same enzyme or pathway can produce strikingly different phenotypes; conversely, an inherited clinical phenotype can be due to several different nonallelic genotypes.^{13,14}

LYSOSOMAL STORAGE DISEASES

Sphingolipidoses

In a Medical Progress article for the *Journal* in 1966, Brady reviewed his important concept that the sphingolipidoses were due to enzymatic defects in the degradation of the sphingolipid; he cited his supporting findings in Gaucher's disease and Niemann-Pick disease and predicted the potential enzyme defects in Tay-Sachs disease and Fabry's disease.⁵⁰ In a brief period from 1965 to 1975, Brady and his colleagues deciphered the enzyme defects of most of the 10 major

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Abbreviations Used:

BH ₄	Tetrahydropteridin
DHPR	Dihydropteridin reductase
L-dopa	L-Dihydroxyphenylalanine
Hex-A (B, S)	Hexosaminidase A (B, S)
5-HT	5-Hydroxytryptophan
PH	Phenylalanine hydroxylase

Outcomes Associated with In-Center Nocturnal Hemodialysis from a Large Multicenter Program

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Background and objectives: The objective of this study was to evaluate epidemiology and outcomes of a large in-center nocturnal hemodialysis (INHD) program.

Design, setting, participants, & measurements: This case-control study compared patients who were on thrice-weekly INHD from 56 Fresenius Medical Care, North America facilities with conventional hemodialysis patients from 244 facilities within the surrounding geographic area. All INHD cases and conventional hemodialysis control subjects who were active as of January 1, 2007, were followed until December 31, 2007, for evaluation of mortality and hospitalization.

Results: As of January 1, 2007, 655 patients had been on INHD for 51 ± 73 d. Patients were younger, there were more male and black patients, and vintage was longer, but they had less diabetes compared with 15,334 control subjects. Unadjusted hazard ratio was 0.59 for mortality and 0.76 for hospitalization. After adjustment for case mix and access type, only hospitalization remained significant. Fewer INHD patients were hospitalized (48 versus 59%) with a normalized rate of 9.6 versus 13.5 hospital days per patient-year. INHD patients had greater interdialytic weight gains but lower BP. At baseline, hemoglobin values were similar, whereas albumin and phosphorus values favored INHD. Mean equilibrated Kt/V was higher in INHD patients related to longer treatment time, despite lower blood and dialysate flow rates.

Conclusions: Patients who were on INHD exhibited excellent quality indicators, with better survival and lower hospitalization rates. The relative contributions of patient selection versus effect of therapy on outcomes remain to be elucidated in prospective clinical trials.

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Despite gradual improvement in survival in the past decade, overall death rates of long-term hemodialysis (HD) patients remain high (1). The Hemodialysis (HEMO) Study failed to show a significant benefit with increasing dialysis dosage based solely on greater urea clearance, within the framework of conventional thrice-weekly HD (2). Efforts to optimize renal replacement therapies to improve patient outcomes have spurred interest in more frequent dialysis regimens (3). While results from the Frequent Hemodialysis Network on two randomized trials that evaluated outcomes from short daily in-center and long nightly home dialysis are pending (4), two recent publications renewed interest in the potential impact of longer hemodialysis session length, also referred to as treatment time (TT), to improve survival within the most prevalent practice of a thrice-weekly regimen. The Australian/New Zealand experience and the pooled international (Europe, Japan, and the United States) experience from the Dialysis Outcomes and Practice Patterns Study (DOPPS) both indicated better survival as TT exceeds 4 h

(240 min), with the US cohort averaging only 211 to 221 min (approximately 3.5 h) (5,6).

In contrast, patients in Tassin, France, have traditionally been prescribed HD for 8 h thrice weekly, performed as daylong treatments (also overnight), and have long been reported to have excellent outcomes (7). Although overnight HD outside the patient's home may have been performed in the early years of dialysis in North America (8), it was first reported as maintenance therapy in a 10-patient (and two-nurse) program initiated around September 1995 at a hospital-based dialysis unit in Montreal, Canada (9). Using a lower blood flow rate (BFR) of 200 ml/min with dialysate flow rate (DFR) at 500 ml/min, they reported an average single-pool Kt/V of 1.83 and noted potential beneficial effects on hypertension, acidosis, and phosphorus control. From 21 patients who had entered the program between September 1995 and January 1998, the authors concluded that long-duration overnight HD was a valuable therapeutic modality.

The first free-standing in-center nocturnal hemodialysis (INHD) program was started in the United States in April 1999 by Dr. Joe T. Chandler, in collaboration with Fresenius Medical Care, North America (FMCNA). As a result, in part, of Dr. Chandler's enthusiasm in sharing his INHD experience, increased physician interest toward INHD resulted in the program's growth to 56 facilities by year-end 2006. Recent publications indicated improvement in laboratory and patient

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outcomes upon conversion from conventional HD (CHD) to INHD in small, single-center experiences (10–12). We sought to evaluate the epidemiology and outcomes of prevalent INHD patients from the largest multicenter outpatient INHD program in the world.

Materials and Methods

Patient Population

For index cases, we collated demographic information (age, gender, race, diabetes, vintage, body surface area, and cause of renal disease) from all patients who were treated by INHD as of January 1, 2007, in 56 FMCNA facilities with an active program. The means of all available values for the month of December 2006 were obtained for TT, BFR, DFR, dialyzer type, systolic BP (SBP) measurements before and after treatments, interdialytic weight gains (IDWGs), fluid removed during dialysis (*i.e.*, ultrafiltration [UF]) volume per treatment, and laboratory results (albumin, hemoglobin, pre- and postdialysis urea nitrogen, phosphorus, and transferrin saturation [TSat]). Albumin was determined by bromocresol green method, whereas equilibrated Kt/V (eKt/V) was derived from single-pool Kt/V obtained by urea kinetic modeling on the basis of two-sample blood urea nitrogen variable volume method, previously described (13). Because INHD facilities were not uniformly distributed around the country (Figure 1), we collated concurrent information from all other prevalent CHD patients treated in 244 FMCNA facilities within the surrounding geographic area as the 56 INHD facilities to serve as control subjects.

All patients were followed up to December 31, 2007, with the two primary outcomes being mortality (a composite of death and withdrawal from dialysis therapy) and hospitalization (*i.e.*, time to first hospitalization event). Patients who were lost to follow-up during the year contributed exposure time until kidney transplantation or the last day before transfer out of the FMCNA system. Secondary outcomes included a comparison of the proportion of patients who were hospitalized and the average number of hospitalization events and hospital days, both normalized to actual exposure years. Because prevalent cases were already on INHD for an average of 51 ± 73 d as of January 1, 2007, laboratory values obtained in December 2006 for albumin, hemoglobin, eKt/V, and phosphorus as well as SBP, IDWG, and UF rate were considered “outcome measures” related to the therapy. Re-

sults from SF-36 quality-of-life surveys were available for one in five patients during the period from December 1, 2006, to March 31, 2007, so physical (PCS) and mental component scores (MCS) obtained during this period (all within 33 ± 23 d of January 1, 2007), albeit incomplete, were also reported.

Treatment Parameters

Within each INHD facility, a section was converted each night for nocturnal treatments, with the majority having only either a Monday–Wednesday–Friday or Tuesday–Thursday–Saturday nocturnal schedule because of the need to disinfect and regenerate the water system on off-nights. The average census was 10 to 12 patients per nocturnal shift, staffed by at least one nurse and one to two patient care technicians. Each nocturnal station used the Fresenius 2008H or 2008K hemodialysis machine (Fresenius USA, Walnut Creek, CA) with the sensitivity, volume, and intensity of machine alarms unaltered. Patients underwent dialysis either in a recliner that converts into a near-flat sleeping surface and can be placed in Trendelenburg position for emergencies (*e.g.*, Champion Chairs [Elkhart, IN] or Winco Inc. [Ocala, FL]) or, in a few facilities, twin-size beds. All patients were treated using biocompatible synthetic high-flux dialyzers (Fresenius USA) without dialyzer reuse.

Individual physicians determined rounding schedules and patient-specific HD prescriptions and ordered additional laboratory tests beyond routine monthly blood draws at their discretion. All laboratory results were sent to a single central laboratory (Spectra Laboratory, Rockleigh, NJ). There were no restrictions on the type of vascular access, although a strict policy was enforced to keep accesses uncovered at all times during the treatment. Central venous catheters required the use of Hemosafe safety-lock connectors (Fresenius USA) to prevent accidental disconnection. Patients who were on INHD were followed by the same team of nutritionists and social workers. Lights were usually dimmed (not turned off) about 1 h after all patients had initiated treatment, and most patients slept, with the rare case requiring prescription sleep-inducing medication.

Statistical Analysis

Descriptive data at baseline were presented as means or percentages of the total. Statistical significance was determined on the basis of *t* tests and χ^2 tests, where appropriate. Cox proportional hazard regression models were used to determine survival differences between INHD and CHD groups, by intention to treat in the main analysis. These models were presented as unadjusted, case mix–adjusted (includes age, gender, race, diabetes, vintage, and body surface area), and a case-mix + vascular access type–adjusted models. Laboratory values were considered as surrogate outcomes of the therapy and were not used as adjusters in the models. For SF-36 scores, a logistic regression model was constructed with treatment group as the outcome variable and PCS/MCS as the independent variable. Subsequent models also included adjustment for case mix and case mix plus vascular access. We performed two sensitivity analyses designed to test robustness of the primary Cox models for mortality and hospitalization: (1) Only concurrent patients who were treated by CHD within the same 56 INHD facilities served as controls; and (2) patients were censored upon changing modality when they did not resume baseline therapy within 30 d. All statistical tests were performed using SAS 9.2 (SAS Institute, Cary, NC).

Results

The study cohort included 655 patients who were treated by INHD for an average of 55 ± 73 d as of January 1, 2007, along with 15,334 control subjects who were treated by CHD, with



▲ FMCNA Facilities with INHD Programs in 2007

Figure 1. Location of FMCNA facilities that provide INHD as of January 1, 2007, in the United States.

patient characteristics shown in Table 1. Patients who were on INHD were younger (51.2 *versus* 62.4 yr) but with longer vintage (4.8 *versus* 3.6 yr), were more likely to be male (69 *versus* 53%) and black (52 *versus* 45%), had larger body surface area (2.01 *versus* 1.82 m²) and proportionately more fistulas (51 *versus* 42%), and were less likely to have diabetes (42 *versus* 51%; all $P < 0.0001$).

Patients who were on INHD exhibited favorable quality-of-care indicators (Table 2) compared with control subjects, such as higher albumin (3.95 *versus* 3.81 g/dl; $P < 0.0001$) and lower phosphorus (5.3 *versus* 5.5 mg/dl; $P = 0.003$) values. Hemoglobin was similar (12.2 *versus* 12.1 g/dl; $P = 0.3$), although INHD patients had slightly lower TSat (25.4 *versus* 27.2%; $P < 0.0001$). The mean eKt/V was higher (2.21 *versus* 1.46) related to longer TT (470 *versus* 222 min) in INHD patients, despite lower BFR (306 *versus* 414 ml/min), lower DFR (496 *versus* 682 ml/min), and greater use of smaller (membrane) surface area dialyzers (73 *versus* 44% dialyzer membrane surface area of 1.5 m²; all $P < 0.0001$). The extended TT allowed for slower UF rate (6.0 *versus* 8.8 ml/h per kg; $P < 0.0001$) despite greater IDWG (4.0 *versus* 2.8 kg; $P < 0.0001$), requiring larger UF volumes in INHD; however, as a percentage of body weight, IDWG was only slightly greater in INHD patients (4.4 *versus* 3.7%; $P < 0.0001$), reflecting larger body size of patients who were on INHD.

The distribution of mean UF volume in INHD patients was 4.0 ± 1.4 L, matching that for IDWG at exactly 4.0 ± 1.4 kg, likely reflecting appropriate fluid balance. In contrast, the dis-

tribution of mean UF volume in control subjects was 2.5 ± 1.0 L, whereas mean IDWG was 2.8 ± 1.2 kg, reflecting mismatches between fluid gain and fluid removal. In addition, SBPs were lower by 2 mmHg before dialysis ($P = 0.009$) and by 5 mmHg after dialysis ($P < 0.0001$) in the INHD group, although comparative use of antihypertensive medications was not available. Results from SF-36 surveys were available for only 20.5% of patients and 23.4% of CHD control subjects, with mean PCS of 37.5 ± 11.7 compared with 33.1 ± 10.6 ($P < 0.0001$), respectively. Although INHD patients' PCS scores were approximately 4 points higher than those of control subjects, adjustment for case mix and vascular access type reduced the difference to 2.7 points ($P = 0.003$), still favoring INHD. MCS scores were not significantly different between groups.

Overall exposure time at risk was 570 patient-years on INHD and 13,014 patient-years on CHD. Unadjusted 1-yr survival and hospitalization-free survival, both of which were significantly better for INHD relative to CHD ($P < 0.0001$), are depicted using the Kaplan-Meier method in Figure 2. The unadjusted hazard ratio (HR) was 0.59 (95% confidence interval [CI] 0.46 to 0.75) for mortality and 0.76 (95% CI 0.68 to 0.85) for hospitalization (both $P < 0.0001$). Adjustment for case mix and vascular access type indicated mortality HR of 0.90, although the difference with control subjects was no longer statistically significant ($P = 0.4$); however, the difference in hospitalization risk remained significant after adjustment for case mix and access type (HR 0.88; 95% CI 0.78 to 0.98; $P < 0.02$; Figure 3). Fewer INHD patients were hospitalized (48 *versus* 59%) during the

Table 1. Characteristics of Patients Treated by INHD and control subjects on CHD as of January 1, 2007

Characteristics at Baseline	In-Center Long-Term Dialysis	
	INHD ^a	CHD
Patients (<i>n</i> [%])	655 (4)	15,334 (96)
Age (yr; mean $\pm$ SD)	51.2 $\pm$ 12.7	62.4 $\pm$ 15.0
Male gender (%)	69.2	52.9
Race (%)		
black	52.4	44.6
white	44.1	49.0
other	3.5	6.4
Any diabetes (%)	42.3	51.3
Vintage (yr; mean $\pm$ SD)	4.8 $\pm$ 4.5	3.6 $\pm$ 3.7
Body surface area (m ² ; mean $\pm$ SD)	2.01 $\pm$ 0.34	1.82 $\pm$ 0.28
Cause of ESRD (%)		
diabetes	31.0	41.3
hypertension	36.6	34.7
glomerulonephritis	16.6	8.9
hereditary/cystic	3.5	2.3
other (includes unknown)	12.3	12.8
Vascular access (%)		
fistula	50.8	41.6
graft	23.7	25.5
catheter	25.5	32.7
unknown	0.0	0.2

^aCompared with CHD, all significant at $P < 0.0001$.

Table 2. Treatment parameters and intermediate outcomes for patients who were treated by INHD and matched control subjects who were on CHD as of January 1, 2007 (includes mean of last recorded values obtained from the previous month)

Parameter	In-Center Long-Term Hemodialysis	
	INHD	CHD
Treatment information		
time (min; mean $\pm$ SD)	470 $\pm$ 29	222 $\pm$ 28
BFR (ml/min; mean $\pm$ SD)	306 $\pm$ 58	414 $\pm$ 57
DFR (ml/min; mean $\pm$ SD)	496 $\pm$ 118	682 $\pm$ 129
dialyzer surface area (%)		
1.5 m ²	72.8	44.0
1.8 m ²	24.9	47.9
2.0 m ²	2.1	7.5
other dialyzers	0.2	0.6
SF-36 quality-of-life scores (mean $\pm$ SD) ^a		
PCS	37.5 $\pm$ 11.7	33.1 $\pm$ 10.6
MCS	49.0 $\pm$ 10.6 ^b	47.9 $\pm$ 11.2
Laboratory variables (mean $\pm$ SD)		
eKt/V	2.21 $\pm$ 0.56	1.46 $\pm$ 0.32
hemoglobin (g/dl)	12.16 $\pm$ 1.43 ^b	12.11 $\pm$ 1.40
albumin (g/dl)	3.95 $\pm$ 0.36	3.81 $\pm$ 0.42
phosphorus (mg/dl)	5.31 $\pm$ 1.54 ^c	5.50 $\pm$ 1.64
TSat (%)	25.4 $\pm$ 9.9	27.2 $\pm$ 11.2
Interdialytic weight gain (kg; mean $\pm$ SD)	4.0 $\pm$ 1.5	2.8 $\pm$ 1.2
Interdialytic weight gain (% of weight; mean $\pm$ SD)	4.4 $\pm$ 1.6	3.7 $\pm$ 1.4
UF volume (L; mean $\pm$ SD)	4.0 $\pm$ 1.4	2.5 $\pm$ 1.1
UF rate (ml/h per kg; mean $\pm$ SD)	6.0 $\pm$ 2.0	8.8 $\pm$ 2.9
Predialysis SBP (mmHg; mean $\pm$ SD)	147.7 $\pm$ 21.1 ^d	149.9 $\pm$ 21.5
Postdialysis SBP (mmHg; mean $\pm$ SD)	130.4 $\pm$ 19.4	135.3 $\pm$ 18.9

^aOnly one in five patients with SF-36 scores in both groups (20.5% for INHD and 23.4% for CHD).

^b*P* = 0.3, ^c*P* = 0.003, ^d*P* = 0.009 *versus* CHD (all others at *P* < 0.0001).

year, with fewer normalized hospitalization events at 1.26 *versus* 1.74 hospitalization events per patient-year and a lower normalized rate of 9.6 *versus* 13.5 hospital days per patient-year (all *P* < 0.0001). The sensitivity analysis using only the 3720 CHD patients who were treated within the same 56 INHD facilities as control subjects yielded results very similar to the primary analysis (data not shown). A second sensitivity analysis censored patients upon switching modality when they did not resume it within 30 d, and results indicated slightly improved HR for INHD compared with those in the primary analysis, although the study conclusions were unchanged (data not shown).

During the year-long study period, patients spent an average of 263 $\pm$ 126 d (median 365 d) on INHD therapy. From 655 patients at baseline, 381 (58.2%) were still on INHD at the end of follow-up. Of these, 334 (51%) were on INHD throughout, whereas 47 (7.2%) discontinued INHD temporarily then resumed therapy by year-end. Other than deaths, 63 (9.6%) patients transferred out of FMCNA and 45 (6.9%) patients underwent transplantation. Only 481 survivors were actively undergoing dialysis (from the original INHD cohort) on December 31, 2007, with 381 of them still being treated by INHD,

indicating 1-yr technique survival rate of 79.2%. Among patients who abandoned INHD during the study period, only five switched to peritoneal dialysis and two to home HD, with the rest opting for CHD. Their median time to discontinuing INHD was 136 d (mean 147 $\pm$ 95 d).

Discussion

To our knowledge, this study is the first to evaluate mortality and hospitalization outcomes in INHD patients relative to patients on CHD and is the largest study of INHD patients reported to date. Patients who were on INHD exhibited 41% lower HR for mortality and 24% lower HR for hospitalization compared with CHD control subjects; however, favorable survival factors related to younger age, longer vintage, less diabetes, more black patients, and larger body size were notable in INHD patients. Thus, although a 10% mortality advantage remained after adjustment for case mix and vascular access, mortality was no longer statistically significant (but hospitalization risk remained significant lower by 12.4% after similar adjustment). The study was underpowered to detect a significant survival difference of only 10%, when considering the great imbalance in demographic characteristics between pa-

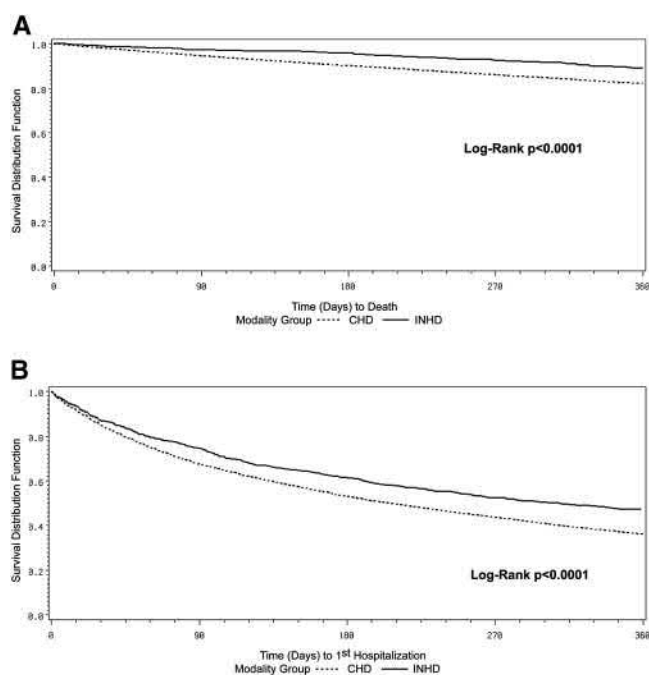


Figure 2. Kaplan-Meier unadjusted 1-yr survival curves comparing patients on INHD (solid line) with patients on CHD (dotted line) in terms of mortality (A) and hospitalization (B).

tients and control subjects and only a 1-yr follow-up period, on the basis of previous power calculation (14). This was further accentuated by a death rate in the control group of only 17%, much lower than the 22.5% rate reported by US Renal Data System for the US HD population (1).

Nevertheless, all laboratory-based quality-of-care indicators that we examined favored INHD (13). Because of doubling of TT, dialysis dosage was markedly increased beyond the differences attained in the HEMO Study (2). Longer treatments eclipsed the impact of lower BFR, lower DFR, and preponderant use of dialyzers with the smallest membrane surface area. Perhaps improved clearance with or without contribution from slower UF rate played a role in subsequent results for albumin, phosphorus, and hemoglobin, all of which tended to improve (albeit not always statistically significantly) in association with INHD in previous reports (10–12). The difference in mean albumin observed between patients and control subjects was only approximately 0.15 g/dl; however, this difference may be clinically significant, because we previously noted that even a 0.2-g/dl differential in albumin levels between groups was associated with marked difference in mortality and hospitalization risk (14). Phosphorus was approximately 0.2 mg/dl lower, even with greater dietary intake, consistent with the higher albumin levels and approximately 1.2-kg heavier IDWG. These results were not surprising considering that extensive phosphorus clearance has been a key advantage of nightly home HD in the setting of improved dietary intake and to a lesser extent also been noted in daylong thrice-weekly HD (7,16). Hemoglobin levels were similar between patients and control subjects, because it was actively managed by careful titration of erythropoietin dosage and maintenance of iron stores. The group

means for TSat were clearly above the minimum target of 20%, although the average TSat was slightly lower in INHD patients *versus* control subjects. This finding may reflect more efficient use of iron for hematopoiesis, a potential benefit of more effective clearance of uremic toxins (17,18).

As in daylong HD treatments, improved fluid management leading to more effective BP control has also been reported as a major benefit of long-duration HD (7,19). Troidle *et al.* (10) showed increased IDWG and subsequent UF in patients who converted from CHD to INHD; overall mean UF rate also declined from 10.3 to 5.9 ml/h per kg. There was an associated decline in post-HD SBP from 136 to 128 mmHg in that study. We confirmed similar differences between patients and control subjects in this study. Despite much greater IDWG, INHD patients were able to balance larger weight gains with appropriately greater fluid removal. In addition, UF occurred gently, at slower normalized UF rates, than in CHD control subjects. Finally, even in this setting of greater IDWG, we determined that both pre- and post-HD SBP were lower in patients than in control subjects.

The growth of INHD therapy is remarkable considering the barriers to implementing INHD in the United States: (1) Criticism that historical outcome data were skewed by highly selected patients; (2) competitive “modality choice” because many patients who are eligible for INHD are often also eligible for home dialysis options; (3) logistical issues facing clinic managers from accommodating longer TT for patients in outpatient dialysis units that are filled to capacity; (4) the constant struggle to convince patients to stay longer for in-center treatments, even by just a few minutes; (5) local staffing issues as a result of a variable supply of dialysis nurses and patient care technicians who are willing to do a night shift; and (6) increased cost of providing therapy without additional reimbursement, becoming apparent when patient participation falls below critical mass. INHD is clearly not for all patients with ESRD (20), but it seems to have a niche among options for renal replace-

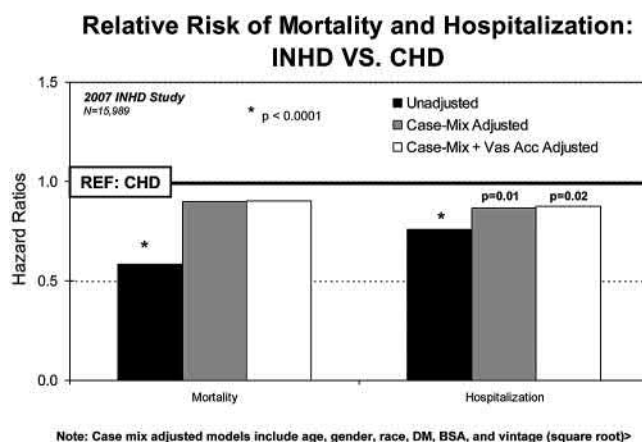


Figure 3. Results from Cox proportional hazard models comparing time to death and time to first hospitalization from patients who were treated by INHD with patients who were on CHD. Case mix-adjusted models included age, gender, race, diabetes, body surface area, and vintage (square root).

ment therapy. Of note, there were proportionately more black patients on INHD, unlike home nocturnal HD programs that were predominantly white (21). Future research is needed to explore the causes and implications of this observation, particularly with continued growth of the program.

The study has several limitations. First, the observational design delineates associations but does not prove causation. A second limitation may be the lack of adjustment for patient comorbidity beyond diabetes; however, recent findings indicated that the contribution of comorbidity in survival studies may be less than expected (22). Third, we studied a prevalent sample of patients, affected by lead time/survival biases; however, mortality was not significantly different between groups in this study, negating the largest potential bias. Furthermore, the bias that is associated with longer vintage tends to narrow potential differences in hospitalization because the cumulative risk for hospitalization and subsequent cumulative incidence inevitably increases over time in surviving dialysis patients. Finally, there remains unmeasured residual confounding because patients who are on INHD are a selected (or self-selected) group. Clearly, this initial evaluation provides an overview of INHD therapy in comparison with CHD but is more hypothesis generating than conclusive, supporting the need for additional studies.

Conclusions

A cross-sectional evaluation of patients who were on INHD exhibited excellent quality indicators with improved fluid balance and slightly lower BP, better survival, and lower hospitalization rates relative to CHD patients within the same geographic area. Characteristics of patients who opt for INHD are not representative of the general CHD population, such that the relative contributions of patient selection *versus* effect of therapy on outcomes remain to be elucidated. Prospective studies are needed to evaluate this novel, rapidly expanding therapeutic option.

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Disclosure

All authors are employees of Fresenius Medical Care, North America.

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Extended-hours hemodialysis is associated with lower mortality risk in patients with end-stage renal disease

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Abstract

Extended-hours hemodialysis offers substantially longer treatment time compared to conventional hemodialysis schedules and is associated with improved fluid and electrolyte control and favorable cardiac remodeling. However, whether extended-hours hemodialysis improves survival remains unclear. Therefore, we determined the association between extended-hours compared to conventional hemodialysis and the risk of all-cause mortality in a nationally representative cohort of patients initiating maintenance dialysis in the United States from 2007 to 2011. Survival analyses using causal inference modeling with marginal structural models were performed to compare mortality risk among 1,206 individuals undergoing thrice weekly extended-hours hemodialysis or 111,707 patients receiving conventional hemodialysis treatments. The average treatment time per session for extended-hours hemodialysis was 399 minutes compared to 211 minutes for conventional therapy. The crude mortality rate with extended-hours hemodialysis was 6.4 deaths per 100 patient-years compared with 14.7 deaths per 100 patient-years for conventional

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Disclosure

None.

hemodialysis. In the primary analysis, patients treated with extended-hours hemodialysis had a 33% lower adjusted risk of death compared to those who were treated with a conventional regimen (95% confidence interval: 7% to 51%). Additional analyses accounting for analytical assumptions regarding exposure and outcome, facility-level confounders, and prior modality history were similar. Thus, in this large nationally representative cohort, treatment with extended-hours hemodialysis was associated with a lower risk for mortality compared to treatment with conventional in-center therapy. Adequately powered randomized clinical trials comparing extended-hours to conventional hemodialysis are required to confirm these findings.

Keywords

end-stage renal disease; maintenance dialysis; in-center hemodialysis; nocturnal hemodialysis; extended-hours hemodialysis; mortality risk

Introduction

Although the past decade has witnessed a modest improvement in survival for patients undergoing maintenance dialysis in the United States, mortality continues to be unacceptably high, approaching 20 percent per year.¹ While early observational studies suggested that a higher delivered dose of dialysis may be associated with improved clinical outcomes, a benefit of increasing the dialysis dose above currently accepted standards has not been confirmed by randomized controlled clinical trial results.^{2–4} This has prompted a search for other modifiable dialysis parameters, including dialysis modality and treatment time, in order to improve long-term clinical outcomes. Consistent with this emphasis, the Institute of Medicine in the United States has identified comparative effectiveness of dialysis therapies as the only kidney disease-related topic among the top 100 national priorities for comparative effectiveness research.⁵

Numerous observational studies over the past two decades have demonstrated that shorter treatment times with conventional hemodialysis are associated with higher mortality.^{6–10} Recently, an increasing number of patients are being treated with extended-hours hemodialysis consisting of substantially longer treatment times, which has been associated in observational studies with lower hospitalization rates and improvements in metabolic parameters, left ventricular mass and hypertension.^{11–14} However, there are limited data on the association of extended-hours hemodialysis with patient survival, as prior studies have been small or single-center investigations, or have not addressed the multiple time-varying and facility-level factors which can cause confounding.^{15–19}

Randomized controlled trials remain the gold standard for comparative effectiveness research. However, trials that have sought to randomly assign patients to one of two different dialysis modalities have encountered substantial challenges in enrolling the target number of patients.^{20–22} These challenges likely reflect that most patients are not willing to leave the selection of dialysis modality to random assignment if the therapies have substantial and widely differing effects on lifestyle, schedule, and weekly commitment to dialysis-related treatment.²² Additionally, no contemporary randomized controlled trial has sought to test the effect of extended hemodialysis treatment time independent of increased treatment

frequency. Observational studies using contemporary causal inference modeling such as marginal structural models utilize robust statistical tools that address time-varying exposures and confounding, and thus represent an important alternative method for investigating the comparative effectiveness of dialysis modalities.²³ In this study, we used marginal structural modelling to address the hypothesis that extended-hours hemodialysis is associated with lower risk for all-cause death compared to conventional hemodialysis.

Results

Study Cohort

The study sample comprised 136,207 individuals with end-stage renal disease who initiated maintenance dialysis from 2007 to 2011 treated in dialysis facilities operated by a large US dialysis provider (Figure 1). Compared to individuals treated exclusively with conventional hemodialysis (n=111,707), patients categorized as treated with extended-hours hemodialysis for one or more 91-day periods (n=1,206) were younger, more likely to be male, black, have diabetes or comorbid cardiovascular disease, have primary insurance other than Medicare or Medicaid, and to live in the western region of the US (Table 1). Other patients, who were never treated with extended-hours hemodialysis and were treated with at least one modality other than conventional hemodialysis, differed from both extended-hours and exclusively conventional hemodialysis patients (Table 1). However, in the first 91-day period of dialysis, laboratory and treatment parameters were similar among patients ever treated with extended-hours hemodialysis, patients exclusively treated with conventional hemodialysis, and other patients (Table 1).

Patients who initiated extended-hours hemodialysis following one or more 91-day periods of conventional hemodialysis had higher serum alkaline phosphatase, ferritin, parathyroid hormone, spKt/V, and lower serum phosphorous, cumulative iron dose (prescribed over each 91-day period), and median erythropoietin dose during treatment with extended-hours hemodialysis compared to values during treatment with conventional hemodialysis prior to transfer (Supplemental Table S1).

The average delivered treatment time per session with extended-hours hemodialysis was 399 ± 64 minutes compared to 211 ± 27 minutes with conventional hemodialysis (intra-patient coefficient of variation 10.8% and 6.8%, respectively) (Figure 1). Treatment frequency was similar among patients treated with extended-hours hemodialysis (2.8 treatments per week, interquartile range [IQR 2.4, 2.9]) and conventional hemodialysis (2.9 treatments per week, [IQR 2.7, 2.9]). Among extended-hours hemodialysis patients, extended-hours hemodialysis was the initial dialysis modality for 353 patients (29%); 823 (67.5%) started dialysis with conventional hemodialysis, 37 (3%) started with peritoneal dialysis, and 6 (0.5%) initiated with home hemodialysis or in-center hemodialysis less than 3 times per week. Overall, median time from initiation of dialysis to start of treatment with extended-hours hemodialysis was 6.7 months (IQR 1.0, 19.2). The median duration between initiation of hemodialysis and transfer to another modality, censoring, or death was 7.6 months (IQR 2.3, 17.6) for conventional hemodialysis and 7.2 months (IQR 3.4, 15.1) for extended-hours hemodialysis. Of patients treated with extended-hours hemodialysis, 535 (44%) transferred to another dialysis modality for one or more 91 day periods. Of these patients, none died and

78 were censored (66 due to end of follow-up) within 91 days of transfer from extended-hours hemodialysis. Of patients treated with conventional hemodialysis, 10% later transferred to another modality.

Extended-hours Hemodialysis and All-Cause Mortality

In total, 82 patients died during a 91-day period in which they were receiving extended-hours hemodialysis, compared to 29,778 deaths during periods of conventional hemodialysis. Crude mortality rates were 6.4 and 14.7 deaths per 100 patient-years for extended-hours and conventional hemodialysis, respectively (Table 2). Adjusted for treatment history and time-varying laboratory and treatment parameters using marginal structural models, as well as for case-mix factors, patients treated with extended-hours hemodialysis had a 33% lower adjusted risk of death compared to those treated with conventional hemodialysis (95% confidence interval [95% CI] 7% to 51% lower) (Table 2).

Attributing deaths to the dialysis modality 90 days prior to death did not meaningfully change the risk estimate (Table 2). An extreme approach—attributing all deaths following initiation of extended-hours hemodialysis to extended-hours hemodialysis, regardless of the actual modality at the time of death—increased the number of deaths attributed to extended-hours hemodialysis to 126, but the risk ratio between extended-hours and conventional hemodialysis did not change substantially (HR 0.62 [0.47 to 0.81]). (Table 2).

Starting follow-up from the 91st day following start of dialysis, further adjustment for vascular access type, or restricting the cohort to patients for whom extended-hours dialysis treatment was most likely to be available did not meaningfully change hazard ratio estimates (Table 3). Additionally, results of analyses among a restricted cohort that excluded patients who never initiated extended-hours hemodialysis, but to whom extended-hours hemodialysis was available, were similar (Table 3). Results from a matched analysis in which each patient ever-treated with extended-hour hemodialysis was matched with up to 20 other patients who had the same dialysis modality treatment history prior to initiation of extended-hours hemodialysis, were not substantially different (Table 3). Finally, in interaction analyses, no evidence of effect modification by age, sex, or race was found ($P>0.2$ for each).

Discussion

Using contemporary causal inference methods in this large study of incident dialysis patients, we found that treatment with three times-weekly extended-hours hemodialysis was associated with 34% lower risk for death compared with conventional hemodialysis. Our results were robust, with consistent treatment effect estimates in multiple sensitivity analyses accounting for temporal assumptions regarding exposure and outcome, facility-level confounders related to the availability of extended-hours hemodialysis to patients, and prior modality history. To our knowledge, this is the largest study of extended-hours hemodialysis reported.

The past decade has seen a resurgent interest in exploring the benefit of more frequent and/or longer dialysis treatments. Culleton *et al.*²⁴ randomly assigned 52 patients in Canada to three times-weekly in-center or home hemodialysis versus six times-weekly nocturnal

hemodialysis, and found that the latter therapy resulted in a decrease in left ventricular mass and systolic blood pressure, and a reduction in serum phosphorus and parathyroid hormone levels. The Frequent Hemodialysis Network (FHN) nocturnal trial compared conventional three times-weekly hemodialysis performed at home with frequent home nocturnal hemodialysis performed six times-weekly for ≥ 6 hours per session, and showed that frequent nocturnal therapy resulted in lower blood pressure and reductions in serum phosphorus.²¹ Surprisingly, long-term follow-up of patients enrolled in the FHN nocturnal trial found an increased risk for death in the nocturnal dialysis group, although caution should be exercised in interpretation of these results given an unexpectedly low mortality rate observed in the conventional dialysis group and high rates of dialysis modality switches in this study.²⁵ Of note, these two trials assessed the impact of increasing both hemodialysis treatment time and treatment frequency together and thus did not allow for assessment of the independent effect of changing treatment time. In the recently reported ACTIVE Dialysis Trial, extending hemodialysis hours to a target of ≥ 24 hours weekly compared to standard dialysis hours (12–15 hours weekly) resulted in reductions in serum phosphorus and blood pressure medication requirements.²⁶ However, similar to the aforementioned FHN and Canadian trials of nocturnal hemodialysis, the intervention in ACTIVE was not designed to assess the independent impact of extending hemodialysis treatment times separate from changes in treatment frequency.²⁷ In contrast, the Time to Reduce Mortality in End-Stage Renal Disease (TiME) trial is an ongoing pragmatic randomized clinical trial designed to test the hypothesis that three times-weekly hemodialysis with session durations of at least 4.25 hours improves mortality, hospitalization, and health-related quality-of-life compared to usual care consisting of treatments with mean duration of 3.5 hours.²⁸ However, given this relatively small increase in treatment time for the intervention group compared to the marked differences in treatment time achieved with extended-hours hemodialysis, the results of the TiME trial will not directly address the impact of extended-hours hemodialysis on clinical outcomes.

In our study, patients treated with extended-hours hemodialysis had average treatment times that exceeded those of conventional hemodialysis by more than 3 hours. This substantial lengthening of the hemodialysis treatment is much greater than what is possible to achieve within the context of conventional in-center hemodialysis or more frequent hemodialysis, whether performed in-center or at home. There are a number of potential mechanisms by which such substantially longer hemodialysis treatments may lead to improved clinical outcomes, independent of any increase in dialysis frequency. Nocturnal extended-hours hemodialysis has been shown to enhance phosphorus removal and reduce arterial stiffness, potential mediators in the pathway between end stage renal disease and clinical cardiovascular events.^{7,29,30} Indeed, in our study, we found that for patients who switched from conventional in-center hemodialysis to extended-hours hemodialysis, serum phosphorus levels declined into the range associated with lower risk for death in prior observational studies.³¹ Prior randomized trials comparing extended-hours to standard length hemodialysis treatment have shown lower pre-dialysis serum phosphorus in patients assigned to extended-hours treatments, though such trials have also included increased dialysis frequency in the intensive therapy arm, preventing determination of the independent effect of dialysis duration.^{24,32} In addition to its impact on markers of mineral and bone

disease, one of the major advantages of extended-hours hemodialysis is that longer treatment times facilitate a slower net fluid removal rate, which has been shown to be associated with lower systemic blood pressure and reduced cardiovascular morbidity and mortality.^{6,33} Prior randomized trials of increased dialysis frequency either with or without increased dialysis duration have demonstrated lower pre-dialysis systolic blood pressures among patient assigned to intensive dialysis therapies.^{32,34} Unfortunately, as with markers of mineral metabolism, there is a paucity of data from clinical trials on the impact of thrice-weekly extended-hours hemodialysis on clinical volume overload or blood pressure. Prior studies have demonstrated an association among conversion to extended-hours hemodialysis, regression of left ventricular mass, and improvement in myocardial mechanics and cardiomyocyte gene expression, which are all likely contributors to improved cardiovascular outcomes.^{35,36} One important benefit potentially favoring thrice-weekly extended-hours hemodialysis over other forms of dialysis intensification is avoidance of the need for more frequent use of the patient's vascular access. In the FHN trials, patients undergoing more frequent hemodialysis were more likely to have complications related to vascular access compared to patients undergoing conventional hemodialysis.^{32,34} In contrast, there is no evidence that thrice-weekly extended-hours hemodialysis is associated with an increase in access-related complications compared to conventional therapy, although no data from adequately powered clinical trials are available.

We found a >30% reduction in the risk for death associated with extended-hours hemodialysis in our study. Due to the potential presence of residual confounding from unmeasured patient and treatment-related factors in an observational cohort study, the actual benefit of extended-hours hemodialysis may be smaller than this estimate. Lacson *et al.*¹⁷ have previously shown a 25% reduction in risk for death associated with conversion from conventional hemodialysis to nocturnal in-center hemodialysis in a propensity score-matched observational analysis. Long-term follow-up of patients from the FHN Daily Trial demonstrated a persistent 46% reduction in risk for death for patients randomized to frequent hemodialysis, even though the majority of such patients returned to conventional thrice-weekly therapy at the conclusion of the initial 12-month intervention period.³⁷ Such results suggest that even short-term changes in the provision of dialysis therapy, such as treatment with extended-hours hemodialysis, have the potential to result in lasting benefit.

Our findings extend those of prior observational studies through a number of important strengths in study design and approach. First, our examination of the largest cohort of patients undergoing extended-hours hemodialysis maximizes statistical power and precision in estimates of treatment effect compared to prior studies.^{15–18} Second, we observed a large difference in the mean and overall distribution of delivered treatment times between patients undergoing conventional versus extended-hours hemodialysis, which enhances our ability to detect an association between treatment time and outcomes. Third, our study allows an examination of the association of longer dialysis treatment time with outcomes independent of increased treatment frequency by comparing in-center extended-hours versus conventional hemodialysis, both delivered three times weekly. Fourth, we used a contemporary marginal structural modelling approach to maximize our ability to account for time-varying exposures and confounders. Use of marginal structural models also directly accounts for between-group differences in time since initiation of dialysis, addressing the

propensity of healthier patients to survive to transfer to extended-hours hemodialysis. Finally, we showed the consistency of our findings across many secondary and sensitivity analyses to ensure robustness of our treatment effect estimates.

Despite its strengths, our study also has limitations. Patients undergoing treatment with extended-hours hemodialysis are likely to differ in important ways from patients undergoing conventional hemodialysis, including attributes such as exercise capacity, cardiovascular function, social support structures, cognitive function, and motivation that are not captured in available data. Furthermore, we were not able to account in our analyses for the full range of patient coexisting illnesses which may differ in prevalence among patients undergoing extended-hours versus conventional hemodialysis and also impact mortality risk. Although we incorporated a large number of demographic and laboratory predictors into the development of the marginal structural models, it is likely that residual confounding by unmeasured characteristics remains, and such confounding may be partly responsible for the observed treatment effects. Although we were able to examine the influence of facility level practices in sensitivity analyses, we were unable to account for physician-level practices. Physicians providing extended-hours hemodialysis may differ systematically from those who do not with respect to care pathways and quality, and this may be a further source of residual confounding. Finally, over 40% of patients treated with extended-hours hemodialysis in our study subsequently transferred to another dialysis modality for at least one 91-day period. We did not find that transfers from extended-hours hemodialysis were followed by a high mortality rate on the subsequent modality, and indeed we observed that no patient who transferred from extended-hours hemodialysis died within 91-days of transfer. However, further studies are needed to investigate reasons and risk factors for transfers from extended-hours dialysis hemodialysis, as such attrition may pose a challenge to large-scale application of extended-hours dialysis therapies.

In conclusion, in a large observational cohort study, we demonstrated that treatment with extended-hours hemodialysis is associated with approximately one-third lower risk for death compared to conventional hemodialysis. Given the inherent limitations of observational studies in definitively determining causation, there is thus a need for well-designed randomized clinical trials to test whether assignment of patients to treatment with extended-hours hemodialysis results in improvement in patient-centered clinical outcomes including not only mortality and hospitalization, but also patient autonomy, care burden and satisfaction, and health-related quality of life. To be successful and to ultimately impact clinical practice, future trials will need to be carefully designed to address barriers to patient enrollment given the substantial recruitment challenges observed in prior randomized studies testing the comparative effectiveness of dialysis modalities on patient outcomes.

Methods

Study Population and Data Source

The study cohort comprised all patients age 18 years or older who started maintenance dialysis in calendar years 2007 through 2011, and received treatment for at least 60 days at a facility operated by DaVita Inc. (N=162,664). Exclusion of patients with fewer than 60 days total dialysis treatment is common practice in analyses of dialysis cohorts.¹⁹ Patients without

a dialysis treatment session at a participating facility within 91 days of ESRD incidence were excluded (N=24,940), as were patients missing information on race (N=1,517), resulting in a final cohort of 136,207 patients (Figure 2). All data were obtained from dialysis facility electronic medical records. All laboratory values were measured using standardized automated methods in a central laboratory (Deland, FL) within 24 hours of blood collection. Coexisting illnesses were coded as prevalent if they were recorded at any time during follow-up.

Modality was categorized as one of six: either conventional thrice-weekly hemodialysis, extended-hours hemodialysis, peritoneal dialysis, home hemodialysis, more frequent in-center hemodialysis (>3 times/week), or less frequent in-center hemodialysis (<3 times/week).¹⁹ Assignment to extended-hours hemodialysis for the present analyses was based on dialysis facility treatment records which identified patients as having received nocturnal in-center hemodialysis; these patients were treated overnight in-center three times-weekly while sleeping. To classify the dialysis modalities received by a patient over time, individual dialysis session records were analyzed for the date and modality of treatment administered. Subsequent to the first modality recorded, each patient was considered to have switched to a different modality if he or she was treated exclusively with that modality over a period of least 60 consecutive days, a rule commonly applied for examining comparative effectiveness of dialysis modalities.¹ Hence, each patient's record was divided into treatment intervals by modality, each interval after the first lasting at least 60 days unless the patient died or was censored.

Next, the follow-up period for each patient was divided into successive 91-day periods from the date of first dialysis; follow-up was available for up to 20 periods. The modality assigned for each 91-day period was that with which the patient was treated for >45 days in that period; however, for the 91-day period in which the patient was censored or died, the modality received for the longest period was assigned. Vascular or peritoneal access was assigned to each 91-day period in an analogous manner. Each 91-day period was assigned the mean of recorded laboratory and clinical measurements during the period. Facility was assigned as the facility at which the patient received the most dialysis sessions in a 91-day period.

All-cause mortality was defined by date of death during the follow-up period (January 1, 2007–December 31, 2011). Censoring reasons included kidney transplant, transfer to a facility operated by another dialysis provider, discontinuation of dialysis, and administrative end of follow-up. The Institutional Review Boards at the Los Angeles Biomedical Research Institute and the University of Washington approved the study as exempt from informed consent.

Statistical Analyses

For an overview of differences between patients according to dialysis modality, descriptive statistics were calculated for the first 91-day period of dialysis (baseline) for the mutually exclusive groups of patients ever treated with extended-hours hemodialysis (N=1,206), patients treated *exclusively* with conventional hemodialysis (N=111,707), and other patients (N=23,294).

The extent of missing data was examined at baseline and in subsequent 91-day periods. At baseline, the extent of missing data varied from approximately 9% for body weight measurements and 8% for single-pool urea Kt/V (spKt/V), to 1–2% for most serum and urinary measurements (e.g., albumin, serum alkaline phosphatase, serum calcium) (Table 1). Overall, approximately 25% of patients were missing information on one or more laboratory or clinical measurements for one or more 91-day period. Therefore, complete-case analysis would have deleted a substantial portion of patients; missing information for time-varying covariates was imputed using multiple imputation with ten repetitions. The multiple imputation model included a wide variety of laboratory and clinical measurements, case-mix variables, facility variables, dialysis modality, the estimated Nelson-Aalen cumulative hazard of mortality, an indicator of death or cause of censoring, and the total time for each patient under observation (see Detailed Statistical Methods available in Supplementary Appendix).³⁸

For the primary analysis, the effect of treatment with extended-hours hemodialysis compared to conventional hemodialysis on all-cause mortality was assessed using marginal structural models, with dialysis modality treated as a time-varying exposure.²³ Hazard ratio estimates from these models have the interpretation as the ratio of the mortality rates comparing cohorts treated with extended-hours versus conventional hemodialysis, and with the same prior treatment history and other covariates. A time-varying exposure approach was utilized to maximize accuracy of event attribution and minimize risk of immortal time bias (Detailed Statistical Methods available in Supplementary Appendix).³⁹ Marginal structural models utilizing time-varying exposures have been shown to be valid even when the exposure of interest changes multiple times over follow-up.^{40,41}

To construct the models, stabilized inverse probability of treatment weights (SIPTW) and stabilized inverse probability of censoring weights (SIPCW) were computed for each 91-day period to account for history of prior dialysis modality treatment and other potential time-varying confounders (see Supplemental Methods).^{23,42} The potential confounders used to separately estimate SIPTWs and SIPCWs included case-mix and demographic variables, dialysis modality from the immediately preceding 91-day period, a variety of time-varying laboratory and clinical measures, and facility-level variables. The final combined stabilized inverse probability weights were estimated by multiplying the SIPTW and SIPCW.

Finally, a Cox proportional hazards models weighted by the stabilized inverse probability weights was fit comparing hazard of mortality while treated with extended-hours dialysis to conventional hemodialysis (reference), adjusted for age, gender, race, type of insurance, diabetes, congestive heart failure, atherosclerotic heart disease, other cardiovascular illness, and year of dialysis incidence. Laboratory and other time-varying intermediate variables were not included as adjustment covariates in the final Cox model.

Several sensitivity analyses were performed to investigate modeling assumptions. First, to assess the potential for delayed effect of changes in dialysis modality, analyses were repeated by attributing death to the dialysis modality with which the patient was treated in the 91-day period prior to the period in which death occurred. Second, analyses were repeated in which any death following initiation of extended-hours dialysis was attributed to

extended-hours dialysis, regardless of whether the patient had transferred from extended-hours dialysis. Third, to remove the immediate impact of dialysis initiation, analyses were conducted in which follow-up was started on the 91st day after initiation of dialysis. Fourth, to investigate the impact of additional patient-level and facility-level variables that could determine availability and initiation of extended-hours dialysis, analyses were performed in a restricted cohort comprising patients who were treated at a facility that had (1) treated any patient with extended-hours hemodialysis or (2) treated any patient who was treated with extended-hours dialysis at a different facility. Additionally, analyses were repeated in a second restricted cohort comprising patients who were ever treated with extended-hours hemodialysis and patients only treated with conventional hemodialysis who were treated at facilities where extended-hours HD was unavailable. Fifth, analyses were repeated on a matched cohort in which patients who were treated with extended-hours hemodialysis were matched with up to 20 patients with identical dialysis treatment modality history in each 91-day period prior to initiation of extended-hours dialysis (by the index patient), year of incidence, age, sex, race, underlying renal disease, Charlson index, and geographic region. The matched cohort analysis was also restricted to patients to whom extended-hours treatment was available as described above (Supplemental Methods and Figure S1).

Effect modification was investigated by first repeating the marginal structural Cox model analysis estimating the association of dialysis modality with mortality, within strata of age, sex, and race. Subsequently, to conduct statistical testing of the interaction, the analysis was repeated adding a multiplicative interaction term between dialysis modality and age, sex, or race to the marginal structural Cox model.²³

All analyses followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.⁴³ Further detail regarding statistical methods, including elimination of immortal time bias, is available in the Supplementary Material. Analyses were performed with Stata 13.1 (Stata Corp, College Station, TX, USA

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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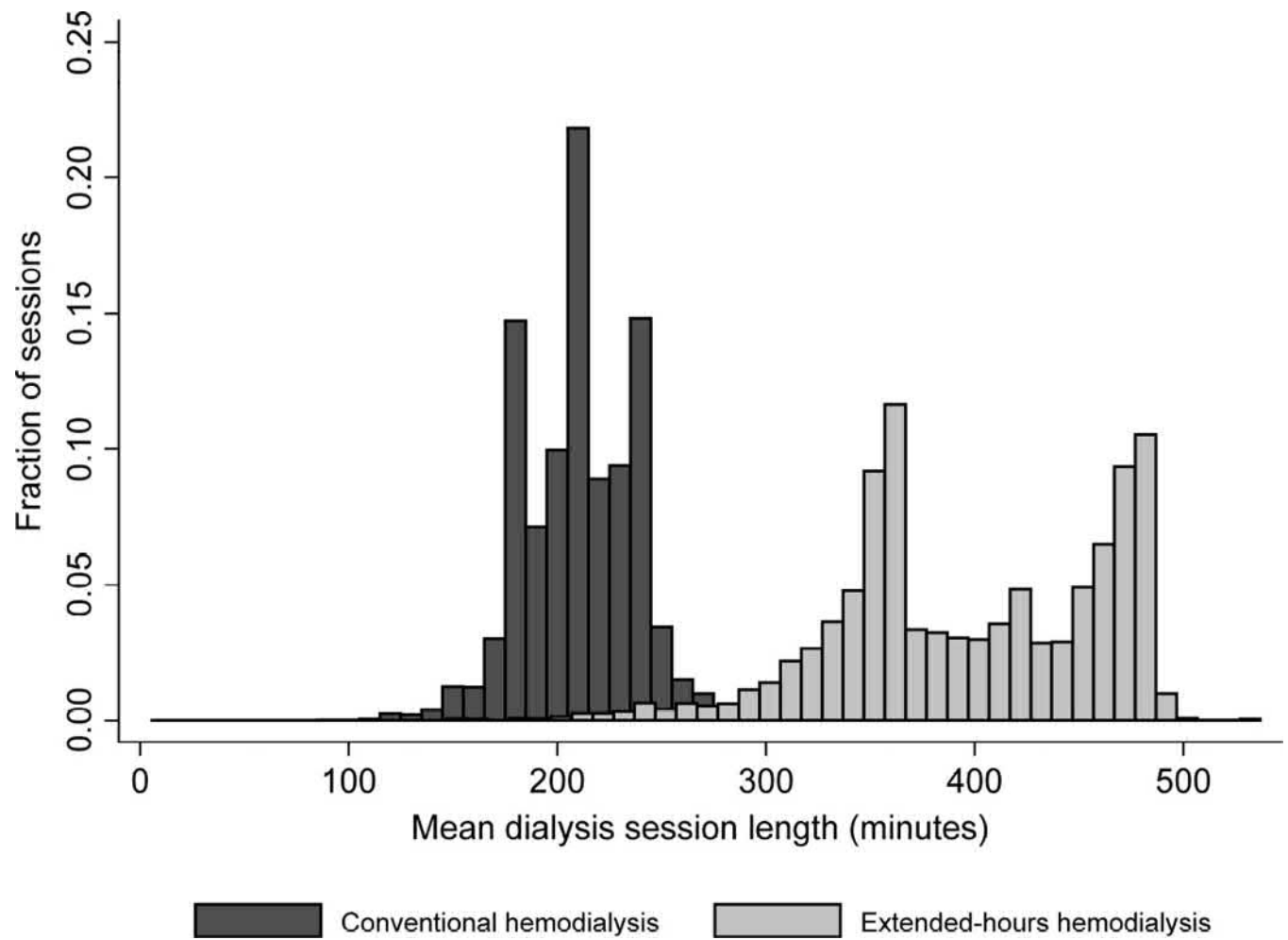


Figure 1. Construction of the study cohort

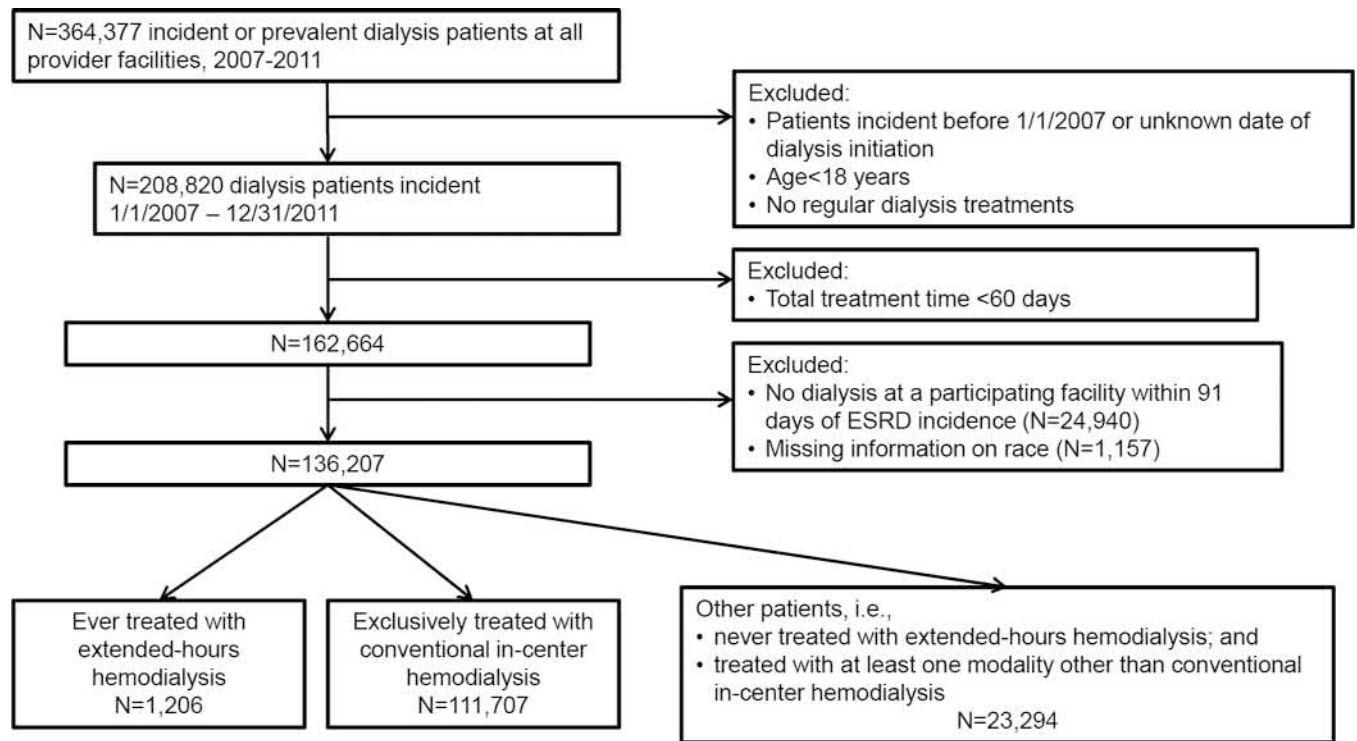


Figure 2. Distribution of mean treatment time per session over each 91-day period, for conventional hemodialysis (dark bars, 899,696 patient-periods) or extended-hours hemodialysis (light bars, 5,610 patient-periods)

For clarity one outlier with mean treatment time 693 minutes was omitted from the conventional-hours group. Three percent of values plotted were imputed with multiple imputation. Bin width is 10 minutes.

Table 1

Patient characteristics at the start of the first 91-day dialysis treatment period after initiation of dialysis, by modality, and total proportion of variables with missing information.

	Ever treated with extended-hours hemodialysis (N=1206)	Exclusively treated with conventional hemodialysis (N=111,707)	Others (N=23,294)	% Missing
Age, years				0
18–24	3	1	2	
25–44	28	11	18	
45–59	42	27	30	
60–74	24	36	33	
≥75	3	24	16	
Race, %				0
Asian	3	3	4	
Black	37	31	21	
White	47	47	58	
Hispanic	10	15	13	
Other	3	4	3	
Male, %	70	57	56	0
Primary Health Insurance,%				0
Medicare	35	53	46	
Medicaid	7	7	5	
Other insurance	58	40	48	
Geographic Location				0
Northeast, %	9	13	12	
Midwest, %	30	18	19	
West, %	40	25	41	
South, %	21	44	28	
Year of Incidence				0
2007	25	20	20	
2008	24	20	21	
2009	24	21	22	
2010	18	21	22	
2011	9	18	15	
Co-existing illnesses, %				0
Atherosclerotic Heart Disease	21	14	18	
Congestive Heart Failure	55	37	30	
Diabetes	68	58	63	
Other Cardiovascular	19	15	16	
Access Type, % ^a				6.5
Arteriovenous fistula or graft	24	20	11	

	Ever treated with extended-hours hemodialysis (N=1206)	Exclusively treated with conventional hemodialysis (N=111,707)	Others (N=23,294)	% Missing
Central venous catheter	73	80	46	
Peritoneal dialysis catheter	3	0	42	
Treatment parameters ^a				
Body mass index	32.5±9.5	28.2±7.4	28.3±7.2	8.7
Pre-dialysis systolic blood pressure, mm Hg	152±18	147±19	148±19	5.9
Weekday inter-dialytic weight gain, %	2.2 [1.5,3.0]	2.3 [1.5,3.2]	0.02 [0.013, 0.029]	9.3
Weekend inter-dialytic weight gain, %	2.8 [2.0,4.1]	3.1 [2.1, 4.2]	0.027 [0.017, 0.038]	8.9
Laboratory Variables				
Serum albumin, g/dL	3.6±0.5	3.5±0.5	3.6±0.5	1.6
Alkaline phosphatase, u/L *	87 [69, 111]	87 [69, 115]	82 [65, 106]	1.8
Serum calcium, mg/dL	9.1±0.6	9.1±0.6	9.1±0.6	1.5
Serum ferritin, ng/mL	234 [138, 373]	282 [164, 484]	237 [133, 413]	2.8
Hemoglobin, g/dL *	11.1±1.2	11.1±1.2	11.3±1.2	1.3
Serum iron saturation, %	21 [17,25]	22 [17, 27]	23 [18, 29]	2.1
Parathyroid hormone, pg/mL	378 [240, 569]	314 [197, 486]	294 [183, 470]	2.0
Serum phosphorous, mg/dL	5.3±1.2	4.9±1.2	4.9±1.1	1.5
spKt/V urea	1.4 [1.2, 1.8]	1.6 [1.4, 1.8]	1.4 [1.2, 1.7]	8.2
Parenteral medications				
Cumulative iron, mg/month	1062 [525,1600]	1000 [400, 1400]	400 [0, 1050]	0
Erythropoietin Dose, median units/week	26,950 [16,500, 36,300]	24,900 [13,200, 33,000]	17,600 [9,000, 29,700]	0

Summary statistics are mean ± SD, median and interquartile range, or proportions (%).

* P>0.05 for the difference between extended-hours and conventional hemodialysis groups using ANOVA, Kruskal-Wallis test, or Chi-squared test.
P<0.05 for all other comparisons.

^a Among patients ever-treated with extended hours hemodialysis, 67% were treated with conventional hemodialysis in the first 91-day period.
Values for the period prior to extended-hours hemodialysis are available in Supplementary Table S1.

Table 2

Risks for all-cause mortality comparing extended-hours hemodialysis to conventional hemodialysis, by time period for dialysis modality death attribution

Death Attribution	Hemodialysis Modality	Number of deaths	Patient-years of follow-up	Mortality rate ^a	Hazard Ratio ^b (95% CI)
Current dialysis modality at time of death ^c	Extended-hours	82	1,279	6.4	0.67
	Conventional	29,796	203,046	14.7	(0.49, 0.93)
Dialysis modality of 91-day period prior to death ^d	Extended-hours	82	1,279	6.4	0.68
	Conventional	29,692	203,028	14.6	(0.49, 0.93)
Extended-hours, for all events after extended-hours initiation	Extended-hours	126	1,865	6.8	0.62
	Conventional	29,761	202,582	14.7	(0.47, 0.81)

Abbreviations: CI, confidence interval.

^aMortality rate per 100 person-years

^bHazard ratio from marginal structural Cox model comparing extended-hours hemodialysis to conventional hemodialysis, reference group: conventional hemodialysis, adjusted for age, sex, race, year of incidence, insurance, CHF, diabetes, ASHD, and other cardiovascular comorbidities.

^cDeath attributed to the dialysis modality for the 91-day period in which the death occurred.

^dDeath attributed to the dialysis modality of the 91-day period prior to the 91-day period in which death occurred.

Table 3

Results of analysis with alternative assumptions: Risks for all-cause mortality comparing extended-hours hemodialysis to conventional hemodialysis.

Analysis	Extended-hours Hemodialysis		Conventional Hemodialysis		Hazard Ratio ^a	95% CI
	Deaths	Patient-years	Deaths	Patient-years		
Beginning analysis 91 days after dialysis initiation	82	1,202	29,654	176,508	0.67	(0.47, 0.94)
Including only patients with access to extended-hours hemodialysis ^b	82	1,279	11,643	76,980	0.68	(0.50, 0.93)
Excluding patients who never initiated extended-hours hemodialysis, but to whom it was available	82	1,279	18,656	122,334	0.67	(0.49, 0.91)
Additional adjustment for vascular access	82	1,279	29,796	203,046	0.69	(0.50, 0.95)
Matched cohort ^c	73	1,470	2,041	17,717	0.58	(0.43, 0.79)

Abbreviations: CI, confidence interval

^a Hazard ratio for all-cause mortality comparing extended-hours with conventional hemodialysis, adjusted for age, sex, race, year of incidence, insurance, CHF, diabetes, ASHD, and other cardiovascular comorbidities..

^b A patient was identified as having access to extended-hours dialysis if (1) s/he was treated with extended-hours dialysis at any time, or (2) s/he was treated at a facility that had treated another patient who was him/herself treated with extended hours dialysis at any time (at any facility).

^c Extended-hours hemodialysis patients were matched with up to 20 other patients with the same modality for each 91-day period prior to initiating extended-hours hemodialysis and the same age category, sex, race, year of dialysis incidence, underlying renal disease, Charlson comorbidity index, and geographic region. All patients were drawn from those to whom extended-hours hemodialysis was available (footnote 2).



GUIDELINES

Open Access

Renal Association Clinical Practice Guideline on Haemodialysis



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Abstract

This guideline is written primarily for doctors and nurses working in dialysis units and related areas of medicine in the UK, and is an update of a previous version written in 2009. It aims to provide guidance on how to look after patients and how to run dialysis units, and provides standards which units should in general aim to achieve. We would not advise patients to interpret the guideline as a rulebook, but perhaps to answer the question: “what does good quality haemodialysis look like?”

The guideline is split into sections: each begins with a few statements which are graded by strength (1 is a firm recommendation, 2 is more like a sensible suggestion), and the type of research available to back up the statement, ranging from A (good quality trials so we are pretty sure this is right) to D (more like the opinion of experts than known for sure). After the statements there is a short summary explaining why we think this, often including a discussion of some of the most helpful research. There is then a list of the most important medical articles so that you can read further if you want to – most of this is freely available online, at least in summary form.

A few notes on the individual sections:

1. This section is about how much dialysis a patient should have. The effectiveness of dialysis varies between patients because of differences in body size and age etc., so different people need different amounts, and this section gives guidance on what defines “enough” dialysis and how to make sure each person is getting that. Quite a bit of this section is very technical, for example, the term “eKt/V” is often used: this is a calculation based on blood tests before and after dialysis, which measures the effectiveness of a single dialysis session in a particular patient.
2. This section deals with “non-standard” dialysis, which basically means anything other than 3 times per week. For example, a few people need 4 or more sessions per week to keep healthy, and some people are fine with only 2 sessions per week – this is usually people who are older, or those who have only just started dialysis. Special considerations for children and pregnant patients are also covered here.
3. This section deals with membranes (the type of “filter” used in the dialysis machine) and “HDF” (haemodiafiltration) which is a more complex kind of dialysis which some doctors think is better. Studies are still being done, but at the moment we think it’s as good as but not better than regular dialysis.

(Continued on next page)

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(Continued from previous page)

4. This section deals with fluid removal during dialysis sessions: how to remove enough fluid without causing cramps and low blood pressure. Amongst other recommendations we advise close collaboration with patients over this.
5. This section deals with dialysate, which is the fluid used to “pull” toxins out of the blood (it is sometimes called the “bath”). The level of things like potassium in the dialysate is important, otherwise too much or too little may be removed. There is a section on dialysate buffer (bicarbonate) and also a section on phosphate, which occasionally needs to be added into the dialysate.
6. This section is about anticoagulation (blood thinning) which is needed to stop the circuit from clotting, but sometimes causes side effects.
7. This section is about certain safety aspects of dialysis, not seeking to replace well-established local protocols, but focussing on just a few where we thought some national-level guidance would be useful.
8. This section draws together a few aspects of dialysis which don’t easily fit elsewhere, and which impact on how dialysis feels to patients, rather than the medical outcome, though of course these are linked. This is where home haemodialysis and exercise are covered.

There is an appendix at the end which covers a few aspects in more detail, especially the mathematical ideas. Several aspects of dialysis are not included in this guideline since they are covered elsewhere, often because they are aspects which affect non-dialysis patients too. This includes: anaemia, calcium and bone health, high blood pressure, nutrition, infection control, vascular access, transplant planning, and when dialysis should be started.

Introduction

Haemodialysis continues to expand in the UK with over 25 000 patients now being treated, representing a 10% increase since publication of the previous Renal Association guideline for haemodialysis. In addition the patient group continues to develop: the typical patient is now 67 years old with a median history of 3.2 years on renal replacement therapy. The authors of this guideline aimed principally to update the previous guideline according to the latest research and experience, but also to expand the scope into areas not previously covered but relevant to haemodialysis practice.

The guideline was written collaboratively: lead and co-authors for each section conducted literature reviews and wrote first drafts of the statements and rationale. Feedback and discussion were provided by all authors via email exchanges and meetings, revised versions were produced with editorial input from the chair, and these were subsequently agreed by all authors. Two current haemodialysis patients gave advice on tone and readability.

Systematic literature searches were undertaken by lead authors to identify all relevant evidence published up until the end of June 2018. Compound search terms were used which included a dialysis identifier (hemodialysis[tiab] OR haemodialysis[tiab] OR dialysis[tiab]) followed by title/abstract-filtered topic terms (“dialysis dose”, Kt/V, augmented, intensive, conservative, incremental, pregnancy, membrane, hydration, “dry weight”, “fluid overload”, dialysate, potassium, bicarbonate, buffer, phosphate, “dialyser reaction”, hypersensitivity, “blood loss”, “needle dislodgment”, exsanguination, “home haemodialysis”, “nocturnal haemodialysis”, exercise, “physical training”) followed by negative terms (e.g. to exclude animal studies and acute kidney

injury) finally with date and language restrictions (“1990/01/01”[dp]: “3000”[dp] AND english[lang]). Searches were conducted in MEDLINE, PUBMED, Embase, and The Cochrane Library, and supplemented with papers hand-picked from the reference lists of review papers.

The strengths of the recommendations and the level of supporting evidence are coded as previously using the Modified GRADE system.

There are a few changes in scope, for example dialysis water treatment is now covered in another guideline, as are many aspects of dialysis, including:

- Planning, initiation & withdrawal of Renal Replacement Therapy
- Vascular Access for Haemodialysis
- Cardiovascular Disease
- Blood Borne Viruses
- Assessment of the Potential Kidney Transplant Recipient
- Nutrition
- Anaemia
- CKD-Mineral and Bone Disorder
- Water Treatment Facilities, Dialysis Water and Dialysis Fluid Quality

We have removed the section on targets for blood testing since these are better covered in other guidelines, and have not covered infrastructure or workforce since these will be addressed separately by the Renal Association in a different format.

However, in most ways the update is broader than previous versions. For example, new sections have been written covering fluid management (surely an essential topic but

not really covered previously or elsewhere) and dialysate (often underestimated in importance). In other areas this update seems to make no substantial change to previous guidance (as with dialysis dose, for example, where the literature remains dominated by previous large trials), however whilst key concepts remain valid, their understanding has developed, and the guideline aims to provide greater context, encouraging a more holistic interpretation.

Discussions about dialysis often become overly technical – these concepts are important but hard to fit into a narrative so we have moved a few aspects into the appendix, where we aim to provide simplified summaries. We have tried to maintain a high standard of readability since conceptual understanding is the key goal, and as the guideline is not intended to replace review articles or original papers, it seems correct to favour readability over detail.

Summary of clinical practice guidelines

Dialysis dose in thrice weekly dialysis schedules

We recommend eKt/V as the most clinically valid small-solute measure of dialysis dose, and recommend monitoring of dialysis dose on a monthly basis for the majority of centre-based dialysis patients. [1B]

We recommend targeting dialysis dose to achieve consistently a minimum eKt/V of 1.2 for thrice weekly patients, in the absence of a measured contribution from residual function. [1B]

We recommend a minimum of 12 hours per week for the majority of thrice weekly patients with minimal residual function. [1B]

Non-standard schedules (Guidelines 2.1 – 2.4)

Guideline 2.1 - Augmented schedules

We suggest offering an augmented schedule to patients who are unable to achieve adequacy targets or fluid control on a standard thrice weekly schedule. [2B]

We suggest that relative contraindications to augmented schedules should be considered, such as significant residual function or problematic fistula access. [2C]

Guideline 2.2 - Incremental schedules

We suggest that lower haemodialysis dose targets may be optimal in patients with significant residual renal function. [2D]

We recommend that residual renal function should be quantified intermittently in patients on incremental dialysis schedules. [1D]

Guideline 2.3 - Conservative schedules

We suggest that lower haemodialysis dose targets may be optimal when quality of life is the primary goal of treatment, rather than longevity. [2D]

Guideline 2.4 - Paediatric schedules

In children and adolescents we recommend an approach to the assessment of dialysis adequacy which goes beyond biochemical targets, incorporating clinical goals such as growth, bone health, cardiac function and quality of life. [1C]

We recommend targeting dialysis dose to achieve a minimum eKt/V of 1.2 for thrice weekly patients, or a standardized Kt/V of 2.2 for those on augmented schedules. [1C]

We suggest an augmented schedule for children on predominantly liquid nutrition, and those with ventricular systolic dysfunction. [2D]

We recommend a blood flow rate of 5-7ml/kg/min for the majority of patients, using consumables appropriate to body size, with extracorporeal volume less than 10% of the patient's blood volume. [1C]

Guideline 2.5 - Schedules during pregnancy

We recommend counselling women of reproductive age who are receiving or anticipating dialysis, so that they are aware of the interactions between renal replacement therapies and pregnancy which may impact on family planning and modality decisions. [1D]

For dialysis patients wishing to continue their pregnancy, we recommend changing as early as possible to an individualised, augmented haemodialysis schedule. For those with minimal residual function this should be at least 20 hours per week, delivered over at least 6 sessions. [1B]

We recommend an individualised dialysate prescription appropriate to the dialysis schedule and biochemistry results, anticipating the frequent need for a high potassium / low bicarbonate dialysate, supplemented with phosphate. [1C]

We suggest an individualised fluid management protocol, with low ultrafiltration rates and regular clinical assessment, anticipating the typical change in weight during pregnancy. [2C]

Membrane flux and haemodiafiltration

We recommend that patients with minimal residual function should be treated with high-flux dialysers. [1B]

We suggest that haemodiafiltration may be considered as a treatment for intra-dialytic hypotension refractory to other measures, and for dialysis patients with favourable prognosis who are unable or unlikely to be transplanted. [2B]

Fluid in haemodialysis (Guidelines 4.1 – 4.2)

Guideline 4.1 - Fluid assessment and management in adults

We recommend assessment of fluid status when prompted by clinical circumstances, and on a quarterly basis for stable patients. [1C]

We suggest a multidisciplinary approach to fluid assessment, with patient involvement and the adoption of patient-friendly terminology such as “target weight”, “fluid gain” and “over-hydration”. [2D]

We recommend clinical assessment of fluid status on a monthly basis for the majority of patients. [1C]

We suggest supplementing clinical assessment of fluid status with a validated objective measurement, such as bioimpedance, at regular intervals, when clinical assessment is unclear, and following an intercurrent illness. [2C]

We recommend a dialysate temperature not greater than 36°C if standardised. [1C]

We recommend avoiding excessive ultrafiltration rates by addressing fluid gains, accepting staged achievement of target weight, or using an augmented schedule, as necessary. [1B]

We recommend prompt nursing intervention to restore haemodynamic stability in symptomatic / severe intradialytic hypotension, with such interventions leading to clinical review. [1C]

Guideline 4.2 - Paediatric fluid considerations

In growing children we recommend clinical assessment of fluid status and target weight, and dietetic assessment, at least monthly. [1C]

We suggest supplementing clinical assessment with a validated objective measure of fluid status such as bioimpedance, on a monthly basis or more frequently during periods of rapid growth or illness. [2C]

We recommend regular assessment of ultrafiltration tolerance, using extended times to avoid excessive ultrafiltration rates. [1D]

Dialysate (Guidelines 5.1 – 5.4)

Guideline 5.1 - Selection of dialysate potassium

We recommend an optimal pre-dialysis serum potassium in the range 4.0–6.0mmol/L, remembering to consider measurement errors (e.g. due to haemolysis) when interpreting levels. [1B]

We suggest choosing dialysate potassium between 1.0 and 3.0mmol/L for the majority of patients, using an individualised approach, in general using the highest dialysate potassium that is sufficient to control pre-dialysis hyperkalaemia. [2C]

We suggest a combined approach to managing hyperkalaemia, which may include decreasing dialysate potassium and/or other measures, including dietary advice, medication review and increased dialysis frequency. [2D]

Guideline 5.2 - Selection of dialysate buffer

We recommend an optimal pre-dialysis serum bicarbonate in the range 18.0–26.0mmo/L, remembering to consider measurement errors (e.g. due to exposure to air) when interpreting levels. [1C]

We suggest the term ‘dialysate buffer’ rather than ‘dialysate bicarbonate’ to avoid confusion arising from differences in manufacturers’ terminology. [2C]

We suggest choosing dialysate buffer below or equal to 37.0mEq/L for the majority of patients, using a standardised or individualised approach. [2C]

We suggest a combined approach to abnormal pre-dialysis serum bicarbonate, which may include increasing dialysis dose, oral bicarbonate, nutritional support, or individualising dialysate buffer. [2D]

Guideline 5.3 - Supplementation of dialysate with phosphate

We suggest considering supplementation of the dialysate with phosphate in patients on augmented dialysis schedules. [2D]

Guideline 5.4 - Paediatric dialysate considerations

We recommend individualisation of dialysate electrolyte concentrations, including potassium, buffer and calcium. [1C]

We suggest an individualised dialysate temperature, between core temperature and 0.5°C below, with monitoring of intradialytic core temperature for neonates and smaller children. [2D]

Anticoagulation

We recommend that patients without increased bleeding risk should be given unfractionated or low-molecular-weight heparin during dialysis to reduce clotting of the extracorporeal system. [1A]

We recommend that systemic anticoagulation should be omitted or minimised in patients with increased bleeding risk. [1C]

We recommend that patients with heparin allergies should be prescribed a non-heparin form of anticoagulation. [1A]

Adverse events during dialysis (Guidelines 7.1 – 7.3)

Guideline 7.1 - Routine blood loss

We suggest that during washback, dialysis lines and dialyser are observed to ensure residual blood loss is kept to a minimum. [2C]

Guideline 7.2 - Disconnection haemorrhage

We recommend maintaining awareness of the risk of disconnection, the limitations of pressure alarms, and importance of direct observation, through a program of education, including patients and carers. [1D]

We suggest regular assessment of individual risk, so that high risk patients can have enhanced monitoring, which could include specific devices. [2B]

Guideline 7.3 - Immune reactions during dialysis

We recommend that dialysis staff should be aware of the features and management of dialysis reactions, and should have access to a range of dialyser types. [1C]

Patient experience of dialysis (Guidelines 8.1 – 8.4)**Guideline 8.1 - Home haemodialysis**

We recommend that home haemodialysis should be available in all units as part of a comprehensive renal replacement therapy programme. [1A]

We suggest training patients and/or care partners to achieve a defined set of competencies, using an individualised approach to training method and speed. [2D]

We suggest units form a contract with patients outlining responsibilities, including an agreement to dialyse as per prescription and trained technique, and including a policy for re-imbursement of directly arising patient costs. [2D]

We suggest supporting patients with a specific team including nephrologists, technicians, and nurses, with rapid access to dialysis in-centre when required. [2C]

We suggest an agreed individualised prescription for home haemodialysis, taking into account lifestyle goals, with the same dose and time target considerations as centre-based patients. [2C]

We recommend enhanced safety measures for patients who dialyse alone or overnight, and an enhanced risk assessment for patients with blood-borne viruses. [1C]

Guideline 8.2 - Shared haemodialysis care

We suggest that all centre-based haemodialysis patients should have opportunity and encouragement to learn aspects of their dialysis treatment, and take an active role in their care. [2D]

Guideline 8.3 - Intradialytic exercise

We recommend that intradialytic exercise should be available in all units, as a treatment for enhancing physical functioning, in patients without contraindications. [1B]

We suggest that intradialytic exercise be considered as a method of enhancing quality of life. [2C]

We suggest that exercise regimes be devised by appropriately trained staff. [2C]

Guideline 8.4 - Dialysis experience for children and adolescents

We recommend that haemodialysis for children and adolescents should be delivered in a dedicated paediatric dialysis centre or at home, with the involvement of a paediatric multidisciplinary team. [1C]

We recommend that adolescents should commence an active transition programme by 14 years, or at the time of presentation in those already over 14. [1D]

Summary of audit measures

Audit Measure 1: Amongst thrice-weekly patients on dialysis for more than a year, the median eKt/V, and proportion achieving eKt/V at least 1.2.

Audit Measure 2: Amongst thrice-weekly patients on dialysis for more than a year, the median dialysis time per week, and proportion receiving at least 12 hours.

Audit Measure 3: The proportion of patients dialysing 4 or more times per week (either in-centre or at home).

Audit Measure 4: The proportion of patients dialysing less than 3 times per week, separated into: (a) patients in their first year of dialysis, and (b) patients on dialysis for more than a year.

Audit Measure 5: The median ultrafiltration rate, and proportion of patients with residual kidney function ($K_{ru} > 2\text{ml/min}$, or urine volume $> 500\text{ml/d}$), separated into: (a) patients in their first year of dialysis, and (b) patients on dialysis for more than a year.

Audit Measure 6: The proportion of patients receiving haemodiafiltration, and the median convection volume in this group.

Audit Measure 7: The most commonly used dialysate sodium level, and proportion of patients using this dialysate sodium level.

Audit Measure 8: The availability of an objective tool for fluid state assessment, the type of tool used most commonly, and the proportion of patients assessed with an objective tool during the last year.

Audit Measure 9: The median pre-dialysis serum potassium, and proportion of patients arriving with average potassium over 6.0mmol/l , and proportion with average under 4.0mmol/l .

Audit Measure 10: The proportion of patients using a dialysate potassium level in the following categories: less than 2.0, 2.0, and more than 2.0mmol/l .

Audit Measure 11: The number of disconnection haemorrhage events each year.

Audit Measure 12: The proportion of haemodialysis patients having all or most of their dialysis at home.

Audit Measure 13: The proportion of in-centre patients recognised as engaging in “Shared Care”.

Audit Measure 14: The availability of a program for intra-dialytic exercise, the resource available (equipment, physiotherapist time), and the proportion of in-centre patients engaging with regular intra-dialytic exercise.

Rationale for Clinical Practice Guidelines**Dialysis dose in thrice weekly dialysis schedules**

We recommend eKt/V as the most clinically valid small-solute measure of dialysis dose, and recommend monitoring of dialysis dose on a monthly basis for the majority of centre-based dialysis patients. [1B]

We recommend targeting dialysis dose to achieve consistently a minimum eKt/V over 1.2 for thrice weekly patients, in the absence of a measured contribution from residual function. [1B]

We recommend a minimum of 12 hours per week for the majority of thrice weekly patients with minimal residual function. This may lead to higher than minimum eKt/V in smaller adult patients which is appropriate. [1B]

Rationale

Dialysis adequacy encompasses concepts including the clinical assessment of general wellbeing, fluid status, and control of laboratory parameters, along with quantification of the dose of dialysis provided.

The purpose of dialysis is to provide enough removal of uraemic solutes and fluid that accumulate in kidney failure to maintain health and quality of life: more specific goals include control of uraemic symptoms, maintenance of safe electrolyte levels, prevention of nutritional decline, and optimum long term mortality. Whilst the earlier items in this list are readily assessed over a short time scale, concepts of dialysis dose are required to define the amount of dialysis likely to achieve longer term goals of treatment.

Due to the simplicity and low cost of measurement of urea in blood, measurement of dialysis adequacy has historically focused on clearance of small solutes, represented by urea. Concentration of a range of uraemic toxins of larger size (e.g. β -2 microglobulin) is likely to be important, but their measurement is not commonly performed. Use of thrice weekly haemodialysis schedules emerged from the realisation during the early era of haemodialysis treatment that once or twice-weekly haemodialysis schedules in patients with minimal residual function was insufficient to control the symptoms and complications of severe uraemia.

Most research on dialysis dose is therefore based on urea clearance, in patients on a thrice weekly schedule.

Urea clearance may be calculated by three methods in common use: Urea Reduction Ratio, and the 'single pool' and 'equilibrated' formulas for Kt/V . Kt/V is less commonly calculated by Urea Kinetic Modelling - these methods are summarised mathematically in [Appendix 1](#). The diversity of methods can lead to duplication of effort, confusion over the meaning of targets, and impedes comparison between centres, so a single widely used method would be desirable. As the most adjusted method, and the one which has been most commonly validated in outcome literature, eKt/V appears to be optimum, and we have therefore given dose targets in terms of eKt/V . Equivalent targets using other methods may be derived for individual patients depending on their dialysis duration and fluid removal.

The literature on clinical outcome at different doses of dialysis is dominated by two randomised studies. The National Cooperative Dialysis Study (NCDS) was the

landmark study which led to the concept of a threshold dialysis dose above which treatment was adequate, as well as the establishment of Kt/V as the accepted index of dialysis dose. Reporting in 1981, the study randomised 151 patients in a 2x2 design to high vs low time-averaged urea, and short vs long dialysis duration - the key finding was a lower rate of treatment failure (death or hospital admission) in the low urea (high dialysis dose) group [1]. When reanalysing the group with the newly proposed Kt/V measure, a clear threshold effect appeared, with Kt/V defining the watershed between 'adequate' and inadequate dialysis (Kt/V over vs under 1.0) [2].

A large number of observational studies subsequently reported an association between higher dialysis doses (beyond merely achieving the NCDS threshold) and improved survival [3–6], and this was tested in the HEMO study. Reporting in 2002 the HEMO study randomised 1846 patients in another 2x2 design to high vs standard dialysis dose (eKt/V 1.45 vs 1.05) and high vs low flux [7]. Over 2.8 years follow-up with groups well separated in terms of achieved eKt/V (1.53 vs 1.16), higher dose provided no benefit in terms of survival or a number of secondary endpoints.

The basic concepts of these studies have not been superseded, hence the recommendation for dialysis dose ($eKt/V > 1.2$) is based largely on the eKt/V achieved in the standard dose group of the HEMO study. Alternative measures such as URR or $spKt/V$ may be more familiar to some clinicians and equally useful for the majority of patients. Equivalent thresholds using these parameters are approximate since they vary between patients, but the differences are small: [Appendix 1](#) summarises the mathematics behind these concepts.

Whether 'adequate' dialysis is the same for all patients or whether dose should be individualised is unclear, but the latter view is supported by several studies suggesting that gender and body size may affect the optimum dialysis dose [8–10]. Observational studies suggest that dialysis dose is more strongly related to survival in women than men, and when the HEMO study analysis is restricted to women, the high dose group show significantly improved survival. The reason for this interaction between gender and optimum eKt/V is unknown, but may be due to the scaling parameter 'V', which is lower in women and in less muscular patients, and is an independent predictor of survival. Alternative scaling factors such as body surface area, have been suggested [11–14], but none is in widespread use, and the collinearity between different body size parameters makes analyses difficult to interpret, but it seems likely that the optimum Kt/V may be higher than 1.2 in women and smaller patients, without a clear definition of 'small' [15].

Dialysis time

The optimum treatment duration for thrice weekly haemodialysis is slightly less clear, since it is difficult

to separate the effect of treatment time from dialysis dose [16].

The evolution of dialysis technology has made dialysis dose targets achievable over short dialysis sessions. However, there are uraemic solutes other than urea, such as phosphate and β_2 -microglobulin, which are also important predictors of outcome, and which are inefficiently removed by dialysis [17, 18]. Extending dialysis duration increases the removal of these highly sequestered and larger molecules, independent of any change in small solute clearance [19, 20]. In the other part of its 2x2 design, the NCDS study also compared session duration (4.5–5.0 vs 2.5–3.0 hours) and although standard significance ‘level’ was not achieved ($p=0.06$), showed reduced treatment failure in the longer session group [1].

Most observational studies also report improved outcomes with longer treatment times. Low mortality rates were reported from Tassin with 8 hour overnight dialysis, attributed to improved blood pressure control and slower ultrafiltration [21, 22], and lower mortality is associated with longer treatment times in national registry studies (over vs under 3.5 hours in US patients [23], and over vs under 4.5 hours in Australia [24]). The international DOPPS study examined the effect of treatment time whilst controlling for confounders using standard regression and instrumental variable approaches, concluding that patients with the longest treatment time (at least 4 hours) had the lowest risk for all-cause and cardiovascular mortality [25]. Other clinical markers such as blood pressure, anaemia and phosphate control were also improved.

Whilst recognising the limitations of observational studies, a minimum duration for optimum dialysis clearly exists, and is most likely close to 4 hours, at least for patients with minimal residual kidney function. A duration threshold may lead to higher than minimum eKt/V in smaller adult patients, which is appropriate since optimal Kt/V may be higher in this group.

Summary

Optimal outcomes in patients on thrice weekly dialysis are achieved with sessions of at least 4 hours, providing eKt/V at least 1.2. Regular monitoring is strongly recommended, and this occurs monthly in the majority of units.

Under achievement may be addressed by attention to vascular access [26], session duration [27], blood or dialysate flow [28–30], dialyser efficiency [31] or anticoagulation [32], and in some patients under achievement may suggest the need for an augmented schedule. Achievement of these targets does not guarantee optimal outcome, with eKt/V being unaffected by missed sessions, for example.

These dose targets apply to thrice weekly patients, with minimal residual function, for whom survival duration is a

primary treatment goal. There are specific clinical scenarios and different patient values for which it may be appropriate to adjust or disregard numeric targets for dialysis dose.

Non-standard schedules (Guidelines 2.1 – 2.4)

Guideline 2.1 - Augmented schedules

We suggest offering an augmented schedule to patients who are unable to achieve adequacy targets or fluid control on a standard thrice weekly schedule. [2B]

We suggest that relative contraindications to augmented schedules should be considered, such as significant residual function or problematic fistula access. [2C]

Rationale

Dialysis dose on a thrice weekly schedule is limited by patient tolerance and the necessity to utilise ‘slots’ efficiently, so that sessions over 5 hours are very uncommon. ‘Augmented’ in this guideline refers to increased frequency (4–6 sessions per week) or thrice weekly dialysis totalling more than 15 hours per week. The latter is usually delivered nocturnally when in-centre, but both are often delivered in the context of home haemodialysis where much of the evidence regarding augmented dialysis schedules has been obtained.

Augmented schedules have been assessed in four randomised studies [20, 33–35], one interventional study with matched controls [36], and a handful of observational studies. Evidence of clinical benefit limited to interventional studies is summarised below, with studies divided into three groups for ease of discussion, according to the type of augmented schedule [20, 33–37]. A fourth group of augmented schedules which might be termed ‘modestly frequent’ (4 or 5 sessions per week, of up to 4 hours each) is poorly represented in studies.

Group	Frequent nocturnal	Short daily	Nocturnal
Definition	> 6 x/week > 6 hours	> 6 x/week < 4 hours	3 x/week > 6 hours
Lead author / study type (patient number in intervention group)	Culleton / RCT (26) Rocco / RCT (45)	Chertow / RCT (125)	Ok / NRI (247) Ipema (metanalysis)
Left ventricular mass	Decreased (Culleton) No change (Rocco)	Decreased	
Blood pressure	Improved	Improved	Improved
Hyperphosphatemia	Improved	Improved	Improved
Nutritional status			Improved
Composite health score / quality of life	No change	Improved	

Abbreviations: RCT randomized controlled trial, NRI non-randomised intervention

Where assessed, improvements in depression, cognition or anaemia parameters were generally not seen in these studies, although improvements in these aspects have been reported in a number of observational studies.

Quality of life is an important outcome since the intervention clearly involves increased treatment burden. Observational studies suggest that quality of life of life is improved in daily dialysis by approximately 6%, whereas nocturnal schedules have not been show to improve quality of life [38–40].

The randomised studies were not designed primarily to assess mortality within the study period, but two of these published mortality results with follow-up extended by approximately 2.5 years [41, 42], and mortality effects have also been reported in other types of study. Findings have been surprisingly inconsistent, however, and are summarised in the table below [36, 41–45].

Group	Frequent nocturnal	Short daily	Nocturnal
Definition	> 6 x/week > 6 hours	> 6 x/week < 4 hours	3 x/week > 6 hours
Lead author / study type (patient number on augmented schedule)	Rocco / RCT (45)	Chertow / RCT (125) Marshall / OS (?) Suri / OS (318)	Ok / NRI (247) Rivara / OS (1206)
Hazard ratio for mortality (less than 1.0 favours augmented schedule)	3.88	0.54 1.00 / 0.41 (unit / home) 1.60	0.28 0.67

Abbreviations: RCT randomized controlled trial, NRI non-randomised intervention, OS observational study

Authors stress that clinical trials of more intensive dialysis were not designed to evaluate mortality, and that observational analyses often employ statistical techniques which do not adequately address the time-varying nature of the risk factors associated with both the initiation of augmented dialysis and mortality.

The larger randomised trials of augmented schedules have also identified potential harms, for example reducing residual function, an important determinant of survival on haemodialysis. In patients who had significant residual function at enrolment, both frequent nocturnal and short daily dialysis led to a more rapid decline in function compared to control groups [46]. Intervention patients had a shorter time to first vascular access intervention, and there were small increases in the burden on carers, as perceived by patients, though the authors highlight that carers themselves were not assessed [47].

Taken together these studies suggest equivalent mortality and modest improvement in some dialysis-related conditions, offset by increased treatment burden and possible harms to vascular access and residual function. Whilst there is no overall advantage for the average

patient these studies do suggest specific groups who would be expected to benefit. For example, adequacy targets could certainly be achieved in those still unable to, despite a reasonably long thrice weekly schedule. Similarly, patients failing to achieve fluid control are likely to benefit from an increase in dialysis frequency - this might include those with resistant hypertension, intra-dialytic hypotension, and those with weekend admissions to hospital. The latter group are the obvious contributors to the excess mortality of the two-day dialysis gap, and may have the most to gain from an increase in dialysis frequency. The augmentation of dialysis in these settings should be aimed at achieving a specific purpose, and it is likely that a fourth session per week would be sufficient in many cases.

In conclusion, augmented schedules offer no clear advantage for the majority of patients, but should be considered as a treatment option for those patients whose adequacy or fluid control targets are not met with a standard schedule. A modestly augmented schedule would be sufficient in the majority of these patients.

Guideline 2.2 - Incremental schedules

We suggest that lower haemodialysis dose targets may be optimal in patients with significant residual renal function. [2D]

We recommend that residual renal function should be quantified intermittently in patients on incremental dialysis schedules. [1D]

Rationale

Incremental haemodialysis is based on the common sense concept that the amount of dialysis required for optimal outcome differs between those with significant residual function and those without. The latter group however is larger, and makes up the majority in studies of dose and outcome, which therefore may not be applicable in the former group. Optimal dialysis dose is therefore not fixed but dependent on the level of residual kidney function, and the prescribed schedule may therefore be reduced in frequency or dose in this setting. The practice of incremental haemodialysis is consistent with a concept of progressively increasing therapy over time, which may include augmented schedules at a later stage (Fig. 1).

Less frequent and reduced dose dialysis practices co-evolved along with standard thrice-weekly schedules: reference is made to twice weekly dialysis in observational studies from the 1990s and in the 1997 KDOQI guidelines [48]. For example, in an observational study of 15 000 American patients published in 1999, Hanson reported twice weekly schedules in 6.1% of patients during their first year, and 2.7% of patients thereafter [49]. Outcomes were at least as good, and in fact a mortality advantage was observed with twice weekly schedules, most

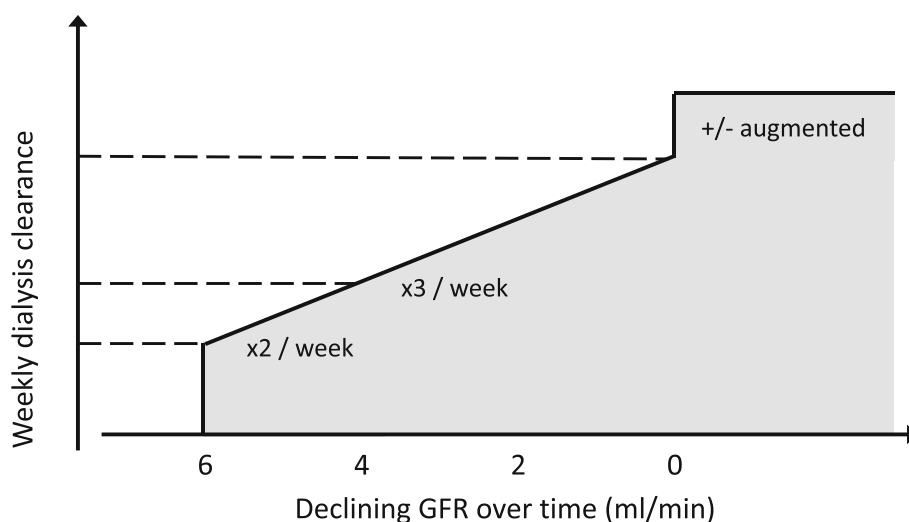


Fig. 1 Schematic to illustrate principle of incremental haemodialysis (numbers only as examples)

likely due to differences in baseline factors: no mortality difference was seen after adjustment for the level of residual function at dialysis initiation.

The non-inferiority of twice weekly schedules in selected patients has been further supported by more recent studies. In a Thai study of 500 twice-weekly patients Panaput reported equivalent mortality and hospitalisation over the next year [50], and in a propensity-matched Korean study of 300 patients followed for one year, Park reported equivalent mortality and improved quality of life with schedules less than thrice-weekly [51]. Non-inferiority of clinical outcome with reduced treatment burden therefore provides a powerful argument in favour of incremental schedules, but additional benefits may exist: incremental haemodialysis schedules have also been associated in some observational studies with reduced decline in residual kidney function [52, 53].

Preservation of residual function is of clinical importance since it provides significant solute and fluid removal, and is associated with improved quality of life and survival [54].

The literature on incremental schedules is limited in particular by its observational nature, with inherent problems of selection and lead-time bias. Variation also exists in the definition of incremental dialysis, which is frequently defined as twice-weekly, without reference to residual function. Clinician bias may also be important: clinicians working in the 1990s will remember twice-weekly schedules principally as a resource-sparing exercise, and even in modern series, financial constraints play a part in their use [55].

Patient selection is therefore crucial: factors currently associated with reduced schedule use in a large Chinese study include early vintage, female sex and minimal comorbidity [56]. And the level of residual function appears

perhaps unsurprisingly to be the most important factor: in a large American study in which 350 twice-weekly patients were matched with a thrice-weekly group, twice-weekly schedules yielded equivalent one year outcome in many, but were clearly inferior in those with the poorest residual function (clearance less than 3ml/min/1.73m²) [57]. Those with residual clearance of 3ml/min or less may still be suitable for a thrice-weekly incremental schedule (i.e. with dose target less than Kt/V 1.2 and/or less than 4 hours).

The use of incremental haemodialysis therefore requires regular monitoring of residual function, with function reassessed after major intercurrent illness [58]. Suitable patients should be aware that dialysis duration is likely to increase over time, and should be willing to cooperate with residual function measurements [59].

Incremental dialysis is entirely consistent with the concepts of adequate dialysis dose established in the NCDS and HEMO studies as discussed in Section 1, but incorporates the contribution of residual function, so that dialysis and residual function are seen as both contributing to overall clearance. There are a number of different methods for quantifying combined kidney and dialysis urea clearance (summarised in Appendix 2) which can help with schedule and dose selection. These should be interpreted in clinical context, with due observation of indirect measures of dialysis adequacy such as control of symptoms, blood pressure, fluid gains and electrolytes, so that dialysis dose can be appropriately escalated if treatment appears clinically inadequate.

Guideline 2.3 - Conservative schedules

We suggest that lower haemodialysis dose targets may be optimal when quality of life is the primary goal of treatment, rather than longevity. [2D]

Rationale

Whilst concepts of dialysis dose have been developed over the last two decades, the dialysis population has been changing, with the median age of the prevalent dialysis population increasing by nearly 20 years, and diabetes becoming one of the leading causes of established kidney failure. For many patients, dialysis is a long-term maintenance therapy that continues until death or dialysis withdrawal, with increasing comorbidity and frailty developing during this time [60].

This changing demographic has important implications for the clinical application of dialysis dose. Firstly, studies have typically focused on younger patients (median age 49 in the NCDS study including no diabetics, and mean age 58 in the HEMO study) so that applying their conclusions in a more elderly group is an extrapolation. Secondly, studies are generally more concerned with mortality, and many strategies in dialysis are aimed at preventing future complications, whereas current symptoms and quality of life are often more relevant to the frailer patient. And thirdly, the burden of dialysis often increases with increasing frailty, so that there is a greater trade-off when considering the burden versus the benefit of treatment. In the context of this changing demography, it is reasonable to question whether conventional dialysis dosing and targets remain appropriate for this population [61].

Frailty as a clinical syndrome can be defined when a number of factors are present including: unintentional weight loss, self-reported exhaustion, weakness and low physical activity. The presence of frailty is associated with increasing disability and hospitalisation, and in dialysis patients, with an adverse quality of life irrespective of dialysis modality.

The optimum dialysis for frail patients has only been studied in small cohorts. Some overlap exists between the features of frailty and those of underdialysis, and it could be argued be that more intensive dialysis might better control some aspects such as fluid overload, intradialytic hypotension or sarcopenia, or conversely that nutritional decline might be accelerated by reduced dialysis. Reductions in dialysis quantity should therefore not be misunderstood as a method of improving these aspects of frailty. However, while increasing hours or frequency of dialysis may theoretically overcome some of these problems, patients often perceive the burden of dialysis on their quality of life more than the symptomatic benefit, and dialysis itself may confer specific harms in this group: a retrospective study identified frequent functional deterioration among dependent patients following the initiation of dialysis [62].

In a challenging clinical area with a paucity of outcome data, it therefore seems entirely appropriate to reduce or disregard numeric targets for dialysis dose, instead individualising dialysis according to specific patient goals.

Goal-oriented care is an established approach in patients with multiple co-morbidities which overcomes the problems inherent in disease-specific care processes, with discussions instead concentrating on a patient's individual aims of treatment.

Shared discussions about dialysis schedule, driven by patient-centred goals can ensure that patients are neither under or over-treated, and in some cases might be a precursor to dialysis withdrawal. Such discussions may need frequent review following changes in the patient's clinical or personal circumstances.

Guideline 2.4 - Paediatric schedules

In children and adolescents we recommend an approach to the assessment of dialysis adequacy which goes beyond biochemical targets, incorporating clinical goals such as growth, bone health, cardiac function and quality of life. [1C]

We recommend targeting dialysis dose to achieve a minimum eKt/V of 1.2 for thrice weekly patients, or a standardized Kt/V of 2.2 for those on augmented schedules. [1C]

We suggest an augmented schedule for children on predominantly liquid nutrition, and those with ventricular systolic dysfunction. [2D]

We recommend a blood flow rate of 5-7ml/kg/min for the majority of patients, using consumables appropriate to body size, with extracorporeal volume less than 10% of the patient's blood volume. [1C]

Rationale

The low incidence of dialysis-requiring kidney disease in childhood, means that many treatment decisions are informed by observational data and studies carried out in adults. The small-solute dose target for adults (eKt/V over 1.2) therefore has some relevance to children, though cautious interpretation of a target extrapolated from a different clinical setting would lead many clinicians to aim for a more conservative (i.e. higher) target dose. In addition, unique physiological aspects of childhood, such as growth, may be improved by increased dialysis dose, and there are strong arguments to suggest that optimum Kt/V may be size-dependent in adults, so that a higher minimum Kt/V may be appropriate [63]. The desirable lower limit for eKt/V is therefore thought to be between 1.2 and 1.4.

However, as is increasingly recognized now in adults, it has long been argued that the optimal quantity of dialysis for children cannot be characterized by a single numerical measurement [64]. In addition to the desirable clinical outcomes shared with adults, the therapeutic goals for children and adolescents receiving dialysis include achievement of normal growth, bone maturation and social development, along with avoidance of cardiac compromise and disrupted education. The increasing evidence that

dialysis dose and schedule is able to improve cardiac function and outcomes in many of these domains argues for a broader concept of “adequacy” which might best be assessed using a constellation of clinical outcomes, as well as biochemical targets.

Augmented dialysis, with increased frequency in particular, is therefore increasingly advised by clinicians, and despite the obvious drawback of treatment burden, does not seem to reduce quality of life, even in adolescents [65]. It is possible that augmented schedules are optimal for all children, but some groups seem particularly likely to benefit, including those with cardiac dysfunction and those on a liquid diet, in whom it might otherwise be difficult to achieve safe fluid control [66].

Safe limits appropriate to body size are advocated for many aspects of the extracorporeal circuit, such as a blood flow rate of 5-7ml/min/kg, which is often adequate to achieve dialysis dose with double needles, with arterial aspiration pressures below 200mmHg, to limit endothelial trauma. For single-needle dialysis the highest blood flow rate is obtained using a double pump system (venous flow higher than arterial) monitored by pressure (time pressure regulation), with clamp techniques used to achieve an acceptable compromise between recirculation and blood flow [67]. Consumables appropriate to body size should be selected so that total extracorporeal volume is less than 10% of blood volume, to reduce the volume load with wash-back at the end of the session. System priming with albumin or even blood may sometimes be required for babies and small infants.

Guideline 2.5 -Schedules during pregnancy

We recommend counselling women of reproductive age who are receiving or anticipating dialysis, so that they are aware of the interactions between renal replacement therapies and pregnancy which may impact on family planning and modality decisions. [1D]

For dialysis patients wishing to continue their pregnancy, we recommend changing as early as possible to an individualised, augmented haemodialysis schedule. For those with minimal residual function this should be at least 20 hours per week, delivered over at least 6 sessions. [1B]

We recommend an individualised dialysate prescription appropriate to the dialysis schedule and biochemistry results, anticipating the frequent need for a high potassium / low bicarbonate dialysate, supplemented with phosphate. [1C]

We suggest an individualised fluid management protocol, with low ultrafiltration rates and regular clinical assessment, anticipating the typical change in weight during pregnancy. [2C]

Rationale

Successful pregnancies in women on haemodialysis are becoming more common: prior to 1995 data from the

USA suggested only 40% infant survival, but outcomes in the current era are substantially better [68]. However, pregnancy complications in haemodialysis patients are still more common than in pre-dialysis and transplant patients, and may result in HLA sensitisation, so delaying until after transplantation may be favourable for some. Conception may be more likely with augmented dialysis schedules [69], but the possibility of pregnancy or need for contraception should be considered regardless of dialysis schedule.

The literature linking haemodialysis prescription to outcome in pregnant dialysis patients is limited to case series and systematic reviews [70]. In a recent meta-analysis of 681 pregnancies in 647 patients between 2000 and 2014, authors found that longer weekly dialysis duration significantly associated with a lower incidence of preterm delivery and babies small for their gestational age [71]. More frequent dialysis was also associated with fewer small babies. Normalisation of biochemistry and fluid status appears to give the best outcome, and virtually every publication advocates intensified dialysis.

The best evidence for this approach to date is the comparison of data from the Toronto and US registries of pregnancy in dialysis patients [72]. In women established on dialysis before becoming pregnant, 11 of 13 pregnancies were successful with at least 36 hours per week, compared to 22 of 46 with up to 20 hours ($p=0.02$). More intensive dialysis was also associated with reduced preterm delivery and greater birth weight.

Residual kidney function facilitates normalisation of fluid and electrolytes, so the accelerated loss of residual function seen with augmented schedules raises concerns about this approach in women with good urine output [73]. In the Toronto/US registry study all of the 17 women who started dialysis partway through the pregnancy had a successful outcome. Since 13 of them were in the shorter treatment group, it appears that longer treatment times would have been unnecessarily burdensome, and possibly detrimental, to patients with significant residual function. In a comprehensive review Hladunewich suggested titrating the dialysis dose to achieve urea 10-15mmol/L after the longest break between sessions [74]. The authors also provide advice on adjusting medication, anaemia management and fetal monitoring which are outside the scope of this guideline.

With augmented schedules dialysate should be individualised, with high potassium / low buffer often required. To ensure the needs of foetal skeletal development are met, low serum calcium and phosphate should be avoided, which may involve adjustment of diet, medication and dialysate: supplementation of the dialysate with phosphate is often necessary. Magnesium should possibly be monitored in the third trimester, since low levels may induce uterine contraction.

Augmented schedules allow patients with minimal residual kidney function to remain close to their target weight and avoid high ultrafiltration rates. Fluid status needs to be assessed frequently during pregnancy, as there is a high risk of fluid depletion, especially in the second and third trimester, and bioimpedance and urine volume may be useful measurements in this setting. Typical weight gains during a healthy pregnancy range from around 150g/week during the first trimester, to around 450g/week during the third trimester.

Membrane flux and haemodiafiltration

We recommend that patients with minimal residual function should be treated with high-flux dialysers. [1B]

We suggest that haemodiafiltration may be considered as a treatment for intra-dialytic hypotension refractory to other measures, and for dialysis patients with favourable prognosis who are unable or unlikely to be transplanted. [2B]

Rationale

Convective clearance Haemodialysis removes uraemic toxins by two very different physical processes: diffusion and convection.

Diffusion is the movement of solutes independent of solvent when the concentration differs between the two sides of a membrane. The rate is dependent on the concentration difference, the diffusion coefficient of the membrane, as well as the blood and dialysate flows, and this process is extremely efficient for small solutes, such as urea. Convection is the movement of those solutes not excluded by pore size, along with their solvent as it crosses the membrane. The rate depends on molecular size and the ultrafiltration rate, and this process is most important for molecules too large for efficient diffusion, but still smaller than the membrane pores, often termed 'middle molecules' [18].

Convective clearance is therefore a measurable component of dialysis, which is qualitatively and quantitatively distinct from urea clearance and treatment time. Diffusion of a solute is usually quantified by its Kt/V (Appendix 1) whereas convection is best quantified by its sieving coefficient and the ultrafiltration rate (Appendix 3).

Ascending quantities of convection are therefore achieved with low-flux dialysis, high flux dialysis, and haemodiafiltration. Historically low-flux dialysis was standard, in part because it requires less accurate ultrafiltration control from the dialysis machine - ultrafiltration in standard low-flux dialysis is simply equal to the fluid removed from the patient, usually around 2 litres. In high-flux dialysis pore size is increased, increasing the sieving coefficient for middle molecules, but also the permeability to water is improved, so that internal filtration (bidirectional movement of water within the dialyser) becomes significant: net

ultrafiltration of course remains the same, but total ultrafiltration, all of which contributes to middle molecule clearance, is greater and may be as much as 10 litres [75]. In haemodiafiltration a large volume of replacement fluid is given, to allow net ultrafiltration to be increased to around 20 litres (Appendix 3). There is little difference in clearance of small solutes between these methods [76].

Of the (over 100) uraemic toxins known, many are middle molecules (with molecular weight in the range 0.6-60kDa) for which clearance is largely dependent therefore on convection [18]. Convective quantity does not improve clearance of all poorly-diffusing molecules, with phosphate clearance for example, largely unaffected, but clearance of many, such as β -2-microglobulin, is progressively increased by high-flux dialysis and haemodiafiltration [77-79]. A contribution of convective dialysis quantity to favourable outcome is strongly suspected.

Membrane flux Several interventional studies give insight into the impact of membrane flux on dialysis outcomes, for example in the other part of its 2x2 design, the HEMO study group compared high-flux with low-flux dialysis [80]. In the whole group (N=1846) high-flux dialysis did not confer a clear survival advantage (RR 0.92, 95%CI 0.81-1.04) although cardiac mortality was reduced (RR 0.80, 95%CI 0.65-0.99). In the roughly one-third (N=577) of patients with over 3.7 years dialysis vintage prior to randomisation, high-flux dialysis improved survival substantially (RR 0.68, 95%CI 0.53-0.86).

The Membrane Permeability Outcome study randomised 738 incident patients to high vs low-flux dialysis, stratified by serum albumin (normal vs subnormal) [81]. Over a mean observation of 3 years, high-flux dialysis reduced mortality in the low albumin group (N=493, HR 0.63, 95%CI 0.45-0.90) with a less clear reduction in mortality in the whole group. High-flux was similarly advantageous in the subgroup with diabetes.

A meta-analysis of 33 studies comparing high-flux with low-flux dialysis in 3820 patients, found reduced cardiovascular mortality (RR 0.83, 95%CI 0.70-0.99) and a less clear reduction in all-cause mortality (RR 0.95, 96%CI 0.87-1.04) [82]. Endotoxin tends to be absorbed within high-flux membranes, rather than passing through, and initial concerns that dialysate endotoxin would be more problematic with high-flux dialysis appear to have been unfounded [83].

Whilst no study has unequivocally demonstrated the superiority of high-flux dialysis for survival, there is clear evidence of improved cardiovascular outcomes, and all-cause mortality appears to be improved in several subgroups [84]. At the same time, evidence of harm is lacking, all modern machines have accurate ultrafiltration control,

and membrane costs are now equivalent. Further research on this question therefore does not seem to be a high priority.

Haemodiafiltration The effect of haemodiafiltration has been informed by four randomised controlled studies, summarised in the table below. In three of these, marginal but non-significant advantages were seen in the haemodiafiltration group, with subgroup analysis suggesting favourable outcome with the highest convection volumes, though the latter to some extent may reflect body size or treatment tolerance [85–87].

A clear advantage with haemodiafiltration was seen in the ESHOL study, which specified a higher convection volume of 23 litres, but consequently may be confounded by subjects' ability to sustain these volumes, which is dependent on high blood flow, so that censoring may be most frequent in the highest risk patients [88]. Apart from the CONTRAST study [85] these were all analysed 'as treated', with right-censoring when treatment was discontinued for any reason, leading to potential bias since endpoints are more likely to be hidden in the haemodiafiltration arm. Another criticism concerns the mechanism of the clinical benefit, since middle molecule levels were not demonstrably improved by haemodiafiltration: plasma levels of β -2-microglobulin increased significantly in both arms of the ESHOL study.

Reduced mortality with haemodiafiltration was observed with pooled analysis of the four studies (HR 0.86, 95%CI 0.75-0.99) due in particular, to a reduction in cardiovascular events, with authors estimating the prevention of one cardiovascular death for every 75 patient-years of treatment [89]. However, due to biases within study designs, considerable doubt over the superiority of haemodiafiltration remains [90].

Study name (location) Year of main publication	Number Int vs Control Mean age	Interventions Mean observation	Mortality % Int vs Control HR (95%CI) if significant
CONTRAST (Europe/Canada) 2012	358 vs 356 64.1	HDF vs low flux 3 years	36.6 vs 38.8
Turkish HDF (Turkey) 2013	391 vs 391 56.5	HDF vs high flux 1.9 years	13.3 vs 16.6
ESHOL (Spain) 2013	456 vs 450 65.4	HDF vs 92% high flux 1.9 years	18.6 vs 22.8 0.70 (0.53 - 0.92)
FRENCHIE (France) 2017	190 vs 191 76.2	HDF vs high flux 2 years	18.9 vs 22.5

Haemodiafiltration was also assessed in a DOPPS study, in which after adjustment, no association between convection volume and survival was observed [91].

Several of these studies also found a lower frequency of intradialytic hypotension with haemodiafiltration compared to the control group, though the authors acknowledge the difficulty in excluding confounding factors such as cooling and positive sodium balance [92].

Fluid in haemodialysis (Guidelines 4.1 – 4.2)

Guideline 4.1 - Fluid assessment and management in adults

We recommend assessment of fluid status when prompted by clinical circumstances, and on a quarterly basis for stable patients. [1C]

We suggest a multidisciplinary approach to fluid assessment, with patient involvement and the adoption of patient-friendly terminology such as “target weight”, “fluid gain” and “over-hydration”. [2D]

We suggest supplementing clinical assessment of fluid status with a validated objective measurement, such as bioimpedance, at regular intervals, when clinical assessment is unclear, and following an intercurrent illness. [2C]

We recommend a dialysate temperature not greater than 36°C if standardised. [1C]

We recommend avoiding excessive ultrafiltration rates by addressing fluid gains, accepting staged achievement of target weight, or using an augmented schedule, as necessary. [1B]

We recommend prompt nursing intervention to restore haemodynamic stability in symptomatic / severe intradialytic hypotension, with such interventions leading to clinical review. [1C]

Rationale

Fluid control is an essential clinical goal of maintenance haemodialysis, but correct fluid management requires clinicians to steer between the two competing / overlapping problems of fluid overload and intra-dialytic hypotension.

Failure to control fluid overload may lead to obvious short-term effects including hypertension and breathlessness, and nephrology trainees quickly become familiar with the emergency dialysis admission with pulmonary oedema. In the longer term also, chronic fluid overload is one of the main drivers of hypertension and is independently associated with poor outcomes: for example, in a US study of over 10 000 prevalent haemodialysis patients, Flythe reported clinical outcomes over 2 years' follow-up, according to achievement of target weight during the baseline month [93]. Compared to those achieving within 2kg of target weight on at least 70% of sessions, the 15% of patients frequently remaining over-hydrated post dialysis had increased mortality (HR 1.28, 95%CI 1.15-1.43) as did the 7% of patients who were frequently under-hydrated post dialysis (HR 1.22, 95%CI 1.05-1.40).

Often competing, though sometimes associated with fluid control, is intra-dialytic hypotension, which also has immediate consequences familiar in the dialysis unit, including dizziness and cramps, as well as more long-term adverse effects. For example, Sands studied the occurrence of intra-dialytic hypotension (defined as a drop in systolic blood pressure of at least 30mmHg, to below 90mmHg) in 1137 patients in 13 dialysis facilities, over an average period of 3 months [94]. With this definition, hypotension complicated 17.2% of sessions, affecting 74.9% of patients at least once, and 16.2% of patients on at least one third of their sessions. Those most prone to intra-dialytic hypotension were older, more comorbid and with lower pre-dialysis blood pressure, with associated sessional factors including high ultrafiltration volume and non-achievement of target weight. Outcomes associated with intra-dialytic hypotension included shortened survival and increased hospital admission.

The two main treatment parameters by which clinicians aim to optimise fluid control, are target weight and ultrafiltration rate.

Since the earliest days of dialysis, setting ultrafiltration to achieve a set target weight post dialysis, at which the patient is at their correct volume (or “dry”) has been the accepted method of maintaining a consistent volume state, but the method is dependent on accurate estimation of the correct target weight. Though most often assessed by clinical examination, the inaccuracy of this method is widely appreciated so that both overestimation and underestimation are common, with the former contributing to hypertension and left ventricular hypertrophy, and the latter accelerating the loss of residual kidney function and perhaps risking myocardial stunning.

To improve on clinical assessment, nephrologists at one time advocated “probing” target weight: gradual reduction until patients report symptoms suggesting hypovolaemia, but this may reduce treatment compliance and a more collaborative approach is more common: where possible, patients should be asked to participate in monitoring their fluid status. To this end terminology should be simple and intuitively understood: for example, when discussing target weight, the term “dry weight” can give the impression that the aim is to remove as much fluid as possible, and “ideal weight” can be confusing as it is also used to describe the preferred body mass index. Although less accurate, “hydration” is a more familiar term than “volume” as a description of fluid status. Stable patients should be assessed for target weight changes perhaps quarterly, but staff and patients should be particularly vigilant when changes in flesh weight are likely, such as following hospital admission, or when starting nutritional supplementation. Fluid management often requires input from a multidisciplinary team, so a documented policy may ensure that the approach is consistent.

Improvement on clinical assessment using objective methods for selecting target weight has been sought for a long time, though no single measurement has so far gained widespread acceptance. Methods have fallen into one of a number of categories: imaging (such as inferior vena cava diameter), biochemistry (such as brain natriuretic peptide), electrophysiology (such as bioimpedance) and dynamic intradialytic measurement (such as blood volume monitoring). Many publications address one or more of these methods, and several detailed reviews are available.

Some of these studies suffer from the limitations of self-referencing design (demonstrating that the use of method X to guide selection of target weight, reduces the frequency of over-hydration as defined by method X) and improvement in clinical outcomes are often harder to demonstrate. For example, Leung studied intradialytic hypotension in 32 haemodialysis patients during 8 weeks of standard care and 8 weeks during which ultrafiltration was informed by blood volume monitoring, but no advantage was seen in terms of hypotension frequency or symptoms [95].

No clear recommendation can be made regarding the optimal method, but when clinical assessment feels uncertain, it seems very reasonable to supplement this with an objective measure, and bioimpedance has some of the most promising data on clinically relevant endpoints. In a randomised study of 156 patients, Nur used bioimpedance data to adjust target weight in the intervention group, whilst control patients had bioimpedance measured but not available to treating physicians [96]. Over the 12 month study, bioimpedance-defined fluid overload was reduced in the intervention group, as was blood pressure and left ventricular mass index (131 ± 36 to $116 \pm 29 \text{ g/m}^2$, $p < 0.001$).

Regardless of the final volume achieved, the rate of ultrafiltration appears separately to influence intra-dialytic hypotension and clinical outcome. In a DOPPS study of 22 000 patients in 7 countries, Saran observed that an ultrafiltration rate over 10ml/h/kg was associated with both intra-dialytic hypotension (RR 1.30, $p = 0.04$) and mortality (RR 1.09, $p = 0.02$) [97]. And using data from the HEMO study ($N = 1846$) Flythe divided patients according to ultrafiltration rate into three groups: less than 10, 10-13, and over 13ml/h/kg, demonstrating increased mortality in the highest ultrafiltration rate group (HR 1.59, 95%CI 1.29-1.96) [98]. In the same study, when treating ultrafiltration rate as a continuous variable (using a cubic spline method) the authors identified 10ml/h/kg as the threshold beyond which mortality begins to increase, possibly quite sharply.

These studies are non-interventional, therefore associations are with observed (rather than prescribed) ultrafiltration rate, and there is also a close interaction with session length (since rate is obviously the volume over

the time) but these data provide a convincing argument for avoidance of excessive rates. This should not however be at the expense of non-achievement of target weight and acceptance of over-hydration (though staged achievement over a number of sessions is frequently appropriate) but rather should focus clinicians on session length or addressing fluid gains between dialysis sessions. The ultrafiltration required during dialysis depends on the degree of over-hydration present at the start of the session, so restricting fluid intake reduces ultrafiltration rate, and is part of standard advice for the majority of patients. Consideration must be given to the cause of increased fluid intake such as habitual drinking or thirst associated with either dietary sodium intake or raised blood glucose. Advice on managing fluid intake is therefore best delivered on an individualised basis, as part of a dietary management plan to support adherence and patient experience. This topic is covered in guidelines for the nutritional management of kidney disease.

Other relevant aspects of the dialysis prescription include dialysate sodium and temperature.

Sodium balance, thirst and fluid control are also influenced by dialysate sodium. Many observational studies report lower fluid gains and lower blood pressure in patients treated with low dialysate Na (typically 136–138mmol/l). Antihypertensive treatment is frequently overlooked in large studies, but reasonable supportive evidence can also be found in interventional studies. For example, Gumrukcuoglu reduced dialysate sodium from 140 to 137mmol/l in 41 patients over 6 months, reporting reduced fluid gains, and no blood pressure change but a reduction in antihypertensive use from 1.9 to 1.2 agents per patient [99]. This potential benefit was not without drawbacks however: in common with other groups, investigators also found that cramps and intra-dialytic hypotension became more frequent.

Lowering dialysate sodium therefore does appear to improve fluid control and blood pressure, albeit with some side effects, however another note of caution arises from observations on mortality in different dialysate sodium groups. Studying almost 30 000 patients from DOPPS phases 1–4, with dialysate sodium varying between 138 and 142mmol/l in 90% of patients, Hecking found that higher dialysate sodium was, as expected, associated with modestly increased fluid gain and systolic blood pressure (increasing by 0.17% body weight and 0.66mmHg per 2mmol/l increase in dialysate sodium) [100]. However, when addressing indication bias by studying only the 56% of facilities using a standardised dialysate sodium, they found that higher dialysate sodium was unexpectedly associated with reduced mortality (HR 0.88 per 2mmol/l increase in dialysate sodium, 95%CI 0.83–0.94). There is insufficient consistency in the literature for a clear recommendation on dialysate

sodium, though if a standardised dialysate sodium is used for all patients, some clinicians would avoid a choice below 140mmol/l.

Dialysate temperature has been consistently associated with intra-dialytic hypotension. Even thermoneutral haemodialysis (temperature-matched so that the dialysis circuit neither heats nor cools the patient) leads to an increase in core temperature, though it is not clear if this is due to reduced heat loss (for example due to cutaneous vasoconstriction) or increased thermogenesis (for example due to increased cardiac output) [101]. Reduced dialysate temperature has therefore been the subject of a number of interventional studies and two meta-analyses [102, 103].

In the most recent of these, Mustafa reported on 26 studies totalling 484 patients [103], observing an average 70 (95%CI 49 – 89) percent reduction in hypotension, though with an increase in cold-related symptoms. Twenty-four of these studies however were either small (less than 20 patients) or of short duration (less than 3 sessions). The two largest studies provide further insight: in Maggiore's study of 95 patients over 12 sessions

[104], isothermic (in which dialysate temperature is set so that core temperature is unchanged) rather than thermoneutral dialysis reduced hypotension from 50 to 25% of sessions. In Fine's study of 128 patients over 10 sessions [105], 35°C dialysate rather than 37°C similarly reduced hypotension, but the benefit was seen only in those with subnormal temperature before dialysis. Preventing temperature rise therefore appears to be more important than cooling, which may be achieved on an individual basis using dialysate 0.5 – 1.0 degree lower than core temperature or in the whole unit by using dialysate temperature 36°C or lower. The latter is probably adequate for most patients, with individualisation seeming a reasonable option for those with persisting hypotension or cold-related symptoms, and it is reasonably clear that if a standardised dialysate temperature is being used, then the choice should be at or under 36°C.

Regardless of the quality of dialysis prescription, intra-dialytic hypotension will still occur, in some patients more than others, for which prompt nursing intervention is essential [106]. Common measures include leg raised positioning, ceasing ultrafiltration, and fluid administration (saline being as good as albumin and far cheaper [107]). Measures for “simple” intra-dialytic hypotension should be coupled with assessment for underlying intercurrent illness (such as infection or cardiac arrhythmia) or less commonly a specific dialysis complication (such as air embolism or dialyser reaction). Frequent intervention should lead to reassessment of target weight / ultrafiltration setting and a medication review – in some cases predialysis hypertension may be preferable to dialysis intolerance. Specific pharmacological measures are rarely used but the α -agonist Midodrine has reasonable supportive evidence: in meta-

analysis the average improvement (increase) in systolic/diastolic post-dialysis blood pressure was 12.4/7.7mmHg [108].

Guideline 4.2 - Paediatric fluid considerations

In growing children we recommend clinical assessment of fluid status and target weight, and dietetic assessment, at least monthly. [1C]

We suggest supplementing clinical assessment with a validated objective measure of fluid status such as bioimpedance, on a monthly basis or more frequently during periods of rapid growth or illness. [2C]

We recommend regular assessment of ultrafiltration tolerance, using extended times to avoid excessive ultrafiltration rates. [1D]

Rationale

Assessment of target weight in children and adolescents is particularly challenging as it needs frequent adjustment in line with growth or periods of illness. This is particularly true for infants and adolescents during rapid phases of growth. Overestimation of target weight will result in chronic fluid overload leading to hypertension and left ventricular hypertrophy, whereas chronic under-hydration is likely to detrimentally affect residual kidney function and lead to increased symptomatic hypotension both during and immediately post-dialysis. Hypotensive tendency is also multifactorial and cannot alone be relied on to ascertain a patient's target weight. It is therefore essential that target weight is adjusted at least on a monthly basis following clinical assessment, in conjunction with dietetic review [109, 110].

Dialysate (Guidelines 5.1 – 5.4)

When the 2nd edition of the RA Guidelines was published in 1997, the only recommendation relating to the composition of the dialysate was that renal units phase out the use of acetate in favour of bicarbonate buffering, since the improved efficiency of dialysis could overwhelm the capacity to metabolise acetate. The need to keep bicarbonate separate from divalent cations to prevent precipitation meant that dialysate had to be produced using two different concentrates, leading to the modern proportioning system in which sodium bicarbonate is mixed with an electrolyte concentrate ('acid concentrate') at the point of use, allowing independent control of most dialysate constituents. Some dialysate constituents have diversified whereas others have gradually become standardized.

Dialysate calcium was often supra-physiological in the 1990's (around 1.75mmol/L) to prevent hypocalcaemia, but this became unnecessary with increasing use of vitamin D analogues and calcium-containing phosphate binders, so that dialysate calcium has become reasonably

standardized, usually in the range 1.25–1.50mmol/L. Non-standard dialysate calcium may sometimes be helpful, for example in the context of calciphylaxis, but this is usually driven by bone-mineral considerations and is outside the scope of this guideline.

In the 1990's, dialysate was usually glucose-free due to cost and microbiological concerns, and hypoglycaemia was often a problem for diabetic patients. Glucose containing dialysate was initially prescribed for diabetic patients, but extended to all as costs improved, so that a dialysate glucose of 5.5mmol/L is now standard in almost all UK dialysis units. The other constituent of dialysis that has become standardised is magnesium, with low (usually 0.25 or 0.375mmol/L) or high (usually 0.75mmol/L) magnesium being replaced by a dialysate magnesium of 0.5mmol/L, close to the lower end of the normal range.

Opposing these trends, there has been significant diversification in dialysate potassium, and similarly, buffer concentrations and practices vary between units and manufacturers, and are discussed below.

Guideline 5.1 - Selection of dialysate potassium

We recommend an optimal pre-dialysis serum potassium in the range 4.0–6.0mmol/L, remembering to consider measurement errors (e.g. due to haemolysis) when interpreting levels. [1B]

We suggest choosing dialysate potassium between 1.0 and 3.0mmol/L for the majority of patients, using an individualised approach, in general using the highest dialysate potassium that is sufficient to control pre-dialysis hyperkalaemia. [2C]

We suggest a combined approach to managing hyperkalaemia, which may include decreasing dialysate potassium and/or other measures, including dietary advice, medication review and increased dialysis frequency. [2D]

Rationale

Historically, it was often difficult to remove the potassium accumulated between dialysis sessions, so dialysate potassium between zero and 2mmol/L was common. The requirement for dialysate with potassium levels that are close to, or within, the normal range reflects the increased efficiency of modern dialysis and the increased age of the modern patient. In most units dialysate potassium is determined by the choice of acid concentrate: zero potassium is no longer used, and suppliers offer concentrates with potassium between 1 and 4mmol/L.

Removal of accumulated potassium by intermittent haemodialysis inevitably leads to a fluctuating profile of serum potassium with a risk of cardiac arrhythmias at both high and low concentrations. This probably contributes to the clustering of sudden cardiac death

around the peridialytic period, and at the end of the weekend gap [111].

Both low and high pre-dialysis potassium are associated with increased mortality, so that the mortality curve is U-shaped. Low potassium often appears more harmful in unadjusted data: for example, in a study of 483 Taiwanese patients followed from 2004 to 2008, Hwang showed that those with pre-dialysis potassium below 3.5mmol/L had more than twice the risk of mortality than those with higher levels [112]. But this link may be due to confounding by comorbidity malnutrition: in a much larger study of 74219 patients between 2001 and 2004, a U-shaped risk curve was seen, with increased mortality with pre-dialysis potassium outside the range 4.3–5.6mmol/L [113]. After adjustment for case mix and malnutrition parameters however, the increased risk of mortality remained only for the high potassium patients (though the less than 4.0mmol/L category was not subdivided). The optimum pre-dialysis potassium therefore appears to be above 4.0 with an upper limit between 5.6 and 6.0mmol/L, though the broader range seems more appropriate given the considerations below.

The relationship between post-dialysis potassium and mortality is unknown, as it is rarely measured, but the risks of post-dialysis hypokalaemia can be inferred from studies of dialysate potassium [114, 115]. For example, Pun compared 502 patients who experienced sudden cardiac arrest in dialysis units between 2002 and 2004, with 1632 age and vintage matched controls, finding that risk was doubled if the patient last dialysed with a low dialysate potassium (less than 2.0mmol/L) [163].

The DOPPS review of modifiable practices associated with sudden death included 36235 patients in 12 countries of whom 6606 were dialysed with dialysate potassium at least 3.0mmol/L [116]. An increased risk of sudden death was observed with dialysate potassium below 3.0mmol/L (HR 1.17, 95%CI 1.01–1.37), though it was not clear if this risk extended to those with pre-dialysis serum potassium over 5.0mmol/L. Others have suggested that lower dialysate potassium may prevent sudden death in this subgroup [111, 113], but the latest DOPPS analysis found no meaningful difference in mortality or arrhythmia events between patients treated with dialysate potassium of 2.0 or 3.0mmol/L [117].

The understandably strong impulse to control pre-dialysis hyperkalaemia should therefore be tempered by consideration of the less visible risk of post-dialysis hypokalaemia. Pragmatically therefore one can conclude the following general principles:

Firstly, pre-dialysis hyperkalaemia should be controlled, though an overly tight range may be counterproductive, so the previously recommended target for pre-dialysis potassium still seems optimal (4.0 – 6.0mmol/L). Caveats to interpreting this range should be noted: firstly, achievement

of pre-dialysis potassium within this range does not necessarily mean that dialysate potassium is optimal, and secondly, consistent adherence to treatment is most likely just as important as specifics of the potassium range or dialysis prescription.

Secondly, non-dialysate approaches to hyperkalaemia may sometimes be more favourable [118, 119]. Dietary reduction may be preferable if it can be achieved without an adverse effect on protein-calorie intake, and other dialysis changes may be appropriate, such as increasing blood flow, duration or frequency. Consideration could also be given to potassium binding resins [120].

Thirdly, lower dialysate potassium does increase the removal of potassium during each session [121], and based on the risk of arrhythmias due to hyperkalaemia, dialysate potassium should be reduced if other measures are not possible or successful [122]. However, dialysate potassium should be no lower than is necessary to achieve this goal – individualization does therefore seem necessary, so that each patient uses the highest dialysate potassium which still controls pre-dialysis hyperkalaemia. This pragmatic approach has probably driven the steady increase in the use of higher potassium dialysates, and reduction in the use of concentrations below 2.0mmol/L, over the 5 DOPPS phases between 1996 and 2015 [117].

Finally, and particularly for measurements taken remote from the laboratory, the relatively high frequency of measurement errors (for example due to in vitro haemolysis) should be remembered when interpreting potassium levels.

Guideline 5.2 - Selection of dialysate buffer

We recommend an optimal pre-dialysis serum bicarbonate in the range 18.0–26.0mmol/L, remembering to consider measurement errors (e.g. due to exposure to air) when interpreting levels. [1C]

We suggest the term ‘dialysate buffer’ rather than ‘dialysate bicarbonate’ to avoid confusion arising from differences in manufacturers’ terminology. [2C]

We suggest choosing dialysate buffer below or equal to 37.0mEq/L for the majority of patients, using a standardised or individualised approach. [2C]

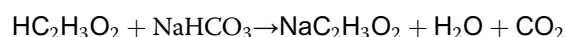
We suggest a combined approach to abnormal pre-dialysis serum bicarbonate, which may include increasing dialysis dose, oral bicarbonate, nutritional support, or individualising dialysate buffer. [2D]

Rationale

We suggest a combined approach to abnormal pre-dialysis serum bicarbonate, which may include increasing dialysis dose, oral bicarbonate, nutritional support, or individualising dialysate buffer. [2D]

The literature on dialysate bicarbonate is difficult to interpret due to unclear definitions when reporting the bicarbonate and additional alkali components. Most commonly the electrolyte concentrate contains a non-bicarbonate acid, to reduce the deposition of calcium and magnesium salts – acetic acid is perhaps the most common, but citric acid and sodium diacetate may also be used.

When mixed to form the dialysate, acetate reacts with sodium bicarbonate to form sodium acetate, water and carbon dioxide:



The addition of 3mmol of acetic acid to a litre solution containing 35mmol of bicarbonate therefore reduces the bicarbonate concentration to 32mmol/L. In publications, bicarbonate concentration in this dialysate may variably be referred to as having a bicarbonate concentration of 32 or 35mmol/L, with the acetate content rarely reported.

In addition, the bicarbonate ‘setting’ on machines from different manufacturers, refers variably to the bicarbonate concentration either prior to (eg. Braun) or after (eg. Fresenius) mixing with the electrolyte concentrate. The terms ‘actual’ bicarbonate (because that is what is actually added as sodium bicarbonate) and ‘final’ bicarbonate (because that is the bicarbonate in the dialysate at the point of use) are sometimes used to separate their meaning. However, the total buffer concentration remains the same before and after this mixing, so this term has a clear unambiguous meaning (equivalent to the sum of bicarbonate and acetate concentrations in the final dialysate). In a discussion of the DOPPS study of dialysate bicarbonate, Tentori observed that when asked either for the bicarbonate or total buffer concentration, most DOPPS units returned the same figure, suggesting that clinicians generally mean ‘actual’ rather than ‘final’ bicarbonate, which is the same as total dialysate buffer [123–125].

The factors affecting pre-dialysis serum bicarbonate levels include protein intake, residual kidney function, interdialytic fluid gain, dialysate buffer concentration, dialysis adequacy, oral sodium bicarbonate and other alkaline medications such as calcium carbonate [126].

Observational studies of pre-dialysis levels usually show a J-shaped mortality curve, with most of the excess risk associated with high levels of bicarbonate [127, 128], but this appears to be due to the close link between high bicarbonate and malnutrition. For example, in a study of 56385 between 2001 and 2003, Wu observed a progressive increase in mortality as pre-dialysis bicarbonate increased beyond 23mmol/L, but also strong associations between higher bicarbonate and worsening markers of

nutrition including albumin, phosphate and protein intake [129]. When adjusted for comorbidity and 12 parameters associated with malnutrition, most of the increased mortality appears with low bicarbonate, at levels below 18–21mmol/L. Some guideline groups have therefore increased the lower limit for optimal pre-dialysis bicarbonate to 20 or 22mmol/L [130, 131].

Post-dialysis bicarbonate is rarely measured, but three considerations argue for caution in attempting to achieve a minimum pre-dialysis bicarbonate. Firstly, the risks associated with abnormal bicarbonate are less clear and of a lower magnitude than those associated with abnormal potassium (mortality hazard ratio of approximately 1.2 for the most extreme category of bicarbonate versus 1.5 for potassium).

Secondly, although it is principally low bicarbonate which carries risk, high pre-dialysis bicarbonate also appears to be harmful. Whilst much of the risk observed is attenuated by adjustment, pre-dialysis bicarbonate is still associated with increased mortality at levels above 27mmol/L [129]. Additionally, an increased risk of peridialytic cardiac arrest has been observed with high pre-dialysis bicarbonate: a Fresenius Medical Care memo in 2011 reported an internal case-control study of 941 patients in 667 facilities who suffered cardiac arrest in 2010. Risk was 4.7 times higher in patients with pre-dialysis bicarbonate over 28mmol/L, and 6.3 times higher if they also had pre-dialysis potassium below 4mmol/L [132].

Thirdly, high dialysate buffer is associated with increased mortality. For example, in a large study of dialysate buffer using DOPPS data (collected from 17031 dialysis patients in 11 countries between 2002 and 2011) Tentori observed a lower risk of mortality in patients treated with dialysate buffer less than or equal to 32mmol/L, regardless of pre-dialysis bicarbonate (HR 0.90, 95%CI 0.80–1.01) and higher risk with dialysate buffer at or above 38mmol/L (HR 1.07, 95%CI 0.97–1.19) [123].

Pragmatically therefore one can conclude the following general principles:

Firstly, pre-dialysis acidaemia should be controlled, though an overly tight range may be counterproductive, so the previously recommended lower target for pre-dialysis bicarbonate still seems optimal, though the upper target could safely be increased (18.0–26.0mmol/L). As with potassium, achievement of this range does not necessarily ensure optimal dialysis prescription.

Secondly, dialysate buffer at or over 38mmol/L should generally be avoided, and the optimal dialysate buffer for the majority of patients is probably in the region of 32–35mmol/L.

Thirdly, many other factors affect pre-dialysis bicarbonate, the dominant ones being nutritional state and dialysis dose, so that abnormalities of pre-dialysis bicarbonate should not lead clinicians automatically to think of

adjusting dialysate buffer. High bicarbonate in particular should prompt a nutritional thought process initially. It is not clear that adjustment of dialysate buffer is a helpful strategy for optimising pre-dialysis bicarbonate, or that such an adjustment has much impact on pre-dialysis bicarbonate levels. Specific groups however, such as patients with abnormal levels despite optimal diet and dialysis strategy, may have something to gain from dialysate buffer adjustment. Conversely, increased dialysate buffer may be more hazardous in certain circumstances, such as in combination with low potassium dialysate [122, 133].

Whilst it is a very reasonable thing to do, and might prove to be beneficial in future studies, it is not currently clear that individualization of dialysate buffer is superior to standardization.

Finally, and particularly for measurements taken remote from the laboratory, the relatively high frequency of measurement errors (for example due to carbon dioxide escape) should be remembered when interpreting bicarbonate levels [134, 135].

Guideline 5.3 - Supplementation of dialysate with phosphate

We suggest considering supplementation of the dialysate with phosphate in patients on augmented dialysis schedules. [2D]

Rationale

The conventional haemodialysis patient struggles to achieve sufficient phosphate removal, and historically dialysate has always been phosphate-free. Guidelines usually focus more on the upper limit than the lower limit for optimal pre-dialysis phosphate and ranges in the region of 1.1–1.7 mmol/L are often suggested, with most of the emphasis on treatments to reduce phosphate - indeed, most of the Renal Association's advice on phosphate can be found in the guideline on mineral-bone management. However, with demographic and

treatment trends of the last decade, low phosphate is becoming more common, and since the symptoms of hypophosphataemia are non-specific [136], this problem may be easily overlooked.

The relationship between pre-dialysis phosphate and mortality is J-shaped, with increased risk occurring at both high and low levels. But phosphate is strongly associated with age and nutritional state, so that the mortality risk associated with low phosphate is substantially (although incompletely) attenuated by adjustment for comorbidity and malnutrition [137]. In the context of low pre-dialysis phosphate therefore, the main clinical focus should be on nutritional assessment and support.

When patients are unable to consume sufficient phosphate to match intradialytic loss, supplementation of the dialysate is a logical approach to managing

hypophosphataemia. The argument for supplementation is generally accepted in the context of augmented dialysis, when post-dialysis phosphate is often measured, and may be found to be very low in well-nourished patients [138]. It is common practice, for example, to supplement dialysate with phosphate in pregnant patients receiving daily dialysis.

Supplementation could also be used to prevent undesired loss of phosphate in patients on conventional regimes with low pre-dialysis phosphate that is refractory to other measures [139]. While this does appear to be clinically helpful in case reports, data to support this approach remain limited. However, as patients with low pre-dialysis phosphate currently receive a form of dialysis which inevitably worsens this abnormality, so the instinct to 'do no harm' may be a sufficiently persuasive argument for some clinicians.

Phosphate precipitates in solutions containing calcium or magnesium, so like bicarbonate, must be added to the electrolyte concentrate at the point of use, but there is currently no commercially available phosphate additive approved for use in intermittent haemodialysis [140, 141]. 'In house' supplementation can be achieved by adding phosphate salts to the electrolyte concentrate at the start of the session, but solutions intended for intravenous use typically contain potassium and are too dilute. Pharmaceutical grade phosphate salts in powder form can be used, but require quality assurance on storing, weighing, adding and ensuring complete dissolution. The most common method is therefore 'off label' use of solutions intended as enemas: Cleen (formerly Fleet) Enema for example, is very suitable for enriching dialysate [142], although it contains antimicrobial preservatives (benzalkonium chloride and disodium edetate) which are widely used in medical products such as eye drops, which might have adverse effects in this context. The use of Cleen Enema in dialysate has a good safety record however: Pierratos first reported its use in nocturnal dialysis in the late 1990s [143], and frequent dialysis programmes in many countries have adopted this method [144, 145]. Practical advice on adding phosphate to dialysate is provided in [Appendix 4](#).

Guideline 5.4 - Paediatric dialysate considerations

We recommend individualisation of dialysate electrolyte concentrations, including potassium, buffer and calcium. [1C]

We suggest an individualised dialysate temperature, between core temperature and 0.5°C below, with monitoring of intradialytic core temperature for neonates and smaller children. [2D]

Rationale

Adult guidelines for dialysate composition (sections 5.1 – 5.3) are generally applicable to children, though there are a number of additional considerations.

In children with residual kidney function, tubular dysfunction is not uncommon, leading to electrolyte wasting and hypokalaemia or acidosis. Calcium balance is also more complex in children: the normal range for calcium is age-dependent and growing children require a positive calcium balance, so that hypocalcaemia may be both more common and more harmful, and yet vascular calcification is sometimes seen even in children and adolescents, in whom calcium-phosphate product is an important risk factor [146, 147]. Similarly, dietary protein intake is often proportionately greater than that of adults, and pre-dialysis acidosis therefore more common. The complexity and clinical heterogeneity of these issues therefore argues strongly for a more individualized approach to dialysate composition in children [148].

Thermal exchanges during dialysis may also be more significant particularly in neonates and younger children, due to the proportionately greater blood flow, and sometimes a reduced capacity for compensation due to body size. Hypothermia should therefore be avoided by individualising dialysate temperature, with intradialytic monitoring in those most at risk. Control of thermal exchanges is available on some modern dialysis machines.

Anticoagulation

We recommend that patients without increased bleeding risk should be given unfractionated or low-molecular-weight heparin during dialysis to reduce clotting of the extracorporeal system. [1A]

We recommend that systemic anticoagulation should be omitted or minimised in patients with increased bleeding risk. [1C]

We recommend that patients with heparin allergies should be prescribed a non-heparin form of anticoagulation. [1A]

Rationale

Platelet activation in the extracorporeal circuit accelerates thrombin generation via the intrinsic coagulation pathway, so that anticoagulation is usually required to prevent thrombosis. Unfractionated heparin is used as the standard anticoagulant worldwide in view of its proven efficacy, ease of use and long safety record unless the patient has recent or active bleeding, thrombocytopenia, heparin allergy or heparin induced thrombocytopenia.

With a mean half-life of 1.5 hours, heparin is usually administered as a loading dose of 1000-2000 IU followed by a continuous infusion of 500-1500U/h that is discontinued approximately 30 minutes before the end of the dialysis

session. Monitoring can be performed by measuring the activated partial thromboplastin time ratio (aPTTr) or the whole-blood activated clotting time aiming for around 150% of pre-dialysis or centre normal values [149, 150]. But in practice the bolus dose, infusion rate and stopping times are adjusted empirically, according to clot formation in the dialysis circuit, and the time for needle sites to stop bleeding. Heparin dose may need to be increased with higher haematocrit, or reduced / withdrawn in patients at risk of haemorrhage, those with thrombocytopenia or on long term anticoagulation [151].

Alternatively, a low molecular weight heparin may be used [152], having a longer half-life, given as a single 'arterial limb' bolus at the start of dialysis [153]. Although monitoring can be performed using anti-Xa activity, these are not always available and laboratory testing correlates less directly with clinical effect, so as with unfractionated heparin, dose adjustment is usually empirical, but larger or repeated doses may be needed depending on convective clearance and session length, and reduced doses for those at risk of haemorrhage [154]. Several systematic reviews comparing low-molecular-weight with unfractionated heparin have found no difference in the incidence of bleeding complications, post-dialysis access bleeding, or thrombosis of the extracorporeal circuit [155–158]. With its convenience for nursing staff, the use of low-molecular-weight heparin is becoming more common in Europe.

For patients at increased risk of bleeding, several options are used in clinical practice. Firstly, several techniques require no anticoagulation to be administered during dialysis, including: combining a high blood flow rate and regular pre-dialyzer circuit flushing every 15-30 minutes [159, 160]; using a heparin coated dialyzer [161, 162]; adding heparin to the rinsing solution [160]; or using a dialysate containing citrate [163–165].

Secondly, a regional anticoagulant can be used such as citrate, prostacyclin (epoprostenol) or nafamostat (not currently available in UK). Regional anticoagulation with citrate [166] and epoprostenol [167] have both been reported to reduce the risk of haemorrhage compared to heparin, though there are drawbacks: epoprostenol may induce hypotension and is costly, whereas citrate administration requires re-infusion of calcium based on electrolyte monitoring, adding complexity and nursing staff time [168]. Finally, lower doses of unfractionated or low-molecular-weight heparin have been used with caution in patients at risk of bleeding [151, 154].

Heparin induced thrombocytopenia, usually occurring shortly after regular exposure to heparin, and sometimes with thrombosis, may occur in heparin-treated dialysis patients [169, 170]. The risk of heparin induced thrombocytopenia can be estimated using the 4T scoring system [171], and is usually confirmed by laboratory testing

and detailed guidelines on diagnosis and treatment are published by the British Society of Haematology, but in suspected or confirmed cases, all heparins should be withdrawn [172]. The risk of thrombosis increases with the severity of thrombocytopaenia, and anticoagulation is usually started with either the direct thrombin inhibitor argatroban [173], or a natural (danaparoid) or synthetic (fondaparinux) heparinoid [174, 175]. Argatroban is reversible, given by continuous infusion, and requires careful laboratory monitoring with aPTT_r. The heparinoids are renally excreted and have prolonged half-lives in dialysis patients, such that monitoring of the bolus given with a dialysis session can be based on anti-Xa activity prior to the following session. Once the platelet count returns to normal, patients are usually anticoagulated with warfarin, but in the majority of cases antibodies disappear with time, and patients have been successfully re-challenged with unfractionated and low-molecular-weight heparins once laboratory testing becomes negative [176].

Adverse events during dialysis (Guidelines 7.1 – 7.3)

Guideline 7.1 - Routine blood loss

We suggest that during washback, dialysis lines and dialyser are observed to ensure residual blood loss is kept to a minimum. [2C]

Rationale

A small amount of blood loss occurs during normal haemodialysis, for example due to blood retained in the dialyser and circuit after washback, and bleeding into the dressing over needling sites, but there is no clear consensus as to what constitutes a 'normal' quantity of blood loss due to dialysis. The literature on minimising blood loss during haemodialysis is sparse, and much of the evidence is of limited quality.

The weighed gauze method has been used to quantify bleeding after removal of needles, with 'excessive' defined as blood-soaked gauze weighing over 4g [177]. And excessive bleeding has been associated with poor outcomes, for example in a study of 4152 dialysis sessions in 143 patients, Lin found that excessive bleeding following dialysis needle removal occurred regularly, and was associated with lower haemoglobin levels [178, 179]. Kalantar-Zadeh suggested patients can lose up to 3g iron per year, with one gram being lost in the lines and dialyser, and a further gram lost in blood sampling [180]. Though it is unclear how they are derived, these estimates suggest that up to 20ml per session may be normal.

In a comparison of buttonhole versus rope-ladder cannulation in 33 patients, Verhallen found no difference in bleeding times after needle removal between the two techniques [181]. Various suggestions have been made, for example McCann suggested needling at an angle of 25 degrees [182], and Fruits suggested flushing the

arterial dialysis needle with saline, and reducing the amount of blood drawn for testing, but none of these measures is well supported by clinical evidence [183]. Currently there is insufficient evidence therefore to support any recommendations regarding blood preservation and management of vascular access.

Clotting of the dialysis circuit leads to much greater blood loss than is routine. Adequate but safe anticoagulation is an important component of prevention, and is covered elsewhere in this guideline, but regular monitoring during dialysis and observation of the colour of the lines and dialyser post-dialysis, also play a role. This concept is supported in literature, for example Kalocheritis noted the contribution of this type of blood loss to anaemia, and the relevance of human factors [184]. Reasonable consensus therefore supports the importance of nursing observation, particularly during washback.

No evidence was found regarding the effects of excessive blood sampling on blood loss. Daugirdas and Tattersall point out that on-line measurement of adequacy may reduce the need for blood sampling, but describe the benefits mainly in respect of cost and staff time [185]. However, ensuring that blood samples are taken only when required for routine monitoring or for additional diagnostic indications, is perhaps obvious common sense.

Guideline 7.2 - Disconnection haemorrhage

We recommend maintaining awareness of the risk of disconnection, the limitations of pressure alarms, and importance of direct observation, through a program of education, including patients and carers. [1D]

We suggest regular assessment of individual risk, so that high risk patients can have enhanced monitoring, which could include specific devices. [2B]

Rationale

Disconnection leading to haemorrhage may occur at any part of the dialysis circuit, though venous needle dislodgement may be the most frequent and serious, with rapid blood loss occurring at the rate of the blood flow pump, until it is detected. Disconnection incidents are thought to be uncommon, but the true prevalence is uncertain due to inconsistent reporting. Once detected, management begins with haemostasis and fluid resuscitation, as with any major haemorrhage, and the literature concentrates instead on methods to minimise risk and enhance detection, with publications available from the EDTNA/ERCA and the American Nephrology Nurses Association [186, 187].

Variability in human processes is recognised as an important factor, and most units have established protocols to ensure consistency in aspects of care such as taping

needles in position to minimise the chance of disconnection [188].

Dialysis machines have several types of safety monitor [189] and if disconnection does occur, the drop in pressure should be detected and cause the machine to alarm. However, it has been repeatedly demonstrated that these alarms cannot be relied on to detect all cases [190]. The use of asymmetric windows (such as -30 to +70mmHg) may be helpful to maximise the detection of disconnection, while minimising alarms from increases in pressure at the venous needle [191, 192].

Because machine alarms cannot be relied on, direct observation remains important, involving vigilance on the part of nursing staff, and unit management, so that lines of sight are not obscured, patients are not dialysing alone and their vascular access sites are not covered. Because of the low prevalence of disconnection, complacency may develop: continuous education is therefore advocated to ensure awareness amongst healthcare staff, patients and their carers [193].

Risk of disconnection is greater in some patients, and enhanced monitoring may be appropriate based on individual risk assessment. Simply placing patients closer to the nursing desk may be sufficient, but reliable monitoring can also be achieved by use of blood loss detection devices, which typically are secured at the site of vascular access and alarm on the detection of blood [194, 195]. Device monitoring may be appropriate for patients at high risk, such as confused or agitated patients, and may have a greater role in home haemodialysis programmes [196–199]. One interventional study considered the effect of blood loss detection devices on nursing staff, showing an improvement in self-reported feeling of safety when devices were used [200].

Guideline 7.3 - Immune reactions during dialysis

We recommend that dialysis staff should be aware of the features and management of dialysis reactions, and should have access to a range of dialyser types. [1C]

Rationale

From the early 1980s reports appeared describing abrupt clinical reactions occurring soon after the onset of dialysis [201]. These have traditionally been classified into two types.

Type A reactions were said to affect less than 1% of patients per year, often re-occurring in the same patient, with onset within the first few minutes of dialysis. Mainly occurring with first use, rather than re-used dialysers the features were quite 'anaphylactic' in nature (itching, flushing, bronchospasm, hypotension, sometimes with burning at the access site) and often severe, with cardiac arrest occasionally described [202]. Associated with eosinophilia, these reactions were caused

mainly by residual ethylene dioxide (used to sterilize membranes) with antibodies detectable in many cases [203]. Similar reactions were described to polyacrylonitrile membranes, especially in ACE inhibitor treated patients (by increasing kinin activation) and in hydrogen peroxide treated re-used membranes [204]. Immediate cessation of dialysis was usually necessary, along with anaphylaxis-type treatment. Extra rinsing or a change of membrane sterilisation would often prevent reoccurrence.

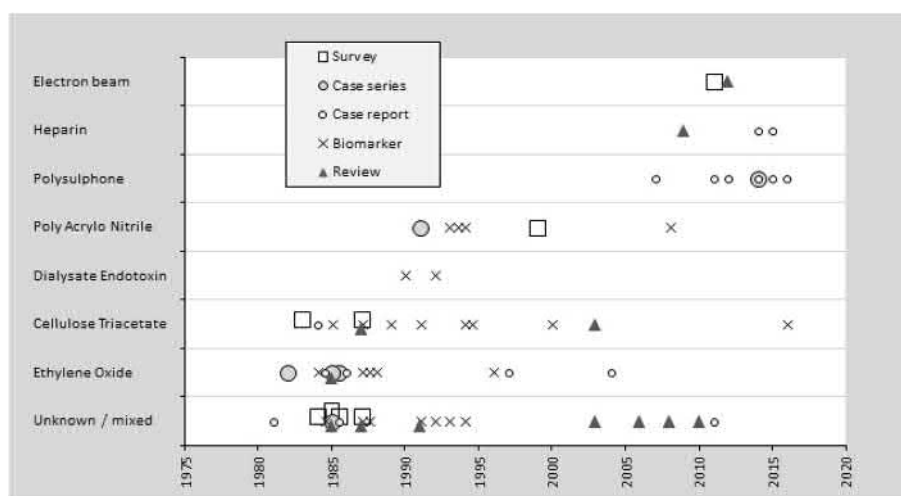
Type B reactions, said to be more common, occurring later in the dialysis session, were typically less severe, improving with continued dialysis. Characterised mainly by chest and back pain (also sometimes with vomiting, breathlessness and hypotension) they were caused by complement activation and pulmonary cell sequestration, and associated with transient reductions in circulating white cells. These reactions were clearly linked with the 'bio-incompatibility' of cellulose-based membranes [205].

Dialyser re-use, ethylene dioxide sterilisation and unmodified cellulose membranes are all now very uncommon, and as dialysis practices have evolved, the epidemiology of these reactions has changed, reflected in the changing literature (Fig. 2). In modern practice dialysis reactions are uncommon but do still occur, including polysulphone allergy, heparin allergy and isolated thrombocytopenia.

Reactions with 'type A' (anaphylactic) features continue to occur with polysulphone membranes, though many variants are described, including those with fever as the predominant symptom [206]. Eosinophilia is an important clue, though not invariably present, and other blood tests (tryptase, total IgE) may be useful [207]. The diagnostic hallmark is resolution of the syndrome following a change of membrane type, and (though little guidance is available from literature) anaphylaxis treatments are often given, with steroid pre-treatment sometimes used before dialysis sessions. Stopping ACE inhibitors may also reduce the severity.

Reactions to intra-dialytic heparin are sometimes described, ranging in severity from asymptomatic to a serotonin-like syndrome of breathlessness and flushing, often with hypertension. These are usually but not always associated with thrombocytopenia (persisting between dialysis sessions) and thrombotic complications may occur. Transient asymptomatic thrombocytopenia has also been described, often recovering between dialysis sessions so that pre-dialysis platelet count may be normal. This reaction has been associated with electron beam membrane sterilization, but the mechanism is unknown [208].

Several complications other than dialyser reactions may present with similar peri-dialytic symptoms. More common ones include bacteraemia and hypovolaemia,



Training on a '1 to 1' basis with a specific training staff is widely accepted as optimal, with the learning style and training duration adapted to the individual [221]. Type of vascular access should not be a limiting factor, but appropriate training, surveillance

and technique assessment form essential parts of the home haemodialysis programme [224, 225].

The success of a home haemodialysis programme is dependent upon a skilled and specific multi-disciplinary team facilitating education, training and patient support in the community, and optimal individual outcomes are dependent on patient understanding, and appropriate cooperative liaison with this support [218]. This may be facilitated with an explicit contract, so that the manner in which this clinical responsibility is shared is clear. The financial responsibility for treatment rests with the provider, and re-imburement of directly arising patient costs should be readily available [216].

A home haemodialysis Programme requires adequate medical, nursing and technical support, and should support at least 12 to 20 patients, and train at least 10 patients per year in order to maintain appropriate staff expertise and cost effectiveness, so smaller renal units may find it more appropriate to share resources with other centres. Minimum safe staff to patient ratios are not well defined, but recommendations for peritoneal dialysis (such as minimum of 1 nurse per 20 patients) may be relevant [218–220]. However, as training for home haemodialysis is more complex, additional staffing should be considered to ensure that training new patients does not detract from the support of established patients [217]. Patient mix should also be considered, so that programmes with a greater number of complex patients are staffed more favourably [224, 226].

Home haemodialysis patients should receive the same level of medical supervision, and the same monitoring and dose considerations as in-centre patients, and as for other patients, the schedule should be individualised depending on patient values and therapeutic goals. Dialysis dose should be quantified as for other augmented schedules, but should be interpreted with the flexibility of the patient's schedule also in mind. To ensure that the home dialysis team can provide the best possible support that is responsive to the individual, recording of sessional details by the patient or carer is desirable [229].

Specific circumstances may require additional risk assessments and/or additional measures: enhanced safety measures, for example to detect disconnection, should be available for patients dialysing alone or overnight, and protection of household contacts of patients with blood-borne viruses should be considered, particularly for those directly involved in therapy [187, 224, 227, 228].

Guideline 8.2 - Shared haemodialysis care

We suggest that all centre-based haemodialysis patients should have opportunity and encouragement to learn aspects of their dialysis treatment, and take an active role in their care. [2D]

Rationale

There is little research that has been directly conducted into shared haemodialysis care, however there is considerable evidence of the benefits of supported self-care in other long term conditions [230]. Low health literacy amongst dialysis patients is associated with worse survival [231] whereas self-motivation and education can result in better care, for example, in phosphate control and fluid balance [232, 233]. As with the broader NHS, dialysis services are experiencing considerable pressure to deliver high quality in the face of fiscal challenge, and an important mechanism to ensure that quality of care is maintained, is to engage service users as true partners in their own treatment: self-management is an ambition in 'Kidney Health: Delivering Excellence' [234]. To achieve this, health care professionals need to enhance their roles, becoming educators and facilitators, supporting patients to take a greater role in their own care, and increasing their opportunities for dialysing at home.

Shared haemodialysis care impacts on all domains of health. Central among these are: the enhanced patient safety that comes from education on infection control (see the WHO campaign 'Save lives: clean your hands' [235]); the enhanced equity consequent on offering all patients training in their treatment rather than only those planning haemodialysis at home; and the enhanced experience when patients can put themselves onto dialysis, or manage their own alarms, without waiting for a nurse [236].

The process of haemodialysis can be broken down into approximately 14 tasks (Appendix 5). The exact arrangements may vary between units but the concept is essentially the same: that centre-based patients are given the opportunity to train to perform one or more of these tasks. It is key that patient involvement is voluntary, and that learning is individualised to the style and speed of the individual. Shared haemodialysis care is associated with a range of barriers and enablers that are best explored through quality improvement work, in order to design favourable conditions for successful implementation.

Guideline 8.3 - Intradialytic exercise

We recommend that intradialytic exercise should be available in all units, as a treatment for enhancing physical functioning, in patients without contraindications. [1B]

We suggest that intradialytic exercise be considered as a method of enhancing quality of life. [2C]

We suggest that exercise regimes be devised by appropriately trained staff. [2C]

Rationale

Whilst cardiovascular disease remains the principal causes of death in dialysis patients [237], there is a significant interaction with body composition, with

muscle wasting in particular exacerbating mortality [238]. Muscle wasting and poor physical fitness also reduce functional abilities including activities of daily living, thus reducing quality of life in haemodialysis patients [254]. However, muscle wasting is modifiable by exercise, and epidemiological studies suggest that regular exercise can even reduce mortality [239], but unfortunately daily physical activity is typically low in haemodialysis patients, perhaps due to the time burden and symptoms associated with treatment [240].

Based on evidence from eight systematic reviews and meta-analyses [241–248], analysing data from 1000 adult participants on dialysis, the clinical effectiveness of exercise on physical function and health related quality of life can be summarised as follows:

- 1) Despite the high-risk status of dialysis patients, no serious exercise-related adverse events have been reported from over 30 000 patient-hours of exercise observed [244, 246]. Adverse events reported include post-exercise hypotension, fatigue, myalgias, painful feet, and aggravation of foot ulcers, though not with increased incidence in exercise groups. Compliance with exercise programmes ranged from 43 to 100%, and dropout rates from 15 to 50%.
- 2) Short term (2–6 months) prescribed exercise of any type, frequency and intensity, resulted in significant and clinically moderate/large improvement in cardiorespiratory fitness, with a mean increase in peak VO₂ of 5ml/kg/min [243, 246].
- 3) Any prescribed exercise delivered during hemodialysis sessions produced significant and clinically moderate improvement in muscle strength [245], with a mean increase of 9.9kg [243].
- 4) Any type of prescribed exercise consistently produced significant and clinically large improvements in some indices of functional capacity, such as ‘sit to stand’ transfers [247], whereas other indices, such as walking performance, were improved according to some reviews [247] but not others [243, 245].
- 5) Self-reported physical function was significantly improved in exercising patients [247]. This often contributes to quality of life scores, and may therefore explain why some studies conclude that exercise improved quality of life.

Taken together there is therefore good evidence that the uptake of regular exercise improves physical function and quality of life in haemodialysis patients, without causing significant harm, and that delivery of exercise within haemodialysis sessions can achieve this.

Exercise during the dialysis process may also assist with solute clearance. Enhanced urea clearance is predicted by

modelling but an impact on Kt/V is found in some studies (nine of eighteen studies reviewed) but not others [249], whereas improvements in phosphate clearance and serum levels are consistently observed [249–253].

Some evidence suggests the type of exercise most likely to be beneficial: larger improvements were observed with interventions delivering a progressively increasing exercise volume, at least three times per week, for at least 30 minutes, lasting for at least four months, and including an additional resistance-training component [244, 246–248]. Comparative evidence for specific exercise programmes is currently unavailable, but some guidance on practical implementation of intradialytic exercise is offered in [Appendix 6](#).

Guideline 8.4 - Dialysis experience for children and adolescents

We recommend that haemodialysis for children and adolescents should be delivered in a dedicated paediatric dialysis centre or at home, with the involvement of a paediatric multidisciplinary team. [1C]

We recommend that adolescents should commence an active transition programme by 14 years, or at the time of presentation in those already over 14. [1D]

Rationale

Haemodialysis sessions are associated with physical symptoms, social restriction, and loss of control, which for children and adolescents may be particularly depersonalising and unpleasant. These effects may be mitigated by an appropriate environment and trained support staff, and in-centre dialysis is therefore best delivered in a dedicated unit, with paediatric nephrologists working alongside the full multidisciplinary team, including nurses, dietitians, psychologists, play therapists, teachers and social workers [148, 255, 256]. In this way children can be supported to reach their full potential despite the burdens of treatment. The first dialysis session is of particular importance in establishing therapeutic trust and parental confidence - psychological preparation for this event can alleviate anxiety, reduce symptoms and improve the tolerability of dialysis.

Children and adolescents can be supported to take on aspects of their own care, often along with parents or guardians, and are likely to gain as much benefit as adults from involvement in a shared care program [257]. And home haemodialysis has many advantages for children, allowing an augmented schedule without institutionalisation, and providing a flexibility which can reduce the impact of dialysis on social development.

Transition describes the process of preparing adolescents, along with their families, for the move from paediatric to adult care. It should be individualised, taking into consideration the physical and psychological development of the adolescent, and requires a variable

amount of time [258]. Adolescents will suffer the least disruption if moved to adult care following engagement with a transition programme, and should be introduced to the concept of transition in early adolescence (12-14 years). For those over 14 when presenting to paediatric services, transition planning should commence immediately alongside other aspects of care.

Appendix 1

Simplified mathematics of urea clearance

Urea Kinetic Modelling and Kt/V

In the design of the NCDS study, 'dose' of dialysis was defined as a target for time-averaged urea (low urea = high dose group). However, urea level in dialysed patients depends as much on protein intake as the amount of dialysis: loss of appetite may lead to low urea, so this cannot be relied on to indicate sufficient dialysis. The concept of Kt/V emerged from this study, where K is dialyser clearance (of urea), t is treatment time and V is volume of distribution (of urea). Despite its appearance, Kt/V is not intended as something to calculate from its constituents K, t and V, since only t is accurately known, but by consideration of the following relationship: the rate of removal of urea is proportional to its concentration. Following this basic rule, the concentration of urea after a dialysis session of duration t, is therefore approximated by:

$$U_{\text{post}} = U_{\text{pre}} \times e^{(-Kt/V)}$$

where

$$U_{\text{post}} = \text{urea post dialysis}$$

$$U_{\text{pre}} = \text{urea pre dialysis}$$

Kt/V is therefore the negative exponent in a numerical model describing the fall in urea during a single dialysis session. Different forms of Kt/V reflect models with differing levels of complexity, which in addition to the concept above, may also take account of other aspects such as: urea removal by convection, urea generation, and separate "pools" within which urea is distributed.

The gold standard Kt/V is derived from 'Urea Kinetic Modelling': iterative computation to give the best fitting coefficients for urea clearance and generation, based on three urea measurements (spanning an interdialytic interval and a dialysis session). This approach is broadly accepted, but although online programs are available (e.g. Solute Solver, www.ureakinetics.org) the non-formula method hinders widespread use, and a number of simplified approaches are more common - three are commonly used and summarised here.

Log-Ratio and Urea Reduction Ratio

If the basic model above is used, ignoring other factors, with urea assumed to be distributed evenly in body water, then Kt/V is given by the log ratio:

$$Kt/V = -\log_e [U_{\text{post}}/U_{\text{pre}}]$$

This simple form of Kt/V, sometimes called the "Log-Ratio", is mathematically related to the Urea Reduction Ratio (URR), the reduction in urea as a ratio of the pre-dialysis level, often expressed as a percentage:

$$\text{URR} = 100 \times (U_{\text{pre}} - U_{\text{post}}) / U_{\text{pre}}$$

$$Kt/V = \log_e [100 / (100 - \text{URR})]$$

A threshold for URR is therefore precisely the same as a threshold for Kt/V calculated by the Log-Ratio.

URR is the simplest measure of dialysis dose, and is the current audit measure collected by the Renal Registry. URR has the disadvantage that it does not account for clearance due to ultrafiltration, urea generation or urea rebound. It tends to over-estimate dialysis dose in shorter treatments, and under-estimate dose in treatments longer than 4 hours. However, it is long established and there is no argument over its calculation.

Single-pool Kt/V (spKt/V)

Although the above is technically also a single-pool method, the term 'single pool Kt/V' usually refers to the method proposed by Daugirdas, which calculates Kt/V by a formula taking account of the effect of ultrafiltration:

$$\text{spKt/V} = -\log_e \left[\frac{(U_{\text{post}}/U_{\text{pre}}) - (t/7500)}{1 + [(UF/TW) * (4 - (3.5 * (U_{\text{post}}/U_{\text{pre}})))]} \right]$$

where

$$t = \text{dialysis time (min)}$$

$$UF = \text{ultrafiltration (litres)}$$

$$TW = \text{target weight (kg)}$$

This method takes account of more factors but consistently over-estimates Kt/V. Targets have therefore often been expressed with an adjustment factor if using spKt/V (eg. "eKt/V = 1.2, or spKt/V = 1.4").

Equilibrated Kt/V (eKt/V)

The dynamic interaction between urea concentrations in intra- and extra-cellular pools, results in reduced effectiveness of treatment because dialysis removes urea only from the extracellular pool, which is then refilled from the intracellular pool during and after dialysis. This results in a gradual rebound in urea concentration for approximately one hour after dialysis, so that if post-dialysis urea is measured immediately, then the treatment effect is over-estimated.

Equilibrated Kt/V attempts to correct for this by using a post-rebound urea measurement:

$$eKt/V = -\log_e [U_{\text{post-rebound}}/U_{\text{pre}}]$$

Due to the inconvenience of measuring urea post-rebound (an hour after dialysis has finished) a formula is used to adjust for this reasonably predictable effect using urea measured immediately. More than one equation has been published but there is very little difference between them. This one is known as the Tattersall version:

$$eKt/V = (spKt/V \cdot t) / (t + 35)$$

Apparent urea rebound is dependent on vascular access, so 35 is replaced by 22 in patients dialysing via a catheter. This method is non-biased and has most often been used in studies of dialysis dose, such as the HEMO study. Targets given in terms of other measures of dialysis dose such as URR may be useful in comparing units, but are not accurate for individual patients.

All forms of Kt/V (including eKt/V) implicitly use V to normalise for body size, whereas body surface area is conventionally used to normalise renal function. There are theoretical reasons to believe that normalisation of Kt/V to other body size parameters such as body surface area would be more useful, but these concepts have not gained widespread acceptance.

The Log-Ratio is a reasonable approximation of eKt/V since the underestimation (from ignoring ultrafiltration and urea generation) is offset by overestimation (from ignoring urea rebound). In fact, for a 4 hour session, with UF/TW = 0.02, in a fistula patient, the Log-Ratio is almost identical to eKt/V, with URR = 70 being equivalent to eKt/V = 1.2. However, in most other settings, Log-Ratio will underestimate or overestimate dose, so that the target URR required to achieve eKt/V = 1.2 needs to be varied, as in this table:

Urea Reduction Ratio equivalent to eKt/V = 1.2				
Time (h) by access type		UF/TW		
Fistula	Catheter	0.02	0.03	0.04
3.5		71.0	70.2	69.4
4.0		70.0	69.2	68.4
4.5	3.5	69.1	68.3	67.5
5.0	4.0	68.2	67.4	66.6
	4.5	67.4	66.6	65.8
	5.0	66.8	66.0	65.2

Appendix 2

Adjusting dialysis for residual function

Since residual renal clearance (Kru) is continuous, and dialysis clearance is intermittent (with Kt/V referring to clearance during a single dialysis session), the quantities

of both cannot simply be added. When it is planned to reduce dialysis dose by incorporating the contribution of residual function, it is necessary to somehow add these clearances so that the dialysis component is appropriate. Three methods of combining these clearances have been proposed.

Converting Kru to an equivalent eKt/V (Combined eKt/V)

In this method, residual kidney function is converted to an equivalent per-session eKt/V, by multiplying by a factor F, which empirically inflates the time over which residual clearance is measured, to account for its greater efficiency compared to that of dialysis, with the value of F depending on dialysis frequency. A “Combined Kt/V” is calculated:

$$\text{Combined eKt/V} = eKt/V_{\text{Dialysis}} + eKt/V_{\text{Kidney}}$$

$$eKt/V_{\text{Kidney}} = Kru \cdot F / Vu$$

where:

eKt/V_{Dialysis} is calculated as above

Vu = volume of distribution of urea (ml),
approximated by 580 * TW (kg)

F = 5500 (for thrice weekly schedules)

With the method above, a Combined eKt/V can be calculated and the dialysis component adjusted to achieve a target Combined eKt/V of 1.2.

Converting Kt/V to an equivalent renal clearance (EKRC)

An alternative method is to convert per-session Kt/V into an equivalent continuous renal clearance and then add it to Kru. Casino and Lopez computed kinetic estimates of combined dialysis and kidney urea clearance (normalized to volume) which they termed “equivalent renal urea clearance” (EKRC). In the absence of residual function, an eKt/V target of 1.2 equates to EKRC 13ml/min. For a thrice weekly schedule EKRC is given by the formula:

$$EKRC \text{ (ml/min)} = 1 + (10 \cdot eKt/V)$$

With this method Kru is added to EKRC and the dialysis component adjusted to achieve a total of 13ml/min.

Converting both eKt/V and Kru to a weekly dialysis dose (stdKt/V)

Dialysis schedule and dose can be converted to an equivalent weekly clearance, “Standard Kt/V” (stdKt/V) proposed by Gotch, based on kinetic models which relate urea generation to average weekly pre-dialysis urea. This allows comparison between schedules: a frequent schedule with stdKt/V = 2.1 is equivalent (in

terms of small solute clearance) to a thrice-weekly schedule with $eKt/V = 1.2$. Residual function can be incorporated into $stdKt/V$ (sometimes termed “Total Standard Kt/V ”) by formulas available [259].

Appendix 3

Quantifying convection

Convective clearance of a toxin depends firstly on the sieving coefficient. Sieving coefficient (SC) is a measure of the ease with which a solute passes through the membrane relative to solvent, so this depends largely on the relative size of the solute molecule and the membrane pore cross-section. It can be measured during pure ultrafiltration as the ratio of solute concentration before and after passing through the membrane. SC takes values between 0 (the molecule is unable to pass through the membrane) and 1 (the molecule passes just as easily as water).

Secondly, convective clearance depends on the ultrafiltration rate.

In pure haemofiltration, clearance is achieved entirely by ultrafiltration. The loss of fluid by ultrafiltration is replaced by infusion into the blood downstream of the filter (“post-dilution”). In this case, clearance (K) for any solute is equal to convective clearance (Kc) and can be calculated from:

$$K = Kc = Q_{uf} \cdot SC$$

where:

Q_{uf} = ultrafiltrate flow rate

In haemodiafiltration (HDF), there is a mixture of diffusion and convection. Diffusion reduces the concentrations in the ultrafiltrate, reducing Kc. Clearance in haemodiafiltration can be predicted by the following equation:

$$Kc = Q_{uf} \cdot SC \cdot ((Q_p - K_d) / Q_p)$$

$$K = Kc + K_d$$

where:

Q_p = plasma flow rate

K_d = diffusive clearance

The effect of this is to diminish the convective component. In post-dilution HDF, convection will always increase total clearance, but this increase is negligible for small solutes which diffuse easily (such as urea). For larger molecules (such as beta-2-microglobulin) convection can significantly and usefully increase clearance.

Pre-dilution HDF, in which replacement fluid is given upstream of the dialyser, is less commonly practiced, and more complex mathematically. Convection is similarly reduced by diffusion as above, but in addition both

convection and diffusion are substantially reduced by the dilutional effect of the replacement fluid. The ultrafiltrate rate and volume are usually adjusted to account for this.

In publications the convective component of HDF is quantified as the filtration volume. This means the total sessional filtration volume in post-dilution HDF, or the equivalent adjusted volume in pre-dilution HDF.

Appendix 4

Adding phosphate to dialysate

Cleen Ready-To-Use enema comes in a 133ml pack costing 68p (March 2017). The pack is designed to deliver a 118ml dose containing 21.4g of sodium acid phosphate (sodium dihydrogen phosphate dihydrate $NaH_2PO_4 \cdot 2H_2O$) and 9.4g sodium phosphate (disodium phosphate dodecahydrate $Na_2HPO_4 \cdot 12H_2O$). This gives a concentration of 1.38mmol/ml phosphate.

The acid concentrate, together with the added enema, will be diluted according to the proportioning ratio of the dialysis machine. The volume of enema (V_E) that needs to be added to the canister is given by:

$$V_E \text{ (ml)} = C_{PO4} \cdot V_{AC} \cdot DF / 1.38$$

where:

C_{PO4} = target dialysate phosphate
(0.4mmol/l is commonly used)

V_{AC} = volume of the acid concentrate (e.g. 6L)

DF = dilution factor for the dialysate
(eg. 35 for machine proportioning at 1 : 34)

Using these numbers, for example, gives an enema volume of 61ml to be added to the concentrate. Note that this formula depends on the formulation of the enema and is specific to Cleen.

This simple formula ignores the small change in concentrate volume, as the effect is below the 5% tolerance allowed for electrolyte concentrations for haemodialysis and related therapies (ISO 23500 Part 4). Albalate used the above formula to prepare dialysates with C_{PO4} between 0.48 to 1.12mmol/l, reporting good agreement between measured and target C_{PO4} using Gambro and Fresenius machines and a range of acid concentrates [260].

Sodium content in the phosphate-enriched acid concentrate will be reduced (since the enema sodium is 37g/l, compared to around 83g/l for an acid concentrate that proportions at 1:34, and 107g/l for one that proportions at 1:44). This will lead to a lower dialysate sodium (by 0.7 to 0.9mmol/l) with volumetric proportioning, and a higher concentrate pump rate with conductivity feedback. It is possible that this effect could trigger machine alarms, requiring machine re-programming.

Appendix 5

Haemodialysis tasks for shared care

List of dialysis-related tasks that an individual may choose to learn to perform, as part of shared care:

1. Washing your hands prior to all procedures and arm (as appropriate) if fistula or graft is used.
2. Recording your weight
3. Recording your blood pressure and pulse
4. Recording your temperature
5. Setting up your dialysis machine
6. Preparing your dressing pack
7. Programming your prescription on the dialysis machine
8. Putting your needles in or preparing your access line
9. Connecting your lines and commencing dialysis
10. Responding to alerts from your dialysis machine
11. Disconnecting lines and completing your dialysis
12. Applying pressure to needle sites after dialysis or
13. Locking your own access line
14. Administering any of your injections.

Appendix 6

Implementing intradialytic exercise

We suggest the following guidance for implementation of intradialytic exercise:

- a. Exercise should be supervised for greatest compliance and efficacy by an appropriately trained individual (e.g. physiotherapist, sport scientist, cardiac rehabilitation specialist or an assistant physiotherapist/dietitian/nurse with additional training from one of the former groups).
- b. Exercise should be completed between 30 min and two hours of the dialysis procedure.
- c. Exercise should be completed during all dialysis sessions (unless contraindicated).
- d. Exercise should include both aerobic (e.g. intradialytic cycling) and resistance (e.g. TheraBands and/or lifting of ankle weights) components of lower or upper body, dependent on access site.
- e. Exercise should be preceded by warm up activities (e.g. exercising for a minimum of five minutes, gradually increasing intensity until one half of prescribed training intensity is obtained).
- f. Exercise should be completed for at least 30 minutes per hemodialysis session.
- g. Exercise should be completed at moderate to vigorous intensity, ranging from 40-75% of VO_2 reserve or heart rate reserve (if a graded exercise test is completed). When a graded exercise test cannot be completed, and for muscle conditioning exercises, a rating of perceived exertion on the Borg

CR100 scale of “moderate” (20) to “strong heavy (50)” or on the Borg RPE scale of 12 to 15 can be used *with caution* as a method to prescribe exercise intensity.

- h. Volume of exercise should be progressed gradually by adjusting duration, frequency, and/or intensity until the desired exercise goal (maintenance) is attained.
- i. Exercise should be followed by cool down activities (e.g. exercising for a minimum of five minutes, starting at one half of prescribed training intensity and gradually decreasing intensity until exercise is stopped).
- j. Once patients are established exercising during dialysis, they should be encouraged to complete additional exercise on non-dialysis days.
- k. To enhance adoption and adherence in novice exercisers, moderate-intensity activity should be prescribed.
- l. To maintain exercise behaviour, behavioural strategies such as social support, goal setting and motivational interviewing should be implemented.

We suggest the following patient exclusion criteria/contraindications to exercise during haemodialysis:

- a. Less than three months after initiation of haemodialysis.
- b. Any uncontrolled medical condition including (but not limited to) infection or fever; recent (within 8 weeks) myocardial infarction or undiagnosed chest pain.
- c. Patient in class D (unstable condition) as per American Heart Association/American College of Sports Medicine Joint Position Statement: 1) unstable ischemia; 2) heart failure that is not compensated; 3) uncontrolled arrhythmias; 4) severe and symptomatic aortic stenosis; 5) hypertrophic cardiomyopathy or cardiomyopathy from recent myocarditis; 6) severe pulmonary hypertension; or 7) other conditions that could be aggravated by exercise (for example, resting systolic blood pressure >200 mm Hg or resting diastolic blood pressure >110 mm Hg; active or suspected myocarditis or pericarditis; suspected or known dissecting aneurysm; thrombophlebitis and recent systemic or pulmonary embolus).
- d. Symptomatic hyper- or hypotension.
- e. Signs and symptoms of deep vein thrombosis.
- f. Excessive inter-dialytic weight gain that severely impacts upon indices of fluid retention, e.g. blood pressure greater than 160/100; heart rate above 100 bpm; breathlessness at rest; or signs of substantial peripheral oedema.
- g. If diabetic, blood glucose above 16.7 mmol/L (300 mg/dL) AND patient is in ketosis (fruity breath, rapid breathing or shortness of breath, excessive

thirst, frequent urination, stomach pain, nausea, vomiting, fatigue or confusion), is dehydrated, or is feeling unwell.

- h. In individuals taking insulin and/or insulin secretagogues, if hypoglycaemia below 5.5 mmol/L (100 mg/dL) is observed, and glucose containing dialysate fails to elevate blood glucose sufficiently, advise patient to eat or drink approximately 15g carbohydrate and re-assess blood glucose concentration after 20 min. Repeat until blood glucose exceeds 5.5 mmol/L.

We suggest the following safety monitoring:

- a. Prior to exercise, ask patient how they feel, record resting blood pressure and heart rate, and if diabetic, record blood glucose concentration.
- b. During exercise, monitor signs and ask patient to report symptoms of pain, excessive fatigue, altered consciousness, overheating, cyanosis, anxiety, severe breathlessness, chest pain, dizziness/light-headedness.
- c. If hypertensive, regularly check blood pressure during exercise. If values exceed 220/105 mm Hg, reduce exercise intensity or cease exercising until blood pressure reduces.
- d. Use a rating of perceived exertion scale (Borg CR100 or Borg RPE scales) and ensure exercise intensity does not provoke responses greater than 50/strong heavy on the Borg CR100 or 15/hard (heavy) on the Borg RPE scale
- e. Post exercise, monitor blood pressure and heart rate until resting values are approximately obtained, observe patient for at least 20 min, and be aware of possibility of hypotension during remainder of the dialysis session.

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The National Institute for Health and Care Excellence (NICE) has accredited the process used by the Renal Association to produce its Clinical Practice Guidelines. Accreditation is valid for 5 years from January 2017. More information on accreditation can be viewed at www.nice.org.uk/accreditation. This guideline has also been endorsed by the British Transplantation Society.

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and the majority opinion carried. However this was not necessary for this guideline.

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Guideline

Japanese Society for Dialysis Therapy Clinical Guideline for “Maintenance Hemodialysis: Hemodialysis Prescriptions”

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for “Maintenance Hemodialysis: Hemodialysis Prescriptions” Guideline
Working Group, Japanese Society for Dialysis Therapy

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INTRODUCTION

The Japanese Society for Dialysis Therapy (JSDT) has published Clinical Guidelines for Maintenance Hemodialysis: Hemodialysis Prescription. These evidence-based guidelines focus on the characteristics of the dialysis performed in Japan. The number of elderly patients undergoing long-term hemodialysis (HD) is higher in Japan than in other countries. The purpose of the guidelines is to provide recommendation for long-term, stable HD. The main body of the guidelines shows the current recommended minimal standards for HD performed in Japan (i.e. HD at a blood flow rate of at least 200 mL/min using an ultrapure dialysis fluid with a flow rate of at least 500 mL/min and a high-performance membrane (HPM) dialyzer, three times per week for at least 4 h). Although most of the guidelines are evidence based, the recommendations for stably maintaining the condition of patients undergoing long-term HD are presented as opinions. Nevertheless, according to a report by the JSDT Renal Data Registry (JRDR), a considerable number of dialysis facilities have not followed the recommended minimal standards. We hope that at least the minimal standards

recommended in the guidelines will be adopted by all dialysis facilities.

The guidelines consist of three parts. The main part of the guidelines is in Chapters 1–4 and presents the basics of HD prescriptions, such as the removal of solutes (substances of low-to-middle molecular weight), control of body fluid, and evaluation of treatment effect. The patients targeted in these prescriptions are HD outpatients in a stable condition; inpatients and patients with severe complications are excluded.

In Chapter 5, blood purification methods that lack sufficient supportive evidence but may be effective to improve the prognosis of HD patients are explained. Therefore, the evidence level and advisability of these methods are not shown in Chapter 5.

Chapter 6 presents the guidelines for pediatric HD. The number of pediatric HD patients is small and sufficient evidence to formulate guidelines is not available in Japan. Therefore, the evidence level and advisability of HD in pediatric patients are not shown in Chapter 6.

Although survival rates related to dialysis therapy in Japan are the highest worldwide (1), there are still many ongoing discussions on whether or not Japan should have a specific dialysis prescription guideline to achieve standardization. This high HD efficacy rate is based on the comparison between Japan and other countries; there are still differences in survival rate among facilities in Japan. In addition, the current quality level of HD may vary in the future, depending on the changes in economic and social conditions.

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TABLE 1. Grading of recommendations and evidence[†]

Grade for strength of recommendation	Strength	Wording
Level 1	Strong	"We recommend . . . should"
Level 2	Weak	"We suggest . . . might"
No grade [‡]	–	"It is reasonable"
Grade for quality of evidence		Quality of evidence
A		High
B		Moderate
C		Low
D		Very low

[†]Each statement is shown as a combination of the grade and level of evidence, such as 1A or 2C. [‡]The expectation is that it is reasonable to follow this statement as it is a consensus statement based on expert opinion.

Therefore, we believe that this is the appropriate time to establish guidelines, because dialysis treatment has matured technologically, and a certain level of quality of HD has been attained.

Evidence levels and strengths of recommendations are defined and presented in combination, based on an evidence grading system adapted from the Kidney Disease Improving Global Outcomes position paper (2) and JSDT modification (3,4). As shown in Table 1, the strength of the recommendation is graded as either 1 ("strong": i.e. "we recommend" you do it, for positive recommendations, and "we recommend" you do not do it, for negative recommendations) or 2 ("weak": "we suggest" you do it, or "we suggest" you do not do it). For the final category, "No grade" ("it is reasonable"), there is insufficient evidence available to give a grade; however, these ungraded statements are based on a consensus of expert opinion, and the expectation is that consideration should be given to follow the statement.

CHAPTER 1 DIALYSIS DOSE (SMALL SOLUTES) AND DIALYSIS TIME

Statements

1. Dialysis dose is expressed by the single-pool Kt/V for urea (spKt/V). (1B)
2. Measurement of the dialysis dose is done at least once a month.
3. Recommended delivered dialysis dose by spKt/V is the following:
 - 1) The minimal adequate dose is 1.2. (1B)
 - 2) The target dose is 1.4 or higher. (2B)
4. The recommended minimal dialysis time is 4 h or longer. (1B)

*These recommendations are for patients with maintenance HD three times per week for less than 6 h.

Commentary

1. Dialysis Dose (Small Solutes)

Index and frequency of measurement

Among small solutes, urea (molecular weight, 60), a final product of protein metabolism impaired by uremia, is a clinically useful marker (5,6). Urea is water-soluble and diffuses across the cell membrane almost freely. A simple mathematical kinetic model, termed the single-pool model (also known as the one-compartment model), can be applied to urea, because urea is assumed to be uniformly distributed in the body fluid (7). In addition, the National Cooperative Dialysis Study (NCDS) conducted in the USA demonstrated that time averaged concentration of blood urea nitrogen (TAC_{BUN}) and protein catabolic rate (PCR, a nutrition index) are important factors related to the prognosis of dialysis patients, including complications and death (8). In the post hoc analysis of NCDS, Gotch and Sargent (9) demonstrated the usefulness of Kt/V for urea calculated from a single-pool model (spKt/V) where "K" is a clearance for urea (mL/min), "t" is the dialysis time (min), and "V" is the volume of urea distribution ($\approx$ total body fluid volume) (mL). Since then, spKt/V has been widely accepted and used as a dialysis dose. Many studies have been carried out using spKt/V as an index. In particular, several equations of spKt/V have been developed by Daugirdas (10), one of which, the so-called "second generation of Daugirdas' equation" (Daugirdas' equation), is used worldwide. In Japan, an equation developed by Shinzato et al., which correlates well with Daugirdas' equation (11), has been used for many years. Considering the above as background, the guidelines adopted spKt/V, frequently used at dialysis facilities, as an index. It is recommended to measure dialysis dose regularly at least once a month, along with regular blood tests.

Dialysis dose and prognosis

After NCDS, many observational studies on the relationship between dialysis dose and prognosis were conducted in Europe and in the USA. Results showed that crude death rate decreases with increasing dialysis dose and with increasing time (12,13), the mortality decreases with increasing dialysis dose (14–17), and the decrease in mortality slows down when the urea reduction rate (URR) is approximately 65% (spKt/V $\approx$ 1.2) (14) or spKt/V is approximately 1.3 (16). On the basis of these findings, the guidelines of the National Kidney Foundation in the USA, the "Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines," recommended spKt/V of 1.2

as the minimal adequate dose (18). In the subsequent second large-scale prospective intervention study on dialysis dose, the Hemodialysis (HEMO) study (19), improvement of prognosis was not observed when the dialysis dose was increased to spKt/V of more than 1.2 as recommended by the KDOQI guidelines. However, note that the dialysis prescription in the HEMO study was short high-efficiency HD and the dialysis prescriptions were quite different from those in Japan.

According to the JRDR report, mortality rate tends to decrease with increasing dialysis dose, similar to the results of studies in foreign countries. The decrease in mortality rate is statistically significant for spKt/V of up to 1.8 using $1.0 \leq \text{spKt/V} < 1.2$ as a standard reference (20,21). A recent report has also shown that the decrease in mortality was statistically significant for spKt/V exceeding 1.8 using $1.4 \leq \text{spKt/V} < 1.6$ as a reference (22). In addition, the possibility of decreasing mortality rate by increasing dialysis dose through prolonged dialysis time, not by short high-efficiency HD, was suggested.

Issues related to Kt/V

Previous observational studies showed a relative increase in mortality rate (reverse J-shaped curve phenomenon) at $\text{spKt/V} \geq 1.68$ (23) or $\text{URR} \geq 71\%$ ($\text{spKt/V} \approx 1.4$) (24). However, the results in Japan indicate that mortality gradually decreases for spKt/V of up to approximately 1.8, and the reverse J-shaped curve phenomenon was not observed (20–22). The factors underlying the reverse J-shaped curve phenomenon may be the high proportion of patients with a small body size and thin malnourished patients in the high dialysis dose group. In other words, the phenomenon is due to the fact that $\text{Kt/V}_{\text{urea}}$ is affected by the body size of patients, although the adverse effect of a high dialysis dose may not be excluded (23,24). When the relationship between dialysis dose and prognosis is examined, the mortality decreases up to Kt_{urea} (that is not indexed by V) values of 50.7 L (25) and 47.7 L (22) for the patients in the USA and Japan, respectively, and the reverse J-shaped curve phenomenon was not observed with increasing dialysis dose. From these findings, it may be difficult to determine overdialysis only from $\text{Kt/V}_{\text{urea}}$.

Sex, body size, and dialysis dose

According to previous reports, lower mortality at higher spKt/V was observed to be more pronounced in females than in males (26–28). The reasons behind this are considered to be a higher urea production per unit body fluid volume in females, or the higher sensitivity to uremic toxin in females, rather than the

smaller body size of females (29). Therefore, when dialysis dose is expressed by $\text{Kt/V}_{\text{urea}}$, the target dialysis dose may not be the same between sexes (30,31).

The factors related to body size (body mass index [BMI], body weight [BW], body fluid volume, body surface area [BSA]) are independent prognosis factors and the relationship between dialysis dose and prognosis is reported to depend on body size (32–34). The reason behind this is the difference in the body composition depending on body size. Specifically, because the organs producing uremic toxin are relatively larger in patients with a small body size than in patients with a large body size, a higher dialysis dose may be required for patients with a small body size when the dialysis dose is expressed by $\text{Kt/V}_{\text{urea}}$ (35,36). Therefore, normalizing methods of dialysis dose using uremic toxin generation (metabolism) level or indices related to metabolism (BSA and $\text{BW}^{0.67}$) have been proposed (37–40). A report showed that dialysis dose corrected by using BSA correlated with mortality and that the reverse J-shaped curve phenomenon was not observed (41).

Recommended dialysis dose

According to the KDOQI guidelines (18), the minimal adequate dose is spKt/V of 1.2 and the target dose is spKt/V of 1.4; a higher dose is recommended for females and patients with small body size ($V \leq 25$ L). The European Best Practice Guidelines (EBPG) (42) recommend the prescribed dose (prescribed Kt/V) to be a urea-equilibrated Kt/V (eKt/V) of 1.2 ($\approx \text{spKt/V}$ of 1.4), considering the possibility that the delivered dose is lower than the prescribed dose. Moreover, eKt/V of 1.4 is recommended for females and patients with high comorbidities. In Japan, a minimal adequate dose higher than that stated in the guidelines in Europe and the USA, that is, an $\text{spKt/V} \geq 1.4$, is desirable on the basis that

- 1) the higher the Kt/V , the lower the mortality in observational studies in Japan and,
- 2) the body size of Japanese patients is significantly smaller than that of patients in Europe and the USA.

Note that spKt/V of 1.2 is recommended as the minimal adequate dose for patients for whom a high dialysis dose is not applicable or patients with a large body size.

2. Dialysis Time

Dialysis time and prognosis

To increase $\text{Kt/V}_{\text{urea}}$, it is necessary to increase dialysis efficiency (K), dialysis time (t), or both.

According to the JRDR report, the mortality rate of patients with a dialysis time of less than 4 h increases with decreasing dialysis time, and the mortality rate of patients with a dialysis time of more than 4 h decreases with increasing dialysis time among patients on conventional dialysis [three times per week for 3 to 5 h] (20–22). The Dialysis Outcomes and Practice Patterns Study (DOPPS) (43,44) also showed that mortality rate decreases with increasing dialysis time up to 4.5 h. When the results of studies in Japan are compared with those in Europe and in the USA, the decrease in mortality with increasing dialysis time is more pronounced in Japan (43,44). In addition, the poor prognosis of patients receiving dialysis for less than 4 h has been shown in many reports (45–47). A Japanese report showed that a decrease in mortality rate may not be expected even when Kt/V_{urea} is increased for the patients receiving dialysis for less than 4 h (22).

Recommended dialysis time

Dialysis time is one of the important independent factors that determine dialysis dose. According to Japanese reports, mortality rate decreases with increasing dialysis duration adjusted with Kt/V_{urea} (20,21). In DOPPS, dialysis time was examined by stratifying the patients with different values of Kt/V_{urea} , revealing that mortality rate decreases with increasing dialysis time, regardless of Kt/V_{urea} (43). These findings strongly suggest that dialysis time is a prognostic factor that is independent of Kt/V_{urea} . In addition, dialysis with longer time has an advantage in controlling body fluid volume, providing slower ultrafiltration rate (UFR). For example, the incidence of dialysis hypotension decreases owing to a decreased UFR, and the treatment of hypertension is facilitated, because dry weight (DW) can be easily maintained (43,44,48–50). From the above, the recommended dialysis time is 4 h or longer for patients receiving HD three times per week in the guidelines.

Blood flow rate and dialysis fluid flow rate

To increase removal of small solutes, such as urea, increasing not only dialysis time but also blood flow rate (Q_B) and dialysis fluid flow rate (Q_D) is effective (51,52). However, there have been few studies on the relationship between Q_B and prognosis to the best of our knowledge. According to the JRDR analysis (22,53), a decrease in mortality rate with increasing Q_B for up to 250–300 mL/min was suggested when $200 \leq Q_B < 220$ mL/min was used as the reference. Although dialysis facilities in Japan are concerned about the increased load on the cardiovascular

system with increasing Q_B , an increase in blood flow of the vascular access or acute changes in cardiac function or blood pressure was not observed for $400 \leq Q_B < 500$ mL/min (54–59). In fact, an increase in mortality rate was not observed for high-efficiency dialysis performed even under $Q_B \geq 400$ mL/min (56,60). In addition, among patients in the high dialysis dose group with high Q_B in the HEMO study, the incidence of death related to cardiac events did not increase (19,61). On the other hand, to the best of our knowledge, there has been no report on the relationship between Q_D and prognosis, particularly by intentionally changed Q_D . Considering that the effective $Q_B : Q_D$ is approximately 1:2 (52,62,63), prescription of the appropriate Q_B and Q_D is desired in order to effectively utilize the remaining and limited treatment time of patients and new highly functional dialyzers (51,52,63–67).

CHAPTER 2 DIALYSIS DOSE AND EFFECT: β_2 -MICROGLOBULIN (β_2M)

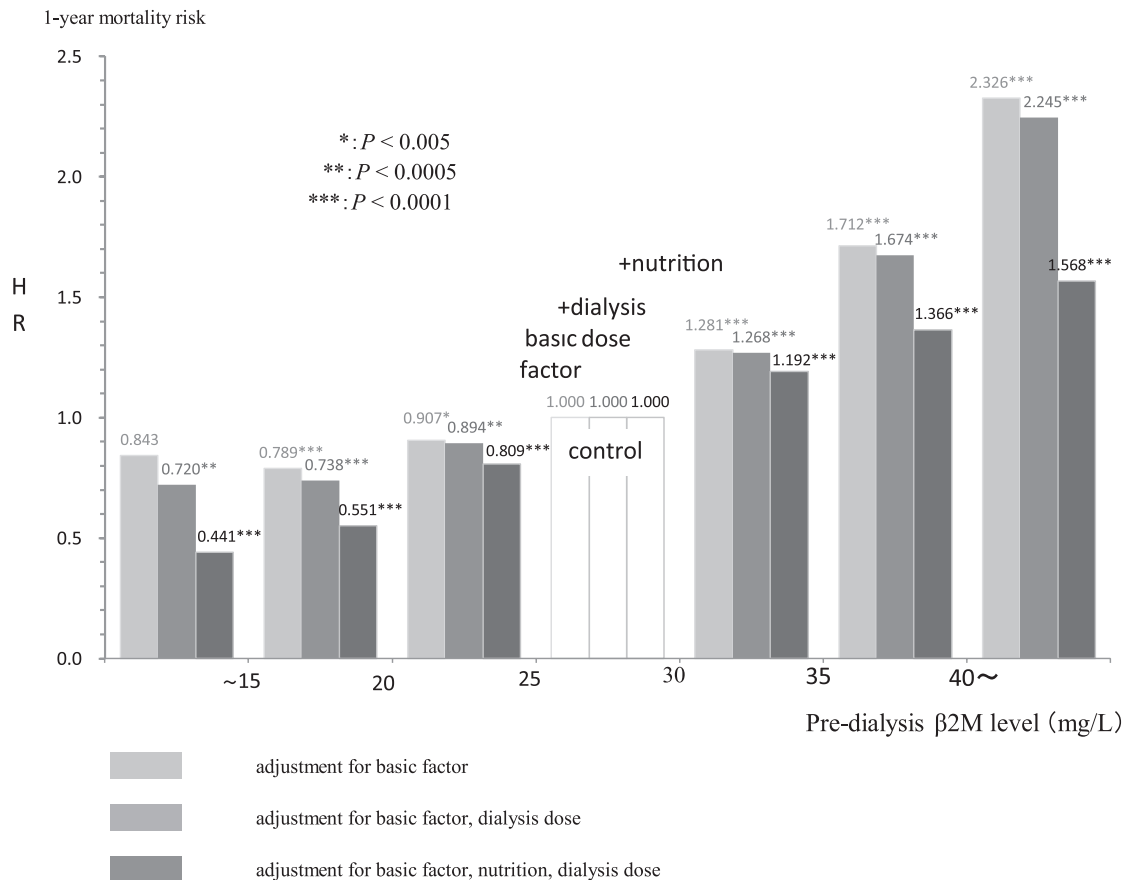
Statements

1. Predialysis serum β_2M level at the maximum intervals is a factor related to prognosis. (1B)
2. The dialysis conditions are recommended to achieve the maximum predialysis serum β_2M concentration < 30 mg/L. (2C)
3. The dialysis conditions are preferred to achieve the maximum predialysis serum β_2M concentration of 25 mg/L. (Opinion)
4. Decreasing the concentrations of substances with greater than β_2M can improve the prognosis of patients. (Opinion)

Commentary

1. β_2M as Uremic Substance

β_2M is the main constituent protein in dialysis amyloidosis, a complication of long-term dialysis treatment, and it needs to be removed proactively during HD therapy (5,68–69). With increasing number of years on dialysis, there is an increase in the number of patients who report symptoms of bone pain, joint pain, mobility disorder, and neuralgia. The clinical condition that is common to these patients is the accumulation of amyloid in tissues such as bones, synovium, and ligaments. These symptoms are called dialysis-related amyloidosis (DRA) (70,71). In Japan, dialysis membranes that can efficiently remove β_2M have been recommended, as β_2M was identified as the main constituent protein



Pre-dialysis serum β2-microglobulin level and outcome

β2M (mg/L)	adjustment for basic factor			adjustment for basic factor, dialysis dose			adjustment for basic factor, nutrition, dialysis dose		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
<15	0.843	(0.711~1.000)	0.0503	0.720	(0.606~0.854)	0.0002	0.441	(0.371~0.525)	<0.0001
15≤<20	0.789	(0.714~0.872)	<0.0001	0.738	(0.668~0.815)	<0.0001	0.551	(0.498~0.609)	<0.0001
20≤<25	0.907	(0.853~0.965)	0.0019	0.894	(0.841~0.951)	0.0004	0.809	(0.761~0.861)	<0.0001
25≤<30	1.000	(control)	control	1.000	(control)	control	1.000	(control)	control
30≤<35	1.281	(1.211~1.355)	<0.0001	1.268	(1.199~1.341)	<0.0001	1.192	(1.127~1.261)	<0.0001
35≤<40	1.712	(1.594~1.839)	<0.0001	1.674	(1.558~1.798)	<0.0001	1.366	(1.271~1.467)	<0.0001
40≤<	2.326	(2.148~2.519)	<0.0001	2.245	(2.073~2.431)	<0.0001	1.568	(1.447~1.700)	<0.0001
no data	1.409	(1.339~1.482)	<0.0001	1.283	(1.217~1.351)	<0.0001	1.053	(0.996~1.112)	0.0672

FIG. 1. Predialysis serum β2M level and mortality. β2M, β2-microglobulin; CI, confidence interval; HR, hazard ratio.

in dialysis amyloidosis by Gejyo et al. (72). It is also reported, however, that there is no correlation between serum β2M concentration and the incidence of dialysis amyloidosis (73).

Recently, researchers have reported that β2M is not only a uremic toxin that should be removed but also a predictor related to the prognosis of dialysis patients (74–76). The mortality rate decreased when the predialysis serum β2M concentration was from 27.5 to 34 mg/L, as reported by the HEMO study and Okuno et al. (76), suggesting that the decrease in concentrations of uremic substances, including β2M, is important in dialysis therapy. In the JRDR report (as of December 31, 2009), predialysis serum β2M levels

were divided into groups at intervals of 5 mg/L. The 1-year mortality rate of the patients who belong to groups with a level lower than 25 mg/L and that of the patients in groups with a level 30 mg/L or higher was compared with the mortality rate of a group with $25 \leq$ predialysis serum β2M level < 30 mg/L as a reference (Fig. 1) (77). When the data were adjusted using basic factors such as sex, age, number of years on dialysis, and primary disease, mortality rate increased with increasing predialysis serum β2M level. This trend remains the same even when the data are further adjusted for Kt/V. This finding suggests that the observed relationship between predialysis serum β2M level and prognosis is almost

independent of the dialysis dose for small solutes. When the data were further adjusted for nutrition-related indices, such as PCR, albumin level, total cholesterol level, BMI, and percent creatinine production rate, the mortality rate of the group with a predialysis serum $\beta 2\text{M}$ level less than 25 mg/L decreased further, and the high mortality of the group with a predialysis serum $\beta 2\text{M}$ level of 30 mg/L or higher also decreased. Therefore, this finding suggests that the prognosis of patients with good nutritional status is improved by further decreasing the serum $\beta 2\text{M}$ level.

According to the JRDR report (as of December 31, 2010), approximately 71% of patients had a predialysis serum $\beta 2\text{M}$ concentration of less than 30 mg/L (78). A predialysis serum $\beta 2\text{M}$ concentration of less than 25 mg/L is considered to be achievable by optimizing the dialysis conditions.

2. Determination of Dialysis Conditions

In current dialysis therapy with super high-flux dialyzers, $\beta 2\text{M}$ can be removed by diffusion without the aid of convection (ultrafiltration), because the molecular weight of $\beta 2\text{M}$ is not very high and is just about 11 800 (79). Therefore, one of the efficient methods for decreasing $\beta 2\text{M}$ concentration in HD is increasing blood flow rate (Q_B) (80), which would also increase the so-called internal filtration. In addition, increasing the area of dialysis membranes increases the rates of diffusion and internal filtration, thus providing higher clearance for $\beta 2\text{M}$ (80). Furthermore, serum $\beta 2\text{M}$ concentration can be more efficiently decreased when a dialysis membrane with a higher permeability for $\beta 2\text{M}$ is used (80). The reduction rate for $\beta 2\text{M}$ per dialysis session is reported to be 60% or more under $Q_B \geq 200$ mL/min using an HPM dialyzer with $\beta 2\text{M}$ clearance ≥ 50 mL/min (80). In addition, use of a $\beta 2\text{M}$ adsorption column is another option to obtain a high $\beta 2\text{M}$ removal rate (81). Increasing the dialysis time to more than 4 h is also known to be effective (82).

It is important to monitor serum $\beta 2\text{M}$ concentration regularly. The monitoring interval is recommended to be every 3 months. Purification of dialysis fluid is most important for dialysis performed under the above-mentioned conditions and the use of ultrapure dialysis fluid is indispensable. Serum albumin concentration should also be measured regularly, because some HPM dialysis membranes cause a large amount of albumin loss (refer to Chapter 5-1). In Japan, hemodiafiltration (HDF) and protein-permeable HD have been actively carried out, and it has been frequently reported that the prognosis of patients is improved by decreasing

the concentrations of substances greater than $\beta 2\text{M}$ (79,83–86). Then it is important to prescribe dialysis conditions to achieve effective clearance of such substances.

CHAPTER 3 OPTIMIZATION OF DW

Statements

1. Body fluid control in dialysis patients is important. BW gain after maximum interdialytic period is within 6%. (2B)
2. A fluid removal rate of 15 mL/kg/h or lower is recommended. (2B)
3. To control the BW gain, dialysis patients are requested to receive guidance on limitations of salt and water intake. (1B)
4. Quality of life (QOL) and prognosis of dialysis patients depend on the optimization of DW. (2B)

Definition of DW

The term DW was first proposed by Thomson et al. in 1967 (87) and is the BW of patients after the maximum removal of extracellular fluid by dialysis. DW is further defined as follows:

1. The BW of a patient without symptoms of overhydration, such as edema.
2. The BW of a patient when the amount of body fluid is reduced to the minimum by fluid removal during dialysis.
3. The BW of a patient who expects to develop hypotension or shock with any further fluid removal.

The DW of a patient is the BW when the patient may have gone into shock as a result of any further removal of fluid. The DW based on this definition is the “true DW.” Several ultrafiltration methods are currently used, including extracorporeal ultrafiltration method (ECUM), HDF, and long-time dialysis. Fluid removal to a state of “true DW” is possible if the patients undergo dialysis for a long duration; however, patients may go into shock. The concept of DW that is the BW of patients following the removal of extracellular fluid by dialysis is widely accepted even today.

In this chapter, as the index of DW, we use the “BW at which an appropriate volume of body fluid is maintained, a marked decrease in blood pressure does not occur during dialysis, and the load to the cardiovascular system is small for long-term dialysis life” defined in the JSDT guidelines for management of cardiovascular diseases in patients on chronic HD (88).

An appropriate control of body fluid eventually leads to normal blood pressure of patients, which is important in terms of improving the QOL and prognosis of dialysis patients.

Commentary

1. Body fluid control in dialysis patients is important. BW gain after maximum interdialytic period is within 6%.

The amount of body fluid in dialysis patients is dependent on the amounts of salt and water intake, urine volume, and amount of fluid removed by dialysis. Improper control of body fluid volume induces hypertension and adversely affects the cardiovascular system (89–92). Although there is also a discussion on whether the maximum allowable BW gain of 6% is appropriate or not, according to the JRDR report, the prognosis of patients with BW gain $\leq 2\%$ or $\geq 6\%$ in interdialytic period is poor (93,94).

According to the United States Renal Data System (USRDS), a BW gain $\geq 4.8\%$ leads to a poor prognosis (95). There are several other reports: BW gain $\geq 5.7\%$ leads to a poor prognosis (96); BW gain = 3.5% is appropriate (97); and mortality rate is the lowest in patients with a BW gain in the range of 2.5–5.7% of DW (98–100). However, these are all observational studies and no randomized controlled trials (RCTs) have been done that provide evidence. Then the guidelines recommend that BW gain after a 2-day interdialytic period is within 6% on the basis of the reports by JRDR.

2. A fluid removal rate of 15 mL/kg/h or lower is recommended.

The rate of fluid removal is not necessarily based on sufficient medical data. However, a fluid removal rate of 15 mL/kg/h is equivalent to a fluid removal of 6% of total BW in a 4-h dialysis. Excessive fluid removal may adversely affect prognosis, as reported by the JRDR, that is, the prognosis of patients with a BW gain $> 6\%$ is poor (94) and a dialysis duration < 4 h leads to a poor prognosis (94). Therefore, a fluid removal rate of 15 mL/kg/h is reasonable.

Results in DOPPS showed that a fluid removal rate of 10 mL/kg/h or higher increases mortality rate (43); this report, however, does not aim to evaluate an optimal fluid removal rate. According to a 5-year prospective multicenter study, the mortality rate increases at fluid removal rate ≥ 12 mL/kg/h (100).

The guidelines recommend a BW gain of less than 6% in a maximum interdialytic period as stated in Statement 1. If a BW gain of 6% is removed in a 4-h

treatment, a fluid removal rate of 15 mL/kg/h is derived. Similar results are obtained by the analysis of the relationship between the fluid removal rate and prognosis by the JRDR (94).

In actual dialysis, food intake during dialysis, the saline load by priming, and the amount of saline used for blood return are added, and the fluid removal associated with these factors is not reflected by BW. Therefore, if a fluid removal rate of 15 mL/kg/h is followed, BW is decreased by approximately 5% by dialysis for 4 h. Patients with a BW gain greater than 5% should receive guidance on limiting salt intake first. If the BW cannot be controlled by limiting salt intake, a dialysis longer than 4 h is taken into consideration.

Recent papers have reported that a dialysis time of 5 h produces a better prognosis than that of 4 h (49,100). According to the JRDR report, better prognosis is obtained for 4.5 or 5 h dialysis than for 4 h dialysis (94). Therefore, it is recommended to prolong the dialysis time rather than to carry on 4 h dialysis with an unreasonably high fluid removal rate.

3. To control BW gain, dialysis patients are requested to receive guidance on limitations of salt and water intake.

BW gain during the interdialytic period indicates the accumulation of body fluid and salt in the body. A serum Na concentration of 140 mEq/L is equivalent to a saline solution of 8.2 g/L. Namely, accumulation of 8.2 g of salt in the body means accumulation of 1 L of water (amount of body fluid = BW). As stated in Statement 1, to suppress a BW gain within 6% after the maximum interdialytic period, control of salt intake is indispensable. By limiting salt intake, blood pressure decreases (101,102), body fluid volume becomes normal (103), and thirst is alleviated, which reduces the amount of water intake (103–105).

The KDOQI guidelines recommend a daily salt intake of 5 g or less (106). A daily salt intake of 5 g is equivalent to a BW gain of 1.5 kg during the interdialytic period. Indeed, 1 g of salt is excreted with the sweat and stool. However, Na salts other than NaCl are included in the diet and no correction is needed for these salt intake levels. Medical staff should limit the amount of salt intake of patients with a high BW gain and should not limit the amount of water intake without limiting the amount of salt intake of such patients. Limiting the amount of salt intake is of primary importance for patients with a high BW gain.

For patients with hyponatremia, limiting the amount of water intake is recommended. For most patients, predialysis serum Na concentration is in the range of 136–145 mEq/L. The amount of water intake should be limited for patients with predialysis serum Na level ≤ 135 mEq/L. The sources of fluid leading to excess water intake include rice gruel, tea, and water for oral medicine.

4. QOL and prognosis of dialysis patients depend on optimization of DW.

Scribner stated that administration of drugs for antihypertension is not necessary for dialysis patients if their DW is properly maintained (107). Proper control of body fluid could achieve normal blood pressure in most dialysis patients (108,109). As stated above, improper control of body fluid volume induces hypertension and adversely affects the cardiovascular system. Therefore, the prognosis of dialysis patients can be improved by optimizing DW (48,104,106,110–113). The decrease in blood pressure during dialysis causes muscle cramps and general malaise after dialysis, as well as poor outcomes (93,114). Setting excessively high DW would induce a burden on the heart, which may lead to a need for emergency dialysis.

APPENDIX I

Optimal salt intake

In the formulation of the guidelines, we considered a salt intake of less than 6 g/day, which is recommended for patients with hypertension by the Standards for Dietary Prescription for Patients with Chronic Kidney Disease 2007 (115), the Japanese Society of Hypertension (116), and the Japan Diabetes Society. However, this value is not included in the statements, because a salt intake of 6 g/day is equivalent to a BW gain of 2.2 kg after a 2-day interdialytic period, that is, 7.3% BW gain for patients with a BW of 30 kg.

APPENDIX II

Determination of DW

In general, the following are used as indices for determining DW.

- ① No marked decrease in blood pressure during dialysis.
- ② No hypertension (blood pressure is approximately 140/90 mm Hg at the start of the first dialysis in a week).
- ③ No edema.
- ④ No lung congestion on chest X-ray images.

- ⑤ A cardiothoracic ratio of 50% or less (53% or less for female patients).

However, each of the above indices has problems and we should always pay attention to the following exceptions.

- ① (No marked decrease in blood pressure during dialysis.) Blood pressure decrease is caused by dysfunction of the autonomic nervous system, decreased cardiac function, arrhythmia, and acetate intolerance, in addition to the decrease in circulating blood volume during fluid removal. These factors should be eliminated.
- ② (No hypertension [blood pressure is approximately 140/90 mm Hg at the start of the first dialysis in a week.]) A DW decrease of approximately 0.3 kg per week is desirable to decrease DW for the purpose of controlling blood pressure. One should pay attention to the fact that a decrease in blood pressure occurs several weeks after the decrease in DW (time lag phenomenon) (117).
- ③ (No edema.) Factors that worsen symptoms of edema, such as hypoalbuminemia and venous thrombosis, should be eliminated.
- ④ (No lung congestion on chest X-ray images.) Lung congestion can continue for patients with decreased cardiac function and left heart failure.
- ⑤ (A cardiothoracic ratio of 50% or less [53% or less for female patients.]) For patients with myocardial hypertrophy, valvular disease, decreased cardiac function, transverse position of the heart, increased shunt blood flow, and marked anemia, the cardiothoracic ratio does not necessarily reflect the circulating blood volume. The cardiothoracic ratio should always be evaluated on a regular basis.

When the “BW of patients with an appropriate amount of body fluid, without the risk of marked decrease in blood pressure during dialysis, and with the long-term dialysis treatment with a limited load to the cardiovascular system” (88) defined in the guidelines for management of cardiovascular diseases in patients on chronic HD by the JSDT is used as the index of DW, the following questions may arise.

- ① What is the optimal body fluid volume?
- ② What is the extent of blood pressure decrease during dialysis?
- ③ What is the BW at which the load on the cardiovascular system is small for long-term dialysis?

Please refer to the JSDT guidelines for the determination of DW (88).

CHAPTER 4 EVALUATION OF DIALYSIS QUALITY IN ORDER TO ACHIEVE THE OPTIMAL DIALYSIS DOSE AND SUFFICIENT CLINICAL EFFECTS

Statements

1. The therapeutic efficacy of dialysis is evaluated regularly using both short-term and medium- to long-term indices. (1B)
 - 1) Intra-dialytic hemodynamics and the efficiency of removing small solutes are used as the short-term indices.
 - 2) Predialysis serum β 2M concentration, nutritional status, and QOL are used as the medium- to long-term indices.
2. Dialysis prescription is changed based on the evaluation of dialysis treatment to satisfy the above indices. (Opinion)

Commentary

The aim of regular maintenance dialysis treatment is to provide longer survival with higher QOL of patients. To this end, dialysis facilities should regularly evaluate whether the dialysis dose is high enough to improve the uremic symptoms of patients. The therapeutic efficacy of dialysis should be evaluated both by short-term indices, including the safety and stability of each dialysis session and the efficiency of removing uremic toxins, and medium- to long-term indices, including maintenance levels of uremic toxins, improvement of uremic symptoms, and nutritional status.

1. Evaluation of Treatment Effect Using Short-Term Indices

The short-term indices include the intra-dialytic hemodynamic changes and the efficiency of removing small solutes. To assure a sufficient dialysis dose, safe and stable dialysis treatment should be consistently provided to patients. In this respect, intra-dialytic hypotension is the main issue. A marked blood pressure decrease during dialysis and postdialysis orthostatic hypotension are the factors that worsen the prognosis of patients (114,118). Causes of dialysis hypotension include inappropriate DW, decrease in the circulating plasma volume caused by rapid fluid removal, deteriorated cardiac function, and dysfunction of the autonomic nervous system. Causes of intra-dialytic hypotension should be immediately clarified and be treated (88).

The efficiency of removing small uremic toxins during each dialysis session, particularly the normalized urea clearance (Kt/V), has been proved to be one of the prognostic factors of dialysis patients by

various cross-sectional and cohort studies. In these studies, the target Kt/V to decrease mortality rate has been addressed (9,20). In the recent analysis of JRDR, Kt/V is identified as an independent prognostic factor (22). The guidelines recommend a regular monthly monitoring of Kt/V (refer to Chapter 1).

2. Evaluation of Treatment Effect Using Medium- to Long-Term Indices

The treatment effect should also be evaluated using medium- to long-term indices, such as the maintenance level of uremic toxins (predialysis serum β 2M concentration), nutritional status, and QOL indices (e.g. depression, sleep disorder), which are confirmed to be closely related to the dialysis dose and prognosis of the patients.

Early in the history of dialysis therapy, the target substances of dialysis were small solutes, such as urea and phosphate. However, in the last two decades, the target has been changed to β 2M, and other low molecular weight proteins (LWMPs) greater than β 2M, and protein-bound uremic toxins. Among these uremic toxins, only β 2M can be commercially measured worldwide and has been proved to be closely related to uremic symptoms and DRA. It was also found in previous major cohort analyses that the predialysis serum β 2M level is a prognostic factor (74,76). From the above, the guidelines recommend regular monitoring of predialysis serum β 2M level as explained in Chapter 2.

Nutritional status is one of the most important prognostic factors (119) and is a good medium- to long-term dialysis index. In particular, muscle mass estimated from percent creatinine generation rate (120) is an independent prognostic factor (121). Dialysis prescription and nutritional care that can maintain muscle mass are essential factors for the success of treatment. The nutritional status should be evaluated comprehensively by the subjective assessment of nutritional status, physical measurements, body composition analysis, and blood biochemical parameters. Malnutrition in dialysis patients is a complex of various factors, such as the accumulation of uremic toxins, weak inflammatory responses caused by poor biocompatibility of dialysis treatment, poor appetite, and nutrient loss during dialysis (122). To develop a treatment intervention after nutritional assessment, causes of malnutrition should be clarified. First, the presence of inflammation should be excluded. Therefore, it is desirable that serum C-reactive protein is also measured in the nutritional screening. Repeated nutritional assessment at least once every 6 months is recommended to evaluate the effect of the intervention.

TABLE 2. *Change in dialysis prescription*

Increase (decrease) dialysis efficiency
• Increase (decrease) blood flow rate
• Increase (decrease) dialysate flow rate
• Increase (decrease) membrane area of dialyzer
• Change the membrane type of dialyzer
Increase (decrease) the duration and frequency of dialysis
Use of special dialysis membrane
• High performance membrane
Addition of filtration-based treatment
• Online hemodiafiltration

Among uremia-induced neuropsychiatric symptoms that deteriorate the QOL of dialysis patients, depression (123), insomnia (124), and pruritus (125) are reported to be prognostic factors. It is reported that most uncomfortable uremic symptoms would disappear when nocturnal long home HD is carried out (126). It suggests that underdialysis is one of the most important keys that cause the multiple complaints in dialysis patients. It is recommended to develop an appropriate dialysis prescription to improve such symptoms, instead of simply treating symptoms by medications.

3. Changing Dialysis Prescription

When the current dialysis prescription provided to a patient is considered to hinder improvement of the uremic symptoms or to adversely affect the daily life of the patient, the dialysis prescription should be changed as summarized in Table 2. Unfortunately, we are not able to propose a common dialysis prescription that would be effective for every patient and every symptom. One prescription may cause different responses in each patient. Therefore, the intervention plan should be evaluated whether it could improve the symptom. If the intended effect is not obtained, another prescription may be taken into consideration. A comprehensive approach is necessary, because the blood pressure changes during dialysis and uremic symptoms are closely related to patients' compliance in medication, diet, and other lifestyle elements.

CHAPTER 5-1 DIALYSIS MEMBRANE SELECTION

Statement

HPM dialyzers should be used.

Commentary

The KDOQI guidelines state that the use of poorly biocompatible cellulose membranes should be dis-

couraged. The EBPG recommends the use of highly biocompatible high-flux membranes with large pores to improve morbidity and mortality. The EBPG also recommends avoiding dialysis membranes that strongly activate complement, white blood cells, and inflammatory responses. However, a meta-analysis conducted by MacLeod et al. failed to clearly demonstrate the superiority of synthetic polymer membranes (127). Unlike in other countries, HPM dialyzers have been adopted in Japan, and the context surrounding the criteria for the selection of dialysis membranes in the Japanese guidelines differs from that in guidelines from other countries. Therefore, during the formulation of these guidelines, HPM dialyzers must be described in the context of the selection of dialysis membranes.

The concepts underlying the development of HPM dialyzers are explained next. During the 1970s, the identity of middle molecular weight uremic toxins that formed part of the middle molecule hypothesis proposed by Babb et al. (128) and approaches to their efficient removal were discussed. This led to an attempt to remove these middle molecular weight toxins by hemofiltration (HF), but HF did not have beneficial effects on patients. By the end of the 1970s, themes being discussed focused on the accumulation of toxins as a consequence of uremia, substances that could be removed by HF, and the low clearance rates of such accumulated toxins. Focusing on the fact that LMWPs that have lower molecular weights than albumin are removed by glomerular filtration, researchers determined that dialysis using a dialyzer that can remove small proteins can achieve certain clinical benefits, including improvements in anemia and joint pain. HPM dialyzers are discussed in the following sections.

1. Requirements for HPM Dialyzers

When considering the requirements for HPM dialyzers, familiarity with the background to their designation is very important. Membranes with high UFR, including high-flux membranes and high-permeability membranes, were considered to be HPMs and they were referred to as such in the context of dialyzers in the 1970s. Dialyzers equipped with new membranes that provided greater clinical benefits followed, and they included those capable of adsorbing proteins and leaking albumin, despite having low UFRs, and these were also classified as HPM dialyzers. In 1985, Gejyo et al. (72) identified β_2 M as the amyloid precursor protein in DRA. In those days, only a few types of dialysis membrane were available that could efficiently remove LMWP. Therefore, dialyzers performing adsorption-based

removal and those with highly biocompatible membranes that reduced inflammatory protein production were also regarded as HPM dialyzers.

Now, many dialyzers can efficiently remove LMWP, and the definition of HPM dialyzers is changing gradually. In 2005, the JSDT classified dialyzers according to their functions, and defined HPM dialyzers as those with a β 2M clearance of at least 10 mL/min (129). In 2013, the JSDT added albumin permeability and specific functions that included adsorption capability to the classification criteria (130).

2. Clinical Effects

The improvement of DRA is the most important clinical effect required of HPM dialyzers, and this provided the background to their development. The JSDT undertook a statistical survey that showed that HPM dialyzers are effective in the treatment of DRA (131). In addition, Koda et al. reported that the use of HPM dialyzers lowered the risk of carpal tunnel syndrome, which, along with mortality, is a manifestation of DRA (132). Because HPM dialyzers remove substances that cannot be removed by conventional dialyzers and are superior with regard to biocompatibility, they are expected to have a variety of clinical benefits for dialysis patients, including improvements in prognoses, appetite, malnutrition, syndromes associated with DRA, for example, joint pain and suppressing DRA development, renal anemia, pruritus, skin pigmentation, skin keratosis, restless leg syndrome, irritation, insomnia, acute renal failure, and native kidney function (133). An RCT that compared high- vs. low-flux membranes reported that the use of high-flux membranes improves the prognoses of dialysis patients with diabetic nephropathy and those with albumin levels of <4.0 g/dL (83).

3. Uremic Toxins Should Be Removed

Uremic toxins of a relatively high molecular weight that cannot be removed by conventional dialyzers are the targets of HPM dialyzers. Currently targeted uremic toxins include those that conform to the classical definition and those substances associated with vascular lesions and chronic inflammation (134) and, among these, substances with molecular weights of 10 000–30 000 Da should be removed by HPM dialyzers. However, placing limits around the targets is currently difficult, and new target substances will be identified as a result of further pathological clarification in the future.

As noted previously, HPM dialyzers have the potential to improve patients' prognoses and their

dialysis-related complications, and are considered suitable for use in dialysis therapy.

CHAPTER 5-2 CONVECTION-BASED BLOOD PURIFICATION METHODS

Statements

1. HDF should enhance the removal of small proteins, reduce the production of inflammatory cytokines, and improve patients' prognoses.
2. HDF should be considered a therapy for non-specific symptoms, including itching, joint pain, malaise, and poor appetite. Patients with dialysis hypotension should be considered for treatment with HD using a high-flux dialyzer and ultrapure dialysate.

Note: Predilution online HDF using a large volume of dialysate and a hemodiafilter that allows the permeation of small proteins up to the size of albumin is commonly practiced in Japan.

Commentary

In 2008, JSDT formulated a Standard on Microbiological Management of Fluids for Hemodialysis and Related Therapies (135). Online HDF has been available in Japan since April 2010, and it resulted from the approval of corresponding artificial dialysis systems. Since April 2012, online HDF has been covered by national health insurance in Japan. Online HDF is suitable for patients with a variety of pathologies who regularly undergo maintenance dialysis.

1. Comparative Effects of Online HDF and HD

- 1) Reduction in β 2M levels and the effects of treatment on DRA

Online HDF is reportedly superior to HD at reducing β 2M levels, a small precursor protein that is associated with DRA (136–138). Indeed, HDF is highly effective at removing LWMPs, particularly β 2M.

Nakai et al. examined the DRA suppression effects of different blood purification therapies in 1196 patients. They reported that online HDF and push-pull HDF significantly reduce the relative risk of DRA compared with HD using a conventional (low-flux) membrane (relative risk = 1), demonstrating that HDF is effective for treating DRA (131). Furthermore, Locatelli et al. reported that HDF significantly delays the need for carpal tunnel surgery (139).

2) Improvements in anemia

It has been reported that compared with HD, postdilution online HDF significantly decreases the resistance index for erythropoiesis-stimulating agents (ESAs) and the erythropoietin dose-to-hematocrit ratio (140). However, a 21-month RCT conducted in Italy showed that neither anemia nor ESA resistance improved among patients undergoing predilution online HDF (141). Thus, findings regarding the effects of online HDF on anemia and ESA resistance are inconsistent.

3) Improvements in inflammation

The RISchio Cardiovascolare nei pazienti afferenti all'Area Vasta In Dialisi (RISCAVID) study, a prospective observational trial of patients undergoing online HDF or HD with a 30-month follow-up period, showed that online HDF significantly reduces the levels of inflammatory cytokine and interleukin-6 (IL-6) (142). In a crossover study of 31 patients, Caracedo et al. found that online HDF significantly reduces the production of the cluster of differentiation (CD)14⁺CD16⁺ monocyte-derived cells, which frequently generate inflammatory cytokines. Compared with high-flux HD, online HDF suppresses the production of IL-6 and tumor necrosis factor- α , which are generated by stimulating monocytic cells (143). Ramirez et al. reported that online HDF significantly suppresses the increased production of endothelial microparticles and endothelial progenitor cells compared with high-flux HD, which shows its potential to alleviate vascular endothelial damage (144).

4) Effects on dialysis hypotension

Locatelli et al. investigated the effects of online HDF on the prevention of dialysis hypotension in a study carried out in Italy. They reported that predilution online HDF prevents dialysis hypotension in a way that is similar to predilution online HF. This effect was attributed to the increased sodium load as observed in high-sodium HD (145).

5) Improvements in prognoses

Analysis of the results from DOPPS European patients determined that mortality among patients undergoing postdilution online HDF was 35% lower than that among patients undergoing HD using low-flux membranes (146).

The RISCAVID study showed that postdilution online HDF reduced cardiovascular mortality compared with bicarbonate HD (where 95% of patients used synthetic polymer membranes or low-flux mem-

branes) and that online and offline HDF reduced total mortality to a greater extent than bicarbonate HD (142). Vilar et al. carried out a comparative analysis of the long-term outcomes associated with postdilution online HDF and HD using high-flux membranes. They reported that online HDF significantly improved patient prognoses compared with HD using high-flux membranes, although there were no significant differences between the two dialysis methods in relation to their effects on anemia, bone metabolism, nutritional status, and blood pressure (147). A study that compared online HF with HD using low-flux membranes found that patients undergoing online HF had improved prognoses (148).

Recently, the results from three RCTs investigating the effects of online HDF on survival rates have been reported. The three RCTs reported are the CONvective TRANsport STudy (CONTRAST) (149) that compared postdilution online HDF and low-flux HD, a study undertaken in Turkey (150) that compared postdilution online HDF and high-flux HD, and the Estudio de Supervivencia de Hemodiafiltración On-Line or On-Line Hemodiafiltration Survival (ESHOL) (151), which also compared postdilution online HDF and high-flux HD. The CONTRAST study found that all-cause mortality decreased by 38% among patients undergoing online HDF at a convection volume of >21.95 L, but there were no significant differences in relation to all-cause mortality and cardiovascular mortality between patients undergoing postdilution online HDF and low-flux HD (149). The Turkish study also found reductions in all-cause mortality and cardiovascular mortality by 46% and 71%, respectively, among patients undergoing online HDF with a convection volume of >17.4 L, but there were no significant differences between the study groups (150). The ESHOL study found that all-cause mortality, cardiovascular mortality, and infectious disease mortality decreased by 30%, 35%, and 55%, respectively, among patients undergoing online HDF and that the incidence of dialysis hypotension decreased by 28%. In accordance with the CONTRAST study and the Turkish study, the ESHOL study determined that all-cause mortality among patients undergoing online HDF with high convection volumes of >23 L and >25 L decreased by 40% and 45%, respectively (151). These results indicate that patients treated with online HDF have better prognoses than those treated with low-flux HD, and that prolonged online HDF is considered superior to high-flux HD. However, a substantial body of evidence demonstrating the advantages of online HDF in relation to patients' prognoses is yet to be gathered.

2. Status of Online HDF in Japan

Predilution HDF is a feature of the online HDF method used in Japan (152). Hemodiafilters that use HPMS with a β 2M clearance rate of at least 50 mL/min are very frequently used in Japan. Indeed, it has been reported that their rates of use are at least 90% and 95% in HD and HDF, respectively (153).

Although clearances in predilution online HDF have been examined in countries other than Japan, the number of patients investigated is limited, and the relatively large convection volume (≥ 60 L) per dialysis session that is used in Japan is rarely used among overseas patients (154–157). Compared with postdilution online HDF, predilution online HDF, using albumin-permeable hemodiafilters, provides a good balance between albumin leakage and the removal of small proteins (158). In addition, many studies demonstrate that predilution online HDF also alleviates patients' complaints associated with dialysis, including itching, bone and joint pain, and poor appetite; hence, predilution online HDF should be considered a modality that may relieve these complaints (159).

Note that all convection-based blood purification methods, including online HDF, must satisfy the dialysis prescription and the conditions recommended in the guidelines.

CHAPTER 5-3 DIALYSIS SCHEDULE

Statements

1. Long intermittent HD refers to HD performed with a duration of at least 6 h per session, and frequent HD refers to HD administered at least five times per week.
2. The dialysis time or frequency should be increased in the following patient situations:
 - 1) Patients with symptoms that cannot be controlled by conventional HD:
 - (1) Patients with symptoms of cardiac failure or hemodynamic instability during dialysis;
 - (2) Patients who remain hypertensive despite fluid removal, the administration of antihypertensive agents, and the restriction of salt intakes;
 - (3) Patients who remain hyperphosphatemic despite dietary controls and phosphate control
 - 2) Patients who are stable under conventional HD and are expected to benefit more from dialysis with increased dialysis times and/or frequencies.

Commentary

Currently, HD is performed as an intermittent regimen, and many patients undergo HD for a total of 12 h per week only, which means that the complete replacement of their kidney function by dialysis is impossible. While this conventional HD (Table 3) is the minimum treatment necessary to maintain life, it is inadequate in preventing dialysis-related complications and in improving outcomes. Increasing the amount of time spent on dialysis each week would address this issue, and would establish programs of long intermittent and frequent HD. In addition, increasing the amount of time spent on dialysis each week enables patients, including those who are already stable under their current HD program, to achieve internal balances that more closely resemble those of healthy people, which should improve their clinical outcomes.

1. Definitions

The definitions of frequent HD and long intermittent HD are specified in the International Quotidian Dialysis Registry (160) and in the Frequent Hemodialysis Network (FHN) Trials (161), but the definitions differ slightly among studies. In this guideline, long intermittent HD is defined as HD three times per week for at least 6 h, which is based on the International Quotidian Dialysis Registry definition, and it considers the context in which dialysis takes place in Japan. Although data on dialysis for ≥ 5 h per session are included in the International Quotidian Dialysis Registry, dialysis that lasts for < 6 h is categorized as conventional dialysis, because the duration of dialysis that is specified for healthcare reimbursement in Japan is at least 5 h.

Frequent HD is defined as HD that occurs at least five times per week, and it is classified into short frequent HD that lasts for 1.5–3 h and long frequent HD that lasts for 6–10 h that generally occurs at night, and is also known as daily nocturnal HD. Frequent HD with a duration of 3–6 h is not clearly

TABLE 3. Definitions and terms

■ Conventional intermittent HD: 3 sessions per week, 3–6 h per session ■ Long intermittent HD: 3 sessions per week, ≥ 6 h per session ■ Frequent HD (daily HD, quotidian HD): ≥ 5 sessions per week • Short frequent HD (short daily HD): ≥ 5 sessions per week, 1.5–3 h per session • Conventional-hour frequent HD: ≥ 5 sessions per week, 3–6 h per session • Long frequent HD (long daily HD, frequent nocturnal HD, daily nocturnal HD): ≥ 5 sessions per week, ≥ 6 h per session

HD, hemodialysis.

categorized and is defined in the guidelines as conventional-hour frequent HD. The terms “frequent HD” and “daily HD” are used interchangeably by different researchers, with the latter term being used mainly in Western countries. However, the guidelines adopt the term frequent HD.

Note that alternate-day HD (seven times per fortnight) and four times weekly HD are not discussed in the guidelines, because evidence supporting their benefits is limited, but benefits from these approaches can be expected in the future.

2. Adequacy

1) Patients with symptoms that cannot be controlled by conventional HD

This section discusses those patients with symptoms of cardiac failure or hemodynamic instability and those who remain hypertensive despite fluid removal, administration of antihypertensive agents, and restriction of salt intake.

Using long intermittent HD can reduce the UFR and increase the total amount of fluid removed, leading to improved control of body water levels (48,162) and the effective stabilization of hemodynamics (163). Prolonged dialysis can reduce the incidence of dialysis hypotension, particularly in elderly patients with complications (49). An RCT showed that while blood pressure was controlled to a greater extent among patients undergoing HD at home for 6–8 h per session than among patients undergoing in-center HD for 3.5–4.5 h per session, there were no significant differences in relation to changes in BW and the amount of extracellular fluid (164). In addition, an RCT with a fixed DW showed that patients who were undergoing long intermittent HD had well-controlled blood pressures (165). In general, longer dialysis treatments facilitate the achievement of target DWs, and lead to well-controlled blood pressure and the administration of lower doses of antihypertensive agents (48,162).

Frequent HD can suppress increases in BW during interdialysis periods and is effective in stabilizing hemodynamics. Studies show that increasing the frequency of dialysis treatment is beneficial for patients with poorly controlled BW and patients with complications (166,167). Furthermore, a lower incidence of dialysis hypotension has been reported (168). A Japanese clinical study also showed that in-center frequent HD undertaken six times per week for 2 h, which had been switched from conventional intermittent HD, significantly reduced the blood pressure despite increasing DW (169).

Left ventricular hypertrophy tends to be found among dialysis patients and is a factor influencing

their poor prognoses. Frequent HD reportedly decreases the incidence of left ventricular hypertrophy (170). An FHN RCT recently carried out in North America compared in-center HD six times per week for 1.5–2.75 h, total dialysis time of 12.7 ± 2.2 h per week, with HD three times per week for 2.5–4.0 h, total dialysis time of 10.4 ± 1.6 h per week, and it found that frequent HD significantly decreases the left ventricular mass index (LVMI) (171), which may relate to BW and blood pressure being well controlled by frequent HD. A meta-analysis reported that frequent HD and long intermittent HD lead to significant decreases in the LVMI and improvements in the left ventricular ejection fraction (EF) (172). Further reports show that long frequent HD prevents dialysis hypotension, controls blood pressure during dialysis, improves the EF, and prevents left ventricular failure (173,174). Another report showed that daily nocturnal HD reduces peripheral vascular resistance and increases the vasoactive reaction (175). In summary, both long intermittent and frequent HD facilitate the control of BW, resulting in improvements in blood pressure and cardiac function.

2) Patients who have persistent hyperphosphatemia

The benefit of prolonged HD is the clearance of relatively low molecular weight solutes, including urea, because this process depends on diffusion. However, prolonged dialysis is also effective at reducing levels of phosphate, which has a low molecular weight, is more abundant within the tissues than in the blood, and its transport rate is complicated and affected by various factors, including the acid-base equilibrium (176,177). For patients with poor phosphate control, longer and/or more frequent HD is the most effective means of reducing phosphate levels (178). However, the kinetics of phosphate in the body are complicated, and the extent to which it is reduced and its levels in the serum will vary according to the dialysis conditions. For example, a longer dialysis time results in a greater reduction in the phosphate level, (82,177–178) but it rarely increases the removal rate (82). In addition, a much longer dialysis duration may increase the risk of phosphate being transported into the blood from the bones (179).

Frequent HD reduces serum phosphate levels and the need to use phosphate binders (180,181). However, increases in phosphate intake as a result of increased food intake should be considered (182). Therefore, increase in food intake should be accompanied by increase in dialysis time, even when frequent HD is undertaken, to reduce phosphate levels

(181). An FHN trial showed that serum phosphate levels significantly decreased among patients undergoing HD six times weekly, where the mean dialysis duration was 154 min per session (171,183).

Daily nocturnal HD reduces serum phosphate levels and markedly reduces the use of phosphate binders, despite increases in phosphate intake from food (180,183–184). In addition, supplementing the dialysate with phosphate is required to prevent hypophosphatemia (185). In conclusion, reductions in phosphate levels are enhanced as total weekly dialysis times increase. It has been reported that when the total dialysis time is at least 38 h per week, the serum phosphate level can be maintained <5.0 mg/dL without using phosphate binders (178).

- 3) Patients who are stable under conventional HD and are expected to benefit more from dialysis of increased times and frequencies

Short HD times increase mortality, regardless of the delivered dialysis dose (20,43). The JRDR, which includes 71 000 patients, showed that after adjusting for Kt/V_{urea} , mortality decreased with increasing dialysis times among patients undergoing HD for no more than 5.5 h per session (20). In addition, mortality from cardiovascular complications decreased among patients undergoing longer HD that lasted for 8 h and was undertaken three times per week, mainly because blood pressure was well controlled (48,162). A retrospective observational study that involved 415 patients who were undergoing short frequent HD at European and American facilities showed that the 5- and 10-year survival rates were 68% and 42%, respectively. When these data were compared with those in USRDS after matching the patients' characteristics, the 50% survival rate was 2.5–10.9 years longer for patients undergoing short frequent HD than for those undergoing conventional HD. Furthermore, survival was 9–15 years longer among patients undergoing short frequent HD at home compared with those undergoing conventional HD. These data are similar to those from patients receiving cadaveric renal transplantations in North America (186). An analysis of the Canadian Daily Nocturnal HD Registry that included 247 patients undergoing daily nocturnal HD determined that the 1- and 5-year survival rates were 95.2% and 80.1%, respectively (187).

The results from the FHN trials carried out in North America have been published (161,171,183, 188) and are described next. The effects of short frequent treatments with HD were compared with those of conventional HD among patients treated at dialysis centers. The findings obtained were clear, because

the survey comprised a large patient population and was conducted with patients treated at centers (170). The LVMI and physical health composite scores were the primary outcome measures, and they were significantly better among patients undergoing short frequent HD treatments. In addition, serum phosphate levels and systolic blood pressures, which were the secondary outcome measures, were significantly lower.

In another FHN trial, the effects of daily nocturnal HD undertaken at home were compared with the effects of treating patients at home with conventional HD. In this trial, patients receiving conventional intermittent HD at dialysis centers were initially targeted for trial participation, but patients receiving conventional HD at home were selected after the patients had been screened. Therefore, patients who were treated at home and received nocturnal HD were compared with those treated at home by conventional HD. The comparison showed that the conventional HD group included patients who had undergone HD for a relatively long time, and conversely, that the daily nocturnal HD group included patients who had undergone HD less frequently. As a result, no significant differences were found in relation to the primary outcomes, and only the secondary outcomes, which included serum phosphate levels and systolic blood pressures, showed significant differences. These findings may have also been caused by the small patient population (188).

These findings indicate that frequent HD improves cardiac function and QOL to a greater extent than conventional HD undertaken three times weekly. However, no significant differences were found in relation to different dialysis times and frequencies among patients whose HD was undertaken at home, and the results only demonstrate the effectiveness of home HD. The Australia and New Zealand Dialysis and Transplant Registry also shows the advantage of home HD over in-center HD, but no significant differences are apparent in relation to mortality between those patients treated at home with conventional HD and those treated at home with frequent or long intermittent HD (189).

3. Disadvantages

- 1) Longer HD is associated with the excessive removal of solutes during each dialysis session

When HD is performed for longer durations using commercial dialysates, minerals including potassium, phosphorus, and calcium are removed in excess, and complications such as hypokalemia, hypophosphatemia, hypocalcemia, and the resulting reductions

in bone mass, cause concern. In these patients, blood flow and dialysate flow should be adjusted, and a dialysate of an appropriate composition should be selected. Calcium and phosphorus levels in the dialysate, in particular, should be appropriately adjusted during daily nocturnal HD (183,184). Furthermore, losses of trace elements and proteins should also be considered when selecting a dialyzer. Thus, the composition of commercial dialysates is generally designed for use in conventional HD undertaken three times weekly, and if they are used for different HD regimes, their safety must be stringently assured.

- 2) Frequent HD is associated with the deterioration of vascular access and increases in pain levels that relate to frequent punctures

The FHN trials showed that the incidence of failure of vascular access was higher among patients undergoing frequent HD (171,188,190). However, this could mean that abnormalities are being detected earlier, because regular vascular access is accompanied by frequent observations. In addition, self-puncturing techniques, such as the buttonhole puncture method and instruments that facilitate these, have become available. These techniques facilitate home HD and are expected to alleviate the pain associated with punctures.

- 3) The greater use of dialysis-related materials increases the amount of medical waste generated

Frequent HD is currently performed using the same types of dialyzers, blood circuits, and dialysate supply systems as those used for conventional HD. The increased use of these dialysis-related materials cannot be avoided when patients undergo frequent HD. Systems specifically designed for frequent HD should be developed in the future.

CHAPTER 6 PEDIATRIC GUIDELINES ON MAINTENANCE HD PRESCRIPTIONS

Status and features of pediatric patients undergoing dialysis to be considered in the formulation of dialysis prescription guidelines

The number of pediatric patients regularly undergoing HD is much smaller than the number of adult patients regularly undergoing HD, because the number of pediatric patients with end-stage renal failure is small, children tend to undergo kidney transplantation relatively early and before progression to end-stage renal failure, and often, peritoneal dialysis is selected for infants and school children. Therefore, large-scale studies, such as the HEMO Study and

RCTs that are conducted among adult patients cannot be implemented for pediatric patients. Hence, it is very difficult to formulate evidence-based guidelines for maintenance HD prescriptions for pediatric patients.

Furthermore, children's protein and water intakes are higher per unit BW than those of adults, and their BUN levels, blood phosphorus levels, and fluid removal cannot be appropriately controlled by a conventional HD regimen administered three times per week for 4 h. For children undergoing dialysis, the goals of treatment should allow the children to develop physical, psychomotor, and social skills in ways that are comparable with the development of the same skills in healthy children. To achieve these goals, severe dietary restrictions, multiple hospital visits over long periods, and painful therapies, including needle punctures, should be avoided as much as possible. Therefore, pediatric maintenance HD treatment has intrinsic issues. These issues include monitoring the patient's physical growth and nutritional status, difficulties associated with the selection of vascular access through either an arteriovenous fistula or a long-term indwelling catheter, and the challenges associated with the optimization of DW, which involves determining whether the increase in BW has resulted from a patient's growth or overhydration.

This chapter was prepared with reference to previously developed guidelines and recent original research papers. The information from these sources was adapted to provide guidance on diagnosis and treatment in ways that are suitable for Japan. This chapter recommends administering HD to pediatric patients, which has caused fewer complications thus far. Furthermore, given that HD is the most established method for minimizing future adverse impacts, it offers good prognoses. This chapter focuses on pediatric patients who weigh 20 kg or more and who can undergo dialysis using a standard HD machine that is available throughout Japan. However, most of the statements in this chapter are the authors' opinions, because only limited evidence is available on HD for pediatric patients. Therefore, readers are advised that they should completely understand the other chapters that focus on adult patients before they read this chapter.

1. HD Doses for Pediatric Patients and Their Effects

Statement

Pediatric patients should receive a minimum of the same delivered dialysis dose that is recommended for adult patients.

Commentary

1) Small Solute and Dialysis Times

The protein intake per unit of BW for children is necessarily higher than that for adults; hence, solute removal is required. Moreover, the risk of complications should be minimized to ensure the children enjoy long lives. Therefore, on the basis of empirical data, it is recommended that HD should be administered at least three times per week for 4 h.

An analysis of the JRDR for adults shows that mortality tends to decrease as the delivered dialysis dose increases, and the analysis concluded that the target dialysis dose should be spKt/V of 1.4 per dialysis, which is based on the smaller body size of Japanese adult patients compared with their European and American counterparts (refer to Chapter 1). Whether this target value is appropriate for children remains unclear. However, we consider that the minimum adequate dose for children is spKt/V of 1.4 per dialysis, and we recommend that the delivered dialysis dose for each patient be determined considering the patient's body growth, nutritional status, and social activities. Hence, and as mentioned previously, it is recommended that pediatric patients are administered with HD, because this is the most established method, is associated with the fewest complications, and offers the best prognoses for children. However, given that uremia affects physical and psychomotor development in children, it is important to regularly check and evaluate the number of days a child spends in the hospital, the amount of growth attained, and their attendance in kindergarten or school. Appropriate dialysis prescriptions and adequate nutritional intakes are essential for the growth of pediatric HD patients.

For pediatric patients who are stable, the dialysis dose should be evaluated together with the PCR. It has been reported that patients who underwent nocturnal dialysis at hospitals three times per week for 8 h with their spKt/V increasing from 1.74 to 2.15 were energetic because restrictions on their dietary and water intakes had been removed, and that their left ventricular hypertrophy improved. In addition, the number of days that the pediatric patients and their caregivers were absent from school and work, respectively, reduced by 81% (191). If patients are thought to have been administered an insufficient dialysis dose or to have excessive fluid, dialysis should be performed three times or more per week and increasing the amount of time spent on dialysis should be considered. Benefits from frequent dialysis using a simple at-home HD system with children have also been reported (192).

A recent study has proposed normalization of the dialysis dose, which would be based on the amounts by which the level of Glomerular Filtration Rate decreases in relation to the BSA that is associated with metabolism, as opposed to the body fluid volume (Kt/V), because the production of uremic toxins is closely related to metabolism (37). Because children's metabolic rates tend to be higher than those of adults, pediatric patients are considered to require a higher dialysis dose than adult patients when the dialysis dose is based on Kt/V . It has been suggested that pediatric patients, particularly those aged <10 years, require dialysis for 6–8 h per session or at least four times per week to achieve a desired dialysis dose that is normalized to the BSA (193).

In the future, higher dialysis doses for pediatric patients will be attempted by administering more frequent or prolonged HD (194). When this occurs, the effects of the time restrictions imposed by dialysis treatments on the social and mental development of children and their relationships with family members must be thoroughly considered.

2) $\beta_2\text{M}$

Kt/V is based on the level of urea, a substance with a low molecular weight, and it is a necessary, but not entirely adequate, parameter. Therefore, for adult patients, it is proposed that the dialysis dose is evaluated based on the level of $\beta_2\text{M}$, a small protein in the blood (refer to Chapter 2).

For pediatric patients, the clearance of urea as well as middle molecular weight toxins and small proteins should be examined to determine the HD dose. However, only limited evidence exists to support the correlation between serum $\beta_2\text{M}$ levels and the prognoses of or complications among pediatric HD patients. Among healthy children, infants aged 5–6 days and 1 year show serum $\beta_2\text{M}$ levels that are 2- and 1.5-fold higher, respectively, than those of adults. Children aged approximately 8 years show serum $\beta_2\text{M}$ levels that are close to those of adults (195). However, much remains to be clarified regarding changes in $\beta_2\text{M}$ production, its distribution capacity, and its clearance in children during their growth periods. Therefore, it is difficult to determine specific target values that will provide the appropriate HD doses for pediatric patients.

2. Appropriate Control of Body Fluids

Statement

The appropriate control of body fluids is important to improve QOL, achieve better prognoses in relation to cardiovascular diseases, and to improve long-term outcomes.

Commentary

A report showed that 80% of pediatric patients with end-stage renal failure already had left ventricular hypertrophy when they began dialysis (196). The appropriate control of body fluids is important to improve QOL, to achieve better prognoses associated with cardiovascular diseases, and to improve the long-term prognoses of dialysis patients. However, appropriately evaluating and controlling BW in pediatric patients are difficult, because compared with adult patients, they have larger amounts of body fluid and require higher energy inputs per unit BW; hence, they show higher rates of BW increases during the interdialysis periods. Thus, greater care should be taken when treating pediatric HD patients compared with adult patients.

1) Evaluation of Body Fluid Volume

Methods for evaluating DW include pre- and post-dialysis blood pressure measurements, measurements of the cardiothoracic ratio, echo-based measurements of the inferior vena cava diameter, bioimpedance-based measurements of body composition, and measurements of various hormone levels, including postdialysis atrial natriuretic peptide levels. The age and body size of pediatric patients must be considered in the DW evaluation, because blood pressures, cardiothoracic ratios, and the water content of children's bodies differ according to their age. For example, the body water content is approximately 75% of the BW at birth, 60% of the BW in 1-year-old infants, and 60% and 50% of the BW of male and female adolescents, respectively, which is almost equivalent to the water content of adults' bodies (197). Pediatric hypertension is defined as blood pressure in the 95th percentile or greater after correction for age, height, and BW. When diagnosing pediatric hypertension, the criteria stated in the Hypertension Treatment Guidelines 2009 provided by the Japanese Society of Hypertension should be referenced (198). Although blood pressure measurements taken during the latter half of dialysis sessions and after dialysis can be used to evaluate DW, blood pressure measurements alone may be insufficient to accurately evaluate DW, because some pediatric patients will not complain about the unpleasant symptoms they are experiencing, and their blood pressures may decrease because of the excessive amount of fluid being removed each hour, despite obtaining the appropriate DW.

2) Control of Body Fluid Volume

The BW gain by pediatric patients during the interdialysis period is inevitably larger than that of

adult patients, because pediatric patients require higher energy levels and water intake per unit of BW. To safely maintain the appropriate body fluid volume and BW, various actions should be taken, including adjusting the fluid removal rate and the sodium level in the dialysate, evaluating changes in the blood volume during dialysis using a hematocrit measurement system, for example, Crit-Line, and increasing the time and frequency of dialysis (199–201). Because fluid removal may be difficult to perform on pediatric dialysis patients during 4-h sessions undertaken three times per week during their growth periods, the dialysis schedule should contain some flexibility, it should not require strict adherence to the regimen described previously, and it should enable the body fluid volume to be adjusted, as necessary. Note that school activities play major roles in the healthy physical and mental development of children; hence, caregivers at dialysis facilities should consider nocturnal dialysis schedules and should consult with the patients, their family members, and school staff to enable patients to participate fully in school and social activities without encountering problems.

3. Appropriate Dialysis Dose and the Evaluation of Treatment Effect

Statements

1. The dialysis dose should be appropriately evaluated to account for the extent of growth and the nutritional status of children.
2. The dialysis dose should be evaluated together with the PCR.
3. Factors that affect the social activities of children should be regularly evaluated, including their hospitalization frequency, growth extent, nutritional status, and attendance at kindergarten or school.
4. DW should be evaluated at least once a month.

Commentary

Children are expected to grow, but malnutrition caused by uremia may impair their growth. Therefore, growth, including changes in BW, should be closely monitored and considered in the treatment of children. It has been reported that mortality is high among pediatric patients who are short in stature and have low BMIs (202). Evaluating both the adequacy of children's dialysis dose and their nutrient intake is important not only for their normal growth but also to assure favorable prognoses. Under stable conditions, the normalized PCR (nPCR), which indicates

the PCR per postdialysis BW, is considered almost equal to protein intake (202). A study has shown that the nPCR does not always correlate with an increase in the dialysis dose (203). The evaluation of the nPCR with the dialysis dose is recommended, because the nPCR reflects the malnutrition status more sensitively than the serum albumin level (204). The BWs and BMIs were higher among pediatric HD patients with nPCRs ≥ 1 g/kg/day than among those with lower nPCRs (205,206).

Uremia also affects physical and psychomotor development. Growth impairment that is observed before the start of dialysis is considered difficult to improve by HD alone (207). The dialysis dose, as well as the extent of growth, hospitalization frequency, and attendance at kindergarten or school, should be checked regularly, and if decreases in the extent of growth or in the frequency of participation in social activities are found, the reasons for them should be identified. The degree of growth of pediatric HD patients is examined regularly by measuring their height and BW, plotting the data onto the growth curve of healthy Japanese children, and evaluating temporal changes in the standard deviation scores with respect to standard height and annual growth rates. For pediatric patients aged 10 years or older, attention should be paid to the development of secondary sex characteristics, in addition to their height and BW.

CHAPTER 7 SAMPLING METHODS OF BLOOD AND DIALYSATE

1. Evaluation of Dialysis Dose

Indices of dialysis dose, solute removal, and the sampling methods of blood and dialysate are mentioned below.

A. Indices

(1) Kt/V_{urea}

Kt/V_{urea} is an index of the degree to which urea is removed in one dialysis session (i.e. dialysis dose). Although various definitive equations of Kt/V_{urea} have been proposed as described below, no absolute equation has been selected. It is important to use one of these appropriate equations consistently for each patient.

1) Gotch and Sargent's equation (Kt/V_{urea}) (9)

This model assumes the one-compartment model with no effect of fluid removal and urea production.

$$Kt/V = \ln(BUN_{\text{pre}}/BUN_{\text{post}}) \quad (1)$$

where BUN_{pre} and BUN_{post} are the predialysis and postdialysis BUN concentrations, respectively.

2) Shinzato et al.'s equation (208)

This model assumes the one-compartment model with no effect of fluid removal. Theoretical representation of this model may be found at the following URL: <http://optimal-dialysis.jp/download.html>

3) Daugirdas' equation

Single-pool Kt/V_{urea} ($spKt/V$) (209)

Daugirdas proposed several definitive equations of Kt/V_{urea} . The following model assumes the one-compartment model with consideration of the effect of fluid removal and urea production.

$$spKt/V = -\ln(R - 0.008t) + (4 - 3.5R) \times \frac{\Delta V}{BW_{\text{post}}} \quad (2)$$

where R is the ratio of the postdialysis BUN to the predialysis BUN concentration ($= BUN_{\text{post}}/BUN_{\text{pre}}$), t is the dialysis duration (h), ΔV is the fluid removal per HD session (L), and BW_{post} is the postdialysis BW of the patient (kg).

Equilibrated Kt/V_{urea} (eKt/V) (10,11)

This equation is based on the so-called regional blood flow model.

$$eKt/V = spKt/V - 0.6 \frac{spKt/V}{t} + 0.03 \quad (3)$$

(2) Reduction rate (RR)

Definition: RR is an index of the solute clearance and is calculated using the predialysis and postdialysis blood solute concentrations (C_{pre} and C_{post} , respectively) as follows.

$$RR = 1 - \frac{C_{\text{post}}}{C_{\text{pre}}} \quad (4)$$

Usually, the obtained value is multiplied by 100 to be expressed in percentage.

For solutes of large molecular weight, the RR should be corrected by considering the effect of blood condensation caused by fluid removal (210).

$$\begin{aligned} RR &= 1 - \frac{V_{\text{Ppost}} C_{\text{post}}}{V_{\text{Ppre}} C_{\text{pre}}} = 1 - \frac{V_{\text{Bpost}} (1 - H_{\text{post}}) C_{\text{post}}}{V_{\text{Bpre}} (1 - H_{\text{pre}}) C_{\text{pre}}} \\ &= 1 - \frac{H_{\text{pre}} (1 - H_{\text{post}}) C_{\text{post}}}{H_{\text{post}} (1 - H_{\text{pre}}) C_{\text{pre}}} \end{aligned} \quad (5)$$

where H_{pre} and H_{post} are the predialysis and postdialysis hematocrit values.

(3) Solute removal (M)

Estimated from the amount of solute in the dialysate discharged from the dialyzer, which is entirely or partially stored. M is considered to be an absolute index of cleared solute but does not include the amount of solute trapped by the membrane. M basically depends on the predialysis solute level (C_{pre}). The higher the C_{pre} , the higher the M when the dialysis prescription (therapeutic conditions) is fixed.

(4) Clear space (CS) and CS rate (CSR)

Definition: CS indicates the normalized amount of removed solute and is given as follows.

$$CS = M/C_{pre} \quad (6)$$

The effect of C_{pre} is eliminated. CS is given in the unit of volume (space), depends on the distribution space of the solute of interest in patients (V), and corresponds to the distribution space for solute removed in one dialysis session. CSR, expressed as CS/V , is used to compare the CS values among patients.

B. Sampling Methods

(1) Predialysis and postdialysis blood sampling

To determine predialysis concentration, the patient's blood should be sampled at the time of puncture of dialysis access before being connected to the blood circuit, in order to avoid the effects of dilution.

To determine postdialysis concentration, the patient's blood should be sampled by the slow flow method (211) to minimize the effects of access recirculation and urea rebound. Specifically, the dialysate flow is stopped immediately after the dialysis session (practical end of dialysis) and the blood flow rate is reduced to 50–100 mL/min. After 1 to 2 min, the patient's blood is sampled from the port close to the patient on the A-side line.

(2) Sampling of spent dialysate

Refer to the following measurement procedure to obtain an accurate value.

- 1) Storing entire dialysate
- 2) Storing entire dialysate every 1 h
- 3) Storing a part of dialysate (syringe extraction method, fluid removal line storage method)

2. Performance Evaluation of Hemodialyzers and Hemodiafilters

Indices for performance evaluation of hemodialyzers and hemodiafilters (dialyzers/diafilters), and the sampling procedure for determining these indices are in accordance with the Methods of Evaluating Performance of Blood Purification Devices 2012 (212) as explained below.

A. Indices of Performance

(1) Clearance (CL)

CL is an index of the solute removal for dialyzers/diafilters and is defined as follows.

$$CL = \frac{Q_{Bi}C_{Bi} - Q_{Bo}C_{Bo}}{C_{Bi}} \quad (7)$$

where Q is the flow rate, C is the concentration of solute, and the subscripts B, i, and o indicate the blood, inlet, and outlet, respectively.

For solutes of small molecular weight, such as urea and creatinine, the flow rate of whole blood is substituted into Q_{Bi} in Equation 7. For solutes of medium molecular weight, such as $\beta 2M$, the flow rate of plasma is substituted into Q_{Bi} . The plasma concentrations obtained from clinical observations are substituted into C_{Bi} and C_{Bo} . For solutes of large molecular weight, such as $\alpha 1$ -microglobulin and albumin, CL-based evaluation is difficult because of their large decrease with time.

(2) UFR

UFR is an index of water permeability of dialyzers/diafilters and is defined as follows.

$$UFR = \frac{V_F}{T_F \cdot TMP} \quad (8)$$

where T_F is the filtration time (h), V_F is the amount of filtrate stored for T_F (mL), and TMP is the transmembrane pressure (mm Hg). TMP is generally calculated using Equation 9.

$$TMP = (P_B - P_D)_{av} - \pi_P = \frac{P_{Bi} + P_{Bo}}{2} - \frac{P_{Di} + P_{Do}}{2} - \pi_P \quad (9)$$

where P is the pressure (mm Hg) and π_P is the colloidal osmotic pressure.

B. Measurement Technique

(1) CL

- Dialysis conditions, including flow rate, should be in accordance with the

Methods of Evaluating Performance of Blood Purification Devices 2012 (212) provided by the JSDT.

- CL should be evaluated 60 min after the start of the dialysis session. If CL is expected to vary by more than 20% over 240 min, measurement of CL 240 min after the start of dialysis treatment is recommended.
- Dialysate outlet (C_{Do}), blood outlet (C_{Bo}), and inlet (C_{Bi}) should be sampled in this order with great care so as not to affect the flow of dialysate or blood.
- Flow rates of blood (Q_B) and dialysate (Q_D) should be measured beforehand. Use of the actual blood flow rate is recommended to evaluate Q_B during dialysis.

(2) UFR

- Dialysis conditions, including flow rate, should be in accordance with the Methods of Evaluating Performance of Blood Purification Devices 2012 (212) provided by the JSDT.
- UFR should be measured in the mode of ECUM after the treatment.

Conflict of interest: The JSDT has been making the best effort to avoid any actual and potential conflicts of interest for there to be a neutral and fair process of guideline development. In 2010, the JSDT developed a new system for working group members to declare any potential conflicts of interest. All members of JSDT guideline development groups are now required to provide signed declaration forms to state any actual or potential conflicts of interest. These forms are updated yearly, or sooner if an individual member's status changes. Further information is available at: <http://www.jsdt.or.jp/jsdt/1236.html> (Japanese).

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APPENDIX I

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Introduction

Bruce F. Culleton

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In 1999, the Canadian Society of Nephrology (CSN) published clinical practice guidelines (CPG) for the treatment of patients with chronic kidney disease (1,2). In 2003, responding to new evidence and emerging controversies, the CSN Executive Committee recognized the need to update these guidelines and establish new guidelines in areas of perceived clinical need. Updating the hemodialysis guidelines was given high priority. Guidelines for other areas of nephrology, such as peritoneal dialysis, anemia management, and nondialysis chronic kidney disease management, would be developed or revised in a staggered manner over 3 to 5 yr. The overriding objective of the guideline process was to establish national guidelines to improve the quality of health care delivered to patients with chronic kidney disease in Canada.

The guidelines that follow are intended to rely on evidence and avoid opinion-based statements where possible. The guidelines are also intended to reflect human and financial resources available throughout Canada at the time of their writing.

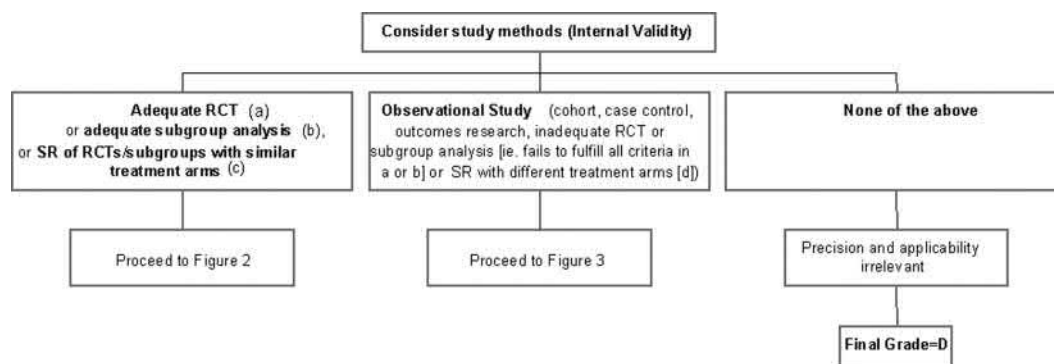
Methods

Guideline Workgroups are directly responsible for the content of each section. A Workgroup Chair is chosen based upon content expertise and participation in the previous CSN CPG. The Workgroup is then populated by nephrologists with rec-

ognized content expertise and, when necessary, allied health professionals and/or patient representatives.

Workgroups are asked to utilize the extensive content and methodologic review of the relevant literature obtained by the prior CSN guidelines (1) and prior publications of the relevant Kidney Disease Outcomes Quality Initiative (KDOQI) Workgroups (3–7). This literature is supplemented by using two methods to locate additional evidence. First, the Workgroup members use their content expertise to identify new evidence. Second, a focused literature search of English-language nephrology and general medical journals is performed by the content experts. The Workgroups assume that new evidence of sufficient magnitude to warrant the revision of existing national guidelines would be discovered using these two methods. Although this approach might be criticized for lack of methodologic rigor, such an approach is pragmatic and has been utilized and advocated by others (8,9).

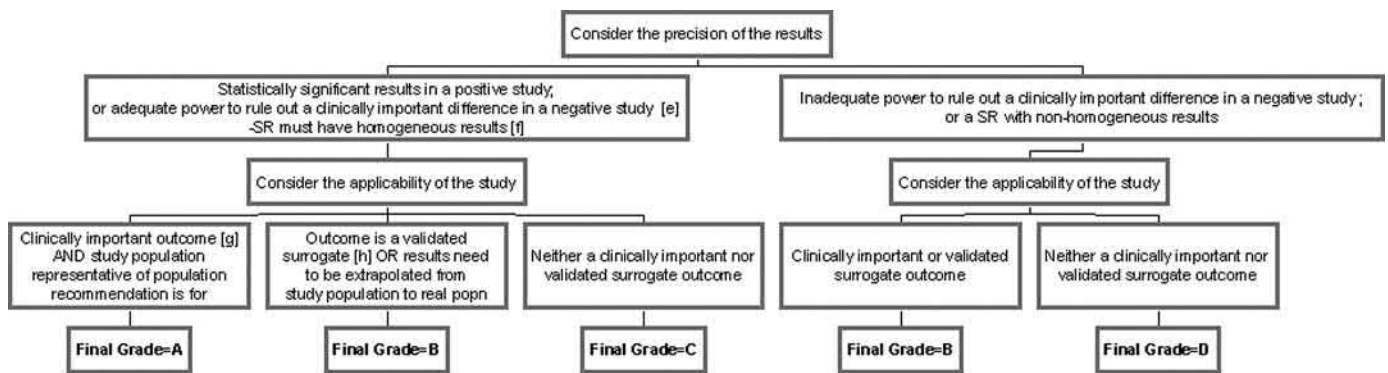
The grading of the evidence supporting each recommendation is based upon the scheme developed by the Canadian Hypertension Education Program (Figures 1, 2, and 3) (10). Recommendations are developed only if they are “strongly recommended” by each Workgroup, *i.e.*, the Workgroup is confident that adherence will do more good than harm. Other status statements within each document are not made. Because



Definitions:

- Randomized clinical trial with blinded assessment of outcomes (if applicable), intention-to-treat analysis, adequate follow-up (*i.e.* at least 90%, or losses to follow-up are too few to materially affect the results), and sufficient sample size to detect a clinically important difference with power > 80%.
- Subgroup analysis was a-priori, done within an adequate RCT, one of only a few tested, and there was sufficient sample size within the examined subgroup to detect a clinically important difference with power > 80%.
- Systematic review (SR, also known as meta-analysis) in which the comparison arms are derived from head-to-head comparisons within the same RCT.
- SR in which the comparison arms are derived from different placebo-controlled RCTs, then extrapolations are made across RCTs.

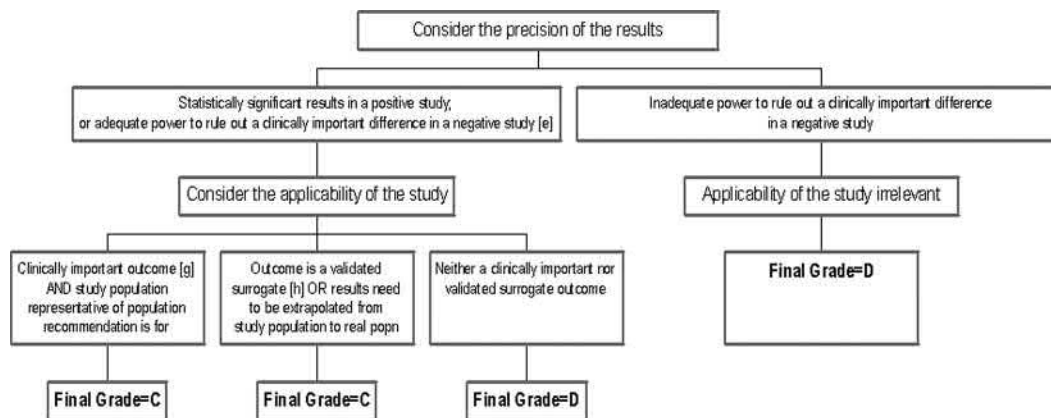
Figure 1. Algorithm for assigning evidence grades to recommendations.



Definitions:

- e Adequate power in a negative study implies that 95% CI exclude a clinically important difference.
- f Effect estimates in each study included in the systematic review are qualitatively similar (ie. in the same direction).
- g “Hard” endpoints such as death, stroke, myocardial infarction, hospitalization, and need for dialysis.
- h Endpoints which have been consistently shown to be associated with the clinical end point in multiple studies (observational or RCT), and RCTs have consistently demonstrated that improvement in the surrogate translates into a consistent and predictable improvement in the clinical end point.

Figure 2. Algorithm for assigning evidence grades to recommendations (continued from Figure 1, for adequate randomized trials, systematic reviews, or subgroup analyses).



Definitions:

- e Adequate power in a negative study implies that 95% CI exclude a clinically important difference.
- f Effect estimates in each study included in the systematic review are qualitatively similar (ie. in the same direction).
- g “Hard” endpoints such as death, stroke, myocardial infarction, hospitalization and need for dialysis.
- h Endpoints which have been consistently shown to be associated with the clinical end point in multiple studies (observational or RCT), and RCTs have consistently demonstrated that improvement in the surrogate translates into a consistent and predictable improvement in the clinical end point.

Figure 3. Algorithm for assigning evidence grades to recommendations (continued from Figure 1, for observational studies).

of limited trial data within several clinically important areas, the Workgroups may be forced to make limited, opinion-based recommendations. These will be explicitly stated. The distinction between grading of evidence and the perceived importance of each recommendation must not be confused. In this regard, a recommendation receiving a Grade D is just as relevant and

important to the Workgroup as a recommendation receiving a Grade A. Finally, in some instances it may not be appropriate to make a recommendation because of lack of agreement between studies or lack of good-quality evidence. In these situations, specific research recommendations will be stated.

The hemodialysis Workgroup met initially in May 2004 at the

CSN Annual Meeting and again in January 2005. The Chair of the CSN CPG Committee (B. Culleton) and the Chair of the Workgroup (K. Jindal) reviewed and modified the first draft of the hemodialysis guidelines. The document was then formally reviewed by four Canadian nephrologists chosen for their specific research or clinical experience. The document was modified in response to this internal review and a second draft was distributed to all members of the CSN. Comments from this external review were considered in detail and the final revised draft of the hemodialysis guidelines was completed in September 2005.

Sponsorship

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CHAPTER 1: Hemodialysis Adequacy in Adults

Kailash Jindal (Workgroup Chair), Christopher T. Chan, Clement Deziel, David Hirsch, Steven D. Soroka, Marcello Tonelli, and Bruce F. Culleton (CPG Chair)

I. Hemodialysis Adequacy

Recommendations

1. **All hemodialysis patients should have regular global assessments of dialysis adequacy. (Grade D, opinion) Assessment of hemodialysis adequacy should include urea clearance, volume control, blood pressure, mineral metabolism, and clinical symptoms. (Grade C)**
2. **The minimum acceptable target for urea clearance during hemodialysis is a single-pool Kt/V of 1.2 or percent reduction of urea (PRU) of 65% three times per week. (Grade C)**
3. **Hemodialysis centers should consider offering a range of options, including more frequent or sustained treatment times, for those patients with dialysis inadequacy. (Grade D, opinion)**

Background

Urea clearance as assessed by Kt/V or PRU is a surrogate for dialysis dose. Although practice guidelines have traditionally emphasized the role of urea clearance, this parameter is only one component of dialysis adequacy.

The National Cooperative Dialysis Study (NCDS) established that higher dialysis dose resulted in reduced morbidity (1), although the intensity of dialysis in both treatment groups was considerably lower than in current practice. More recently, observational studies have suggested that urea clearance below a single-pool Kt/V of 1.2 or PRU of 65% three times per week is associated with increased mortality (2–6). Although observational data from patients treated with thrice-weekly and quotidian hemodialysis suggest that even higher levels of urea clearance are associated with better clinical outcomes (7–12), a well-designed, randomized study found no benefit of a single-pool Kt/V target of 1.65 compared with 1.25 (13). Although this study cannot exclude a mortality benefit <25%, there is no evidence to support increasing the target Kt/V above currently recommended levels. Since no grade A evidence (apart from the NCDS) indicates that increasing hemodialysis dose will reduce morbidity or mortality, it is possible that reducing the target Kt/V to levels <1.2 might not compromise clinical outcomes. However, in the absence of an adequately powered randomized study to confirm this hypothesis, the Committee continues to recommend a target single-pool Kt/V of >1.2.

Higher levels of urea clearance might be a marker for longer dialysis times, better control of blood pressure (BP) and extracellular fluid volume, or higher clearance of larger molecular weight substances. However, the use of high-flux dialyzers, which remove higher molecular weight toxins more efficiently, does not appear to reduce mortality, making the latter possibility less likely (13). Although the hypothesis that improved

volume control will reduce mortality is attractive, it remains untested in hemodialysis patients. Nonetheless, optimal control of extracellular fluid volume and BP are rational goals given the large body of evidence linking these characteristics to better health outcomes. Longer dialysis duration or more frequent dialysis treatments may aid in achieving these clinical objectives.

To ensure that patients are receiving the prescribed urea clearance, the clinician must regularly monitor and measure the dose delivered. Urea clearance should be measured at least every 8 wk. Examples of acceptable techniques for estimating delivered dose are formal single-pool urea kinetics, PRU or urea reduction ratio (URR), and Kt/V natural logarithm formulae.

Of the three suggested techniques, single-pool urea kinetics predicts the dose delivered most accurately. However, the goal of monitoring urea clearance is to ensure that patients receive at least a minimum dose of therapy. Although PRU does not take into account urea removal by ultrafiltration, measurements using this technique will underestimate the dialysis dose, which would not compromise patient care. Similarly, the contribution of residual renal function can be ignored. Because all three parameters correlate with mortality, there is no strong reason to recommend one in particular. Clinicians should consider reproducibility, ease of use, and familiarity when selecting a measure of urea clearance for use in their hemodialysis programs. To facilitate comparisons between units, the index of urea clearance used should be consistent within a hemodialysis program. Methods for measuring urea clearance appear in Appendix A.

Clinicians should recognize that staff and patients may conduct themselves differently on the day when the dose of therapy is being measured. Therefore, clinicians are encouraged to use some additional techniques, which may be less precise but permit the measurement of the dose of hemodialysis delivered on a daily basis (*e.g.*, volume of blood processed, average pump speed, and duration of treatment), and to correlate them with the more formal dosage measurement.

In addition to considering urea clearance and volume status, the clinician must consider many other measures and indicators in assessing a patient's health and prescribing treatment, including control of extracellular volume and BP, uremic symptoms, quality of life, control of hyperphosphatemia, adequate nutritional status, and treatment of anemia. (See the guidelines on Mineral Metabolism and Management of Blood Pressure in Hemodialysis Patients for details).

Hemodialysis centers should have a continuous quality improvement/patient review system in place that recognizes pa-

tients who are receiving suboptimal dialysis adequacy, identifies the cause, and corrects it. This process may be facilitated by the use of multidisciplinary sit-down rounds in addition to regular contact between patients and nephrologists (14).

Although there are no randomized studies demonstrating that nocturnal, daily, or sustained hemodialysis treatments improve clinical outcome compared with standard care (12), multiple observational studies indicate that such treatments may improve surrogate outcomes in select patients at a reasonable cost (7–9,15–20). Recognizing that this evidence base is inconclusive, hemodialysis centers should consider offering a range of options for hemodialysis including more frequent or sustained treatment times, especially for patients in whom standard dialysis appears inadequate. (See the guideline on Frequent and Sustained Hemodialysis). On the other hand, less frequent dialysis may be acceptable for brief periods in patients with greater levels of residual kidney function, or those in whom the primary indication for dialysis is control of extracellular fluid volume rather than solute clearance (*i.e.*, those with renal insufficiency due to severe heart failure).

II. Managing Suboptimal Dialysis Adequacy

Recommendations

1. **Confirm dialysis inadequacy by assessing procedural issues and vascular access function. (Grade D)**
2. **Once dialysis inadequacy is confirmed, increase one or more of the following treatment parameters: dialysis time, needle diameter, dialyzer KoA, or dialysis frequency. (Grade D)**

Background

When the patient fails to receive the minimum target dose of dialysis or when there is a significant drop in the dose of dialysis being delivered, the clinician should consider procedural issues (prescription, anticoagulation, appropriate measurement of dialysis dose, optimization of needle placement) and inadequate access function (Table 1).

The following techniques may be used to increase urea clearance and possibly dialysis adequacy:

- blood flow rate (21,22)
- dialyzer KoA (21)
- dialysis time (23)
- dialysis frequency (23)
- dialysate flow (24–26)
- needle size (27)
- ensuring adequate anticoagulation (28)

Consideration could also be given to use of a newer dialytic modality such as more frequent or sustained hemodialysis.

III. Quality of Care

Recommendations

1. **A single person or a multi-professional team should be responsible for the quality of the medical care and have the authority to establish universal standards of care for the unit. (Grade D, opinion)**

Table 1. Initial approach to low or inadequate delivered hemodialysis

Check Procedural Issues

1. Was the dialysis prescription followed?
 - blood flow rate
 - duration of treatment
 - intradialytic hypotension or other factors necessitating interruption of treatment
 - dialysate flow
 - specific dialyzer
 - volume of blood processed
2. Was anticoagulation adequate?
3. Was the dialyzer total cell volume (TCV) adequate? (for reprocessed dialyzers)
4. Was blood sampling appropriate? Consider repeating the clearance measurement.
5. Was needle placement appropriate and optimal?

Assess Access Function

1. Examine vascular accesses for evidence of dysfunction.
2. In arteriovenous accesses, consider measuring access blood flow, preferably using an ultrasound dilution technique. If indicated, perform angiography to rule out stenosis.
3. If access blood flow measurements are not available, consider estimating access recirculation using blood-based urea measurements.
4. Review needle placement and access configuration. Using loop grafts, ensure accurate knowledge of direction of flow. With needles inserted, compressing the graft between the needles results in pulsation only in the arterial needle.

2. **Validated clinical protocols or algorithms should be considered to reduce inappropriate variability in quality of dialysis care. (Grade D)**

Background

To ensure the quality of medical care for all patients, all those involved in providing care must be accountable. In a multi-professional setting, the combination of a number of different professionals with different priorities dealing with complex situations may lead to variations in standards of practice and care. To ensure that the guidelines are applied uniformly to all patients in the unit, the individual or management team accountable for the quality of medical care must be clearly identified. The multidisciplinary team/dialysis program should evaluate its practice *via* Continuous Quality Improvement.

Maximizing patient adherence is critical to the long-term success of therapy. An environment that encourages optimal care may include the patient's primary care physician and appropriate specialists (*e.g.*, gynecologists, endocrinologists) in the patient's care. There is evidence that an individualized, patient-centered approach improves clinical performance compared with standard care (29).

Nonadherence may be the result of a number of factors (*e.g.*, socioeconomic, educational, emotional) that are beyond the patient's control and may require specific attention from physicians or allied health personnel. The clinician should provide appropriate information about renal failure and its treatment, and encourage patients to have continuing contact with their primary care physicians. The information provided to patients should account for educational level and language differences.

The increasing number of hemodialysis patients may potentially compromise the ability of clinicians to provide optimal care. Although management of hemodialysis patients is complex and multifactorial, many of the individual components of care (management of metabolic bone disease or anemia, control of extracellular fluid volume) are amenable to protocolization. Although no studies indicate that such protocols improve clinical outcomes, they appear to improve process of care in patients with and without end-stage renal disease (ESRD) (30,31). Protocolization of these facets of care would be expected to free more of clinicians' time to devote to other aspects that require more individualized attention.

Recommendations for Research

1. An adequately powered, randomized study to determine the impact of aggressive control of BP and extracellular fluid volume (*versus* standard care) on mortality, morbidity and hospitalization should be a high priority.
2. Since available evidence focuses on process-based outcomes, additional randomized trials evaluating the impact of bedside decision support systems, clinical protocols, or multidisciplinary care teams on clinical outcomes such as morbidity or hospitalization would be useful for formulating policy.

Appendix A

Drawing Samples for Measuring Urea Clearance

1. Predialysis and postdialysis samples must be drawn at the same dialysis session.
2. Draw predialysis blood from the arterial needle before administering any saline or heparin.
3. When central lines are used and if heparin and/or saline is used, withdraw at least 10 cc of blood before drawing the blood sample. The blood withdrawn may then be returned to the patient.
4. The postdialysis [urea] blood sample must not be diluted by either recirculation or saline.
5. For formal urea kinetic modeling, the sample must be drawn before any rebound; therefore, the slow flow/stop pump technique must be used. For other techniques (PRU and log prediction of Kt/V), the blood sample may be taken postdialysis when the possibility of access and cardiopulmonary recirculation is eliminated. To eliminate the possibility of cardiopulmonary recirculation, draw the sample at least 2 to 3 min postdialysis. To facilitate longitudinal comparisons, the sampling technique for the unit should be clearly stated, documented, and consistent from treatment to treatment and between patients.

Background

Because the goal is to ensure at least a minimum standard, a postdialysis sample is preferable and easier to obtain than a

stop flow sample. Although the postdialysis sample may be more variable (due to rebound), it will tend to underestimate rather than overestimate delivered dialysis.

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CHAPTER 2: Management of Blood Pressure in Hemodialysis Patients

Kailash Jindal (Workgroup Chair), Christopher T. Chan, Clement Deziel, David Hirsch, Steven D. Soroka, Marcello Tonelli, and Bruce F. Culleton (CPG Chair)

I. Blood Pressure Measurement—Timing and Targets

Recommendations

1. **Use predialysis blood pressure to guide therapy. (Grade C)**
2. **Target predialysis blood pressure to be <140/90 (Grade C); optimal blood pressure is unknown.**
3. **Ambulatory recording devices or home self-measurement should be applied to patients where difficulty occurs in reaching target blood pressure levels. (Grade D, opinion)**

Background

Blood pressure (BP) varies significantly in hemodialysis patients depending upon the time taken: predialysis, postdialysis, or interdialytic. It is currently unknown which time period correlates best with long-term patient outcome, given the lack of treatment trials (1–3). It is difficult to relate usual clinical BP measurements in hemodialysis patients to published research studies because usual systolic and diastolic pressures both pre- and postdialysis are significantly higher by about 14/5 mmHg than if measured according to standardized American Heart Association criteria (4).

There is convincing evidence in the general population that hypertension is associated with increased cardiovascular mortality and morbidity, and that its control can reduce these adverse consequences (5). Observational studies in the hemodialysis population have demonstrated that hypertension is also associated with adverse consequences in these patients, especially with longer-term follow-up (6–9). Although there are no controlled trials demonstrating that control of BP by dialytic or pharmacologic means in hemodialysis patients reduces these mortality and morbidity rates, it would seem reasonable to generalize from the extensive evidence available for the general population with hypertension (2,3).

Long-term observational studies suggest that even mean arterial BP of >98 mmHg is associated with an increased risk of death compared with lower pressures (8). Other observational studies, performed in populations with older patients having a higher prevalence of cardiovascular comorbidity than the study cited above, suggest that low pre- and/or postdialysis BP may be associated with a higher risk of death than BP in excess of 140 to 150 mmHg systolic (10,11). The discrepancy between the above observations may well be an artifact of the confounding of reduced BP by severe cardiac disease (12).

Given the absence of enough data to define an optimal BP in the dialysis population, the committee selected a target predialysis BP of <140/90 mmHg. The lower target of <130/80

mmHg recommended by the Canadian Hypertension Education Program (13) for patients with diabetes or chronic kidney disease was not selected, because there are two randomized clinical trials documenting no benefit for a lower target in nondialysis patients (14,15) and associative studies (above) suggesting possible risks for the lower target in dialysis patients.

II. Management of Hypertension

Recommendations

1. **Limit patients to a dietary sodium intake of 80 to 100 mEq/d. (Grade C)**
2. **Reduce patient weight gradually by ultrafiltration, targeting for the “dry” weight, as antihypertensive medications are withdrawn. (Grade C)**
3. **“Paradoxical” rises in BP during individual dialysis/ultrafiltration sessions should be corrected by further gradual volume removal. (Grade D)**

Background

In nondialysis hypertensive patients, dietary sodium restriction may lower BP by 4.2/2.0 mmHg to 5.2/3.7 mmHg (16). It is also possible to control hypertension in many hemodialysis patients by restriction of dietary sodium to <100 mEq/d and aggressive and recurrent efforts to reduce body weight by ultrafiltration during dialysis to the “dry” weight. “Dry” weight may be defined as the lowest attainable weight at which patients are normotensive without antihypertensive medications and do not have symptoms of postural hypotension or intra/postdialytic hypotension. During this process of probing for “dry” weight, antihypertensive medications are gradually withdrawn (8,17). In turn, improved survival is associated with better BP control (8,18). Paradoxical elevation of BP during ultrafiltration is associated with volume overload and can be corrected by further aggressive reduction in target body weight (19).

The lag phenomenon has been described in hemodialysis patients whereby BP reduction lags behind reduction in volume status for weeks to months (20). Thus, efforts to control BP by reduction of dry weight must be gradual but persistent.

There is preliminary, nonrandomized evidence that extended forms of hemodialysis such as nocturnal dialysis and short daily dialysis are effective in improving BP control (21). In contrast, there is no convincing evidence at this time that intradialytic volume monitoring is effective in reducing symptoms or improving BP control. In fact, a recent randomized trial

suggests that intradialytic volume monitoring may be harmful (22).

4. **Avoid positive sodium balance induced by hypertonic dialysate and/or sodium profiling during volume status adjustment. (Grade C)**
5. **Reduce dialysate temperature when intradialytic hypotension limits ultrafiltration. (Grade C)**
6. **If antihypertensive agents are required, select agents with pharmacokinetics suitable for dialysis patients and appropriate for existing comorbid conditions. (Grade D)**

Background

Hypertonic dialysate and sodium profiling may induce net positive sodium balance in some patients, worsening hypertension and interdialytic thirst (23–25).

Lowering dialysate temperature is often effective in moderating intradialytic hypotension during attempts to achieve dry weight, particularly for hypothermic patients. A minimum dialysate temperature of 35°C has been used if feedback-controlled isothermic dialysis is not available (26,27).

There are no published controlled trials of specific antihypertensive agents in dialysis patients, and retrospective studies have provided conflicting evidence for the possible survival benefits of various classes of antihypertensive drugs (28–30). Long-acting (renally-excreted) agents such as atenolol, perindopril, or lisinopril can control hypertension occurring in dialysis patients. Administered thrice weekly after dialysis, these agents can assist in BP control without inducing significant hypotension (31,32).

Recommendations for Research

1. Treatment trials are required in which specific BP targets in hemodialysis patients are compared with regard to mortality and morbidity outcomes.
2. Randomized trials are needed to determine the optimal use of specific classes of antihypertensive agents in hemodialysis patients.

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CHAPTER 3: Mineral Metabolism

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Management of Serum Phosphate, Serum Calcium, and Parathyroid Hormone

Recommendations

1. Serum phosphate levels should be monitored and maintained within the normal range. (Grade C)
2. To optimize control of serum phosphate, use restriction of dietary phosphate (Grade D), adjust the dialysis prescription (Grade D), and use oral phosphate binders. (Grade C)

Background

Elevated serum phosphate is common in individuals with stage 5 chronic kidney disease. Multiple studies have shown that elevated serum phosphate is associated with increased morbidity and mortality due to cardiovascular disease in the hemodialysis population (1–5). Increased serum phosphate is also involved in the pathogenesis of secondary hyperparathyroidism (6,7).

The current Kidney Disease Outcomes Quality Initiative (K/DOQI) target level for serum phosphate levels (0.80 to 1.78 mmol/L) was partially based upon studies showing an association between cardiovascular disease morbidity and mortality and elevated serum phosphorus. In at least two of these studies, the association only reached significance at higher levels of serum phosphate (>2 mmol/L) (1,3). Decreasing phosphate levels toward the normal or target range might be associated with decreased mortality. However, to date, no randomized trials support this hypothesis.

To achieve an optimal phosphate level, the following strategies can be used:

- a. Restriction of dietary phosphate. A phosphorus intake of 800 to 1000 mg per day is recommended to help achieve serum phosphorus levels of 0.80 to 1.78 mmol/L. On an intake of 1000 mg per day, about 60 to 70% is absorbed. Dietary counseling has been shown to improve phosphate control in hemodialysis patients (8,9). Further research is warranted to ascertain whether phosphorus levels differ on a diet high in plant protein *versus* animal protein.
- b. Removal of phosphate by hemodialysis. Phosphate is mainly intracellular; therefore, clearance of phosphate during hemodialysis follows a pattern of most efficient clearance within the first 1 to 2 h with a plateau, and then rebounds within the first 4 h after the end of the treatment (10). The amount of phosphate removed is dependent also on the predialysis level. On average, about 900 to 1000 mg of phosphate can be removed per dialysis treatment. High-flux (*versus* low-flux) efficiency membranes may have higher phosphate clearances but phosphate removal is not signifi-

cantly altered. Dialysis phosphate clearance may be improved by the use of frequent and longer dialysis, especially nocturnal hemodialysis (10,11).

- c. Use of phosphate binders. Given that most hemodialysis patients are in positive phosphate balance, there is a need to use phosphate binders to decrease phosphate absorption in the gut.

Because of the concern with aluminum toxicity, calcium-based binders continue to see extensive use. There has been increasing concern about the over-reliance of calcium-based phosphate binders due to the associated calcium load. Studies have found an association between daily calcium intake and coronary artery calcification (12–14) and calcification in other vascular beds (15). These data, plus extrapolation from studies of calcium balance and daily requirements, led the K/DOQI Mineral Metabolism Guideline Committee to recommend not exceeding the use of >1500 mg of elemental calcium in calcium-containing binders with a tolerable upper limit of 2500 mg for total calcium intake per day (16).

Despite the availability of several classes of phosphate binders, the majority of hemodialysis patients continue to have elevated phosphate levels (17,18). This illustrates the lack of efficacy of the available binders. When deciding on the choice and dose of binder(s) to use, it is important to realize that many of the clinical studies are of short duration (19–24), nonrandomized (20–22,25–31), open-label (19–22,25–28,30–38), or use no direct comparator (20–22,26–28,30,31,35). In addition, average medication doses or changes in laboratory parameters are not always reported, and adherence to binders ranges from 69 to 91%. As a result, available evidence does not allow the recommendation of one (or several) phosphate binders as superior to any other.

Recently, interest in the use of noncalcium-, nonaluminum-based binders has increased. Coronary artery calcification scores are lower in subjects treated with sevelamer compared with those treated with calcium binders (37). At the time of writing this guideline, only preliminary results were available from the Dialysis Clinical Outcomes Revisited (DCOR) trial. DCOR was a controlled clinical trial of approximately 2100 hemodialysis patients randomized to receive calcium-based phosphate binders or sevelamer. Three years after randomization, a 9% decrease in all-cause mortality (primary endpoint) was seen in those subjects assigned to sevelamer, although this did not reach statistical significance ($P = 0.30$) (39). Although subgroup analyses demonstrated that sevelamer use was associated with a reduction in mortality in subjects over 65 yr of age, interpretation of these data should await the final peer-

reviewed publication. It should also be kept in mind that, compared with calcium-containing phosphate binders, use of sevelamer is no better at controlling serum phosphate and is associated with greater health care costs (23,40).

3. Serum calcium levels should be monitored and maintained within the normal range. (Grade D)

Background

For the prevention of secondary hyperparathyroidism, individuals with kidney disease should have calcium levels maintained in the normal range defined by the testing laboratory. Although it is generally accepted that total serum calcium levels should be adjusted for serum albumin, Clase *et al.* found that total calcium had a higher correlation with the gold standard of ionized calcium measurement than many formulas (41).

Calcium-based phosphate binders contribute to the total daily calcium load in hemodialysis patients. Higher daily calcium intake is associated with poor outcomes including coronary calcification (13,14) and rapid progression of calcification in other vascular beds (42). Although several studies have reported an association between hypercalcemia and decreased survival (2,18,43), this finding is not consistent across all reports (1,44). Serum calcium is also inversely associated with intact parathyroid hormone (PTH) (44). In the setting of low PTH, suggesting low turnover bone disease, an increased calcium load cannot be incorporated into bone, and thus can precipitate into blood vessels, heart valves, and other soft tissues (45). Given that the above results and hypotheses are based upon associative data, may be confounded by vitamin D use, and have not been tested in controlled clinical trials, firm recommendations limiting the daily oral calcium intake cannot be made by this committee.

Dialysate calcium also impacts calcium balance. Fernandez *et al.* reported that the use of 1.25 mM dialysate calcium resulted in negative calcium balance, despite no change in serum ionized calcium values (46). However, compared with 1.75 mM dialysate calcium, 1.25 mM dialysate calcium led to higher parathyroid hormone levels and greater use of vitamin D.

- 4. Measure PTH levels on a regular basis (at a minimum every 4 mo) (Grade D, opinion) and direct therapy to avoid both high and low PTH levels. (Grade C)**
- 5. Give priority to phosphate and calcium targets over the management of PTH. (Grade D, opinion)**
- 6. Avoid intact PTH (iPTH) levels below 100 pg/ml (10.6 pmol/L) (Grade C); iPTH levels >500 pg/ml (53 pmol/L) should be treated if accompanied by symptoms or clinical signs of hyperparathyroidism. (Grade D, opinion)**
- 7. Vitamin D sterols can be used in the treatment of secondary hyperparathyroidism, but should be discontinued when PTH levels decrease below target levels, or if calcium or phosphate levels increase above target levels. (Grade C)**
- 8. Parathyroidectomy should be considered for those patients who have failed standard treatments and have persistently elevated PTH levels with systemic complications. (Grade D, opinion)**

Background

Given that PTH is a major regulator of bone turnover and skeletal cellular activity, PTH is widely used as a surrogate marker instead of bone histomorphometric analysis (the gold standard). Recently, many questions have been raised about the method of PTH measurement, the normal or optimal range of the PTH level, and the correlation of PTH levels with bone histology. The principal method of measurement of PTH over the last couple decades has been a two-site immunometric technique called the “intact” PTH (iPTH) assay. This form of measurement has been widely used and is the basis of current classification schemes for bone turnover. It is now known that assays measuring iPTH also measure a large PTH fragment (PTH 7 to 84). This has led to assays specific for PTH 1 to 84 (biointact or whole PTH assays). Although these new assays appear promising, much of the data with renal bone disease and the correlation with PTH levels exist for iPTH measurements. On this basis, the current guidelines use target levels based upon the iPTH assay. Users of these guidelines are instructed to determine the assay used locally and use sound clinical judgment if the biointact or whole PTH assay is used.

Much of the research that correlates iPTH values to bone biopsy findings was done at least 10 yr ago, where iPTH levels <165 pg/ml (17.5 pmol/L) were associated with adynamic bone disease (low turnover disease) and iPTH levels >300 pg/ml (31.8 pmol/L) correlated with high turnover bone disease (47–49). However, it has also been shown that use of calcitriol modifies the relationship between iPTH and indices of bone formation and turnover (50).

Coen *et al.* used receiver-operator characteristic (ROC) curves to determine that a cutoff value of 210 pg/ml (22.3 pmol/L) for iPTH had a positive predictive value of 100 and a negative predictive value of 45 in predicting adynamic bone disease *versus* mixed osteodystrophy or high turnover disease (51). In the K/DOQI bone metabolism guidelines, summary ROC curves from 5 individual studies revealed that a threshold iPTH level of 150 to 200 pg/ml (15.9 to 21.2 pmol/L) had a sensitivity of 93% and specificity of 77% for diagnosis of high turnover bone disease, while a PTH value of 60 pg/ml (6.4 pmol/L) or less had a sensitivity of 70% and specificity of 87% for low bone turnover (16).

Controlling or preventing secondary hyperparathyroidism is important in patients with chronic kidney disease. Not only is there concern about renal bone disease, but also increasingly there is concern about other systemic toxicities. Several studies have shown that moderate to severe elevations of iPTH are associated with increased morbidity and mortality (1–3). In addition, decreased iPTH levels are also associated with increased morbidity and mortality (4,44,52). Therefore, iPTH values both above and below the current target range are undesirable.

Specific treatment strategies include maintaining normal calcium and phosphate levels. Calcium supplementation may also be needed to maintain serum calcium with the normal range. Vitamin D analogs $1\alpha(\text{OH})\text{D}_3$ or $1,25(\text{OH})_2\text{D}_3$ are used to treat patients with elevated PTH levels as they act by suppressing prepro-PTH-mRNA in the parathyroid cell. Vitamin D analogs

can be prescribed daily or intermittently, orally or intravenously. Clinical trials have been inconclusive in determining the best route of administration (53–55). Intravenous therapy after dialysis is an effective way to ensure compliance. All vitamin D analogues have the ability to increase serum levels of calcium and phosphate, and although this effect may be less with newer analogues, valid studies with relevant clinical outcomes are not available (5,56–63).

Parathyroidectomy is used for secondary hyperparathyroidism that is not controlled by standard medical therapy, and is associated with other clinical indications, such as elevated serum calcium or phosphate, tendon rupture, resistant anemia, or bone pain. A recent analysis of US Renal Data System data shows that although mortality is higher for the first 3 mo after parathyroidectomy, a survival advantage is apparent 20 mo postoperatively (64).

A calcimimetic agent, specifically cinacalcet, has recently been released for the treatment of secondary hyperparathyroidism in dialysis patients. Cinacalcet binds to the calcium-sensing receptor on the PTH gland cells and increases the sensitivity of the receptor to calcium. The largest study published confirmed that subjects treated with cinacalcet had a therapeutic response, with 43% achieving an iPTH level of <250 pg/ml (26.5 pmol/L) as compared with only 5% in the control group (65). The decrease in iPTH was seen at all levels of baseline iPTH. Additional benefits seen were significant decreases in serum phosphate, calcium and calcium $\times$ phosphorus product. Hypocalcemia can occur, but can be minimized by dose titration plus the addition of vitamin D analogues to maintain a normal serum calcium level. All the published studies with cinacalcet have been of relatively short duration, using the surrogate endpoints of iPTH, phosphate, and calcium. Longer-term use will be needed to determine the impact on use of phosphate binders, calcium supplements, and vitamin D analogues, and perhaps more importantly the impact of decreasing iPTH on morbidity and mortality.

Recommendations for Research

1. Although many studies have shown that elevated phosphate, calcium, and iPTH are associated with increased morbidity and mortality, prospective randomized studies are needed to determine whether achieving suggested targets for calcium and phosphate decreases mortality in hemodialysis patients.
2. Studies are needed to determine the appropriate target range of PTH (intact or whole assays) for normal bone metabolism in stage 5 chronic kidney disease patients on dialysis.
3. Evaluate the impact vitamin D sterols and calcimimetics on morbidity and mortality in hemodialysis patients.

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CHAPTER 4: Vascular Access

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I. Planning for Vascular Access

Recommendations

1. **Each center should establish a dedicated team for vascular access. (Grade D, opinion)**
2. **Preserve arm veins suitable for placement of vascular access. Preservation should begin in patients with progressive kidney disease and an estimated GFR of less than 30 ml/min. (Grade D, opinion)**
3. **The preferred type of vascular access is a radio-cephalic native vessel arteriovenous fistula. (Grade C)**

Background

Arteriovenous (AV) access–related complications result in considerable morbidity. With a dedicated access team, including a nephrologist, an access surgeon, an interventional radiologist, and a dialysis nurse, a center can develop and maintain skills that should lead to better patient care. Arm veins, particularly the cephalic veins of the nondominant arm, should not be used for venipuncture or intravenous catheters. In patients with advanced chronic kidney disease, the dorsum of the hand should be used for intravenous line. When venipuncture of the arm veins is necessary, sites should be rotated. Patients should wear a Medic Alert bracelet to inform hospital staff to avoid intravenous cannulation of essential veins.

The preferred type of access is a native AV fistula, followed by grafts and then central venous catheters (1–5). It has been shown that the relative risk of bacteremia is greater with central venous catheters than with AV fistulae (6). Compared with AV grafts, AV fistulae have been shown to be associated with better long-term survival, require less intervention to maintain patency, have lower infection rates, and lead to less health care expenditure (1–5,7). Data from the Canadian Organ Replacement Registry show equivalent patient survival on hemodialysis and peritoneal dialysis (8). This information should be considered before using central venous catheters for long-term hemodialysis as opposed to peritoneal dialysis, when both are technically feasible.

The preferred sites for placing the AV fistula are (in order of preference) the wrist (radiocephalic) and the elbow (brachiocephalic) (3,9,10). If it is not possible to establish either of these types of fistula, access may be established using either a transposed brachial-basilic vein fistula (3) or an AV graft of synthetic material (*e.g.*, polytetrafluoroethylene [PTFE]). The preferred site and type of graft is a forearm curved looped radiocephalic graft. This is followed by an upper arm straight graft (11). The least preferred sites and type of grafts are forearm straight radial cephalic and looped thigh grafts. However, the location for the graft placement is determined by each patient's unique

anatomical restrictions, previous access history, and the surgeon's skill.

During the planning phase for a new vascular access, venography may be beneficial and may be considered in patients with the following:

- edema in the extremity in which an access site is planned,
- collateral vein development or accessory vein enlargement in any planned access site,
- differential extremity size, if that extremity is contemplated as an access site,
- current or previous subclavian catheter placement of any type in venous drainage of planned access,
- current or previous transvenous pacemaker in venous drainage of planned access,
- previous arm, neck, or chest trauma or surgery in venous drainage of planned access, or
- multiple previous accesses in an extremity planned as an access site.

For patients not yet on dialysis, the benefit of the information gained with venography must be weighed against the risk associated with exposure to radio-contrast media.

II. Access Timing, Placement, and Maturation

Recommendations

1. **Establish AV fistulae when the patient has an estimated GFR of 15 to 20 ml/min and progressive kidney disease. (Grade D, opinion)**

Background

It is important to create an AV fistula *at least* 3 to 4 mo before its anticipated use. More time may be necessary depending upon the site's referral and surgical wait times. Grafts can be used in patients who are not candidates for a primary AV fistula. Place dialysis PTFE AV grafts at least 3 to 6 wk before an anticipated need for hemodialysis. According to the available evidence, PTFE tubes are preferred over bovine grafts (12). There is no evidence available yet on the efficacy of newer synthetic materials. When using these materials, follow manufacturers' recommendations.

Cuffed and uncuffed hemodialysis catheters can be inserted immediately before their use because they do not require maturation time. Cuffed, tunneled, central venous catheters can be a valuable alternative to grafts, although there are concerns about infection, thrombosis, and dialysis adequacy. Adjust the catheter tip to the level of caval atrial junction or beyond. Subclavian access should be used only when jugular options

are not available. Catheter position should be confirmed using radiography, and the catheter tip should be readjusted as necessary to ensure proper position. The use of real-time, ultrasound-guided insertion may be an advantage in reducing insertion-related complications, particularly in patients who have had previous catheter insertions (13,14). Do not place jugular or subclavian hemodialysis catheters on the same side as a maturing AV access.

For patients with chronic kidney disease who need acute hemodialysis vascular access, use a noncuffed or a cuffed percutaneously inserted catheter. These catheters are suitable for immediate use and should not be inserted before needed (15). Femoral catheters should be at least 19 cm long to minimize recirculation. Noncuffed femoral catheters should be sutured in place and can be left in as long as there are no complications.

AV fistulae need time to mature before cannulation (at least one month, preferably 3 mo). Recent data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrates a large intercountry variability in the timing of AV fistula cannulation. The majority of fistulae in Europe are cannulated early—within 8 wk of creation. Early cannulation does not appear to be associated with subsequent fistula failure and may decrease exposure time to central venous catheters (16). As AV fistula maturation depends on artery and vein size and integrity as well as cardiac output, clinical judgment should be used in determining time to first use. The following procedures have been used in an attempt to enhance maturation of AV fistulae:

- fistula hand-arm exercise (e.g., squeezing a rubber ball with or without a lightly applied tourniquet),
- selective obliteration of major venous side branches,
- rest, until swelling is resolved (for a new native AV fistula with induration and edema).

A new PTFE dialysis AV graft should not be cannulated until swelling has gone down enough to allow palpation of the course of the graft—ideally 3 to 6 wk after placement. Ideally, no attempt should be made to cannulate the graft for at least 14 d after placement. Use a venogram or other noncontrast study to evaluate central veins in patients with swelling that does not respond to arm elevation, or that persists >2 wk after dialysis AV access placement.

III. Monitoring and Maintenance of Vascular Access

Recommendations

1. **Measure access flow bimonthly in AV fistulae (Grade D) and venous pressure or access flow monthly in AV grafts. (Grade D)**
2. **Perform angiography if fistula flow decreases to <500 ml/min or drops >20% from baseline (Grade D); if AV graft flow decreases to <650 ml/min or drops >20% from baseline. (Grade D)**

Background

Monitoring AV fistulae and grafts for hemodynamically significant stenosis, combined with corrective treatment, improves patency and decreases the incidence of thrombosis (17–24). A

Table 2. Methods to measure dynamic, static, and slow-flow venous pressures

*Dynamic Venous Dialysis Pressure Monitoring Protocol**

- Establish a baseline initiating measurements when the access is first used.
- Measure venous dialysis pressure from the hemodialysis machine at Qb 200 ml/min during the first 2 to 5 min of hemodialysis at every hemodialysis session.
- Use 15-gauge needles (or establish own protocol for different needle size).
- Assure that the venous needle is in the lumen of the vessel and not partially occluded by the vessel wall.
- Pressure must exceed the threshold three times in succession to be significant.
- Assess at same level relative to hemodialysis machine for all measurements.

Static Venous Pressure Measurement Protocol

- Turn the blood pump off and clamp tubing between the dialyzer and the venous drip chamber.
- Make static measurement (P) from venous transducer exactly 30 s after stopping blood flow.
- Determine in centimeters the height difference between the arm of the chair and blood in the venous drip chamber (H).
- Calculate estimated intra-access pressure: $[eIAP = P + (0.35 \times H + 3.4)]$
- Measure mean arterial pressure (MAP).
- Calculate eIAP/MAP (absolute eIAP/MAP >0.5 or a progressive rise on repeated measurements indicates a stenosis/thrombosis beyond the venous needle site in AV grafts).

Slow Flow Venous Pressure Measurement Protocol

- Measure venous pressure from machine transducer at a blood flow of 50 ml/min during first 15 min of dialysis.
- Measure MAP.
- Calculate ratio of various pressures and MAP.
- Investigate any venous pressure/MAP ratio >0.6.

*To interpret the dynamic protocol, the clinician must obtain three measurements in succession above the threshold to eliminate the effect of variation caused by needle placement. Hemodialysis machines measure pressure with different monitors and tubing types and lengths. These variables, as well as needle size, influence venous dialysis pressure. The most important variable affecting the dynamic pressure at a blood flow of 200 ml/min is the needle gauge. It is essential to set thresholds for action based on machine manufacturer, tubing type, and needle gauge.

quality assurance program should collect and maintain data on each patient from the monitoring tests, clinical assessment, and dialysis adequacy measurements, and make this information available to all staff. The data should also be tabulated and

tracked within each dialysis center and benchmarked against regional or national standards.

Although recirculation studies have been shown to be useful for detecting AV fistulae stenosis, the recirculation only occurs when the total access flow is lower than the blood flow in the dialysate circuit. Therefore, the preferred method for monitoring AV fistulae is direct on-dialysis flow measures (18). When clinicians do not have access to on-dialysis flow measures, they can monitor AV fistulae using regular recirculation studies (25).

When using flow measures, clinicians should be aware that AV fistulae are capable of sustaining a lower blood flow than an AV graft without clotting, so a flow measurement <650 ml/min in an AV fistulae is less likely to indicate a reversible stenosis or subsequent clotting. However, relative changes in flow measurement are still a cause for concern. After a successful angioplasty, AV fistulae should be monitored monthly and investigated if a flow <500 ml/min or a drop of access flow >20% of baseline occurs (18–20).

When using access recirculation measures, clinicians should be aware that any access recirculation is abnormal and should be investigated. Recirculation >5% using non-urea-based methods and recirculation >15% measured using urea-based method is significant and should lead to angiography.

Methods for monitoring AV grafts include:

- intra-access flow including monitoring for changes in flow (26–33),
- static venous pressures (25),
- dynamic venous pressures (34),
- slow-flow venous pressure (35).

Blood access flows through AV grafts can be measured by indicator dilution or conductivity tracer techniques, using the Krivitski reversed line technique (28). In a prospective study of 170 chronic hemodialysis patients, May *et al.* demonstrated that access blood flow measurements were superior in the prediction of access thrombosis compared with static pressure monitoring or urea recirculation measurement (30). However, in a blinded, randomized, controlled trial of AV graft monitoring and angioplasty, monthly blood flow measurement did not improve graft thrombosis rate over and above the standard surveillance (dynamic venous pressure and physical examination) (36).

When using pressure measurements to monitor access, clinicians should be aware that static pressure measurements are more accurate than dynamic pressure measurements (25). Methods to measure dynamic, static, and slow-flow venous pressures are provided in the Table 2.

Other studies or information that may be useful in detecting AV graft stenosis include:

- measurement of access recirculation using urea concentrations;
- measurement of recirculation using dilution techniques (non-urea-based);
- unexplained decreases in the measured amount of hemodialysis delivered (urea reduction ratio, Kt/V);

- physical findings of persistent swelling of the arm with the graft, prolonged bleeding after needle withdrawal, or altered characteristics of pulse or thrill in a graft;
- elevated negative arterial prepump pressures that prevent increasing to acceptable blood flow;
- venography/Doppler ultrasound.

Any finding of access dysfunction, whether based on the presence of access recirculation, low or deteriorating access blood flow rates, positive pressure tests, or any other test should be investigated using angiography to determine the appropriate intervention (*e.g.*, angioplasty, surgery).

In the process of investigating the dysfunction and taking corrective measures, it is vital that the clinician take interim measures to protect the patient. When the dialysis circuit blood flow exceeds the access flow, access recirculation will occur, which leads to inadequate dialysis. To optimize dialysis treatment, the dialyzer blood flow should be reduced to a level at or just below the patient's measured access blood flow rate. The clinician should make the appropriate corrections by time and dialyzer surface area to ensure that the patient receives the desired and prescribed Kt/V (urea).

IV. Infection Prevention in the Vascular Access

Recommendations

1. **Instruct all staff and patients on infection control measures. (Grade D, opinion)**
2. **Change catheter exit site dressings at each hemodialysis treatment (Grade D, opinion). Use dry gauze dressings and povidone iodine (Grade C), mupirocin (Grade C), or polysporin triple ointment (Grade A) at the catheter exit site.**

Background

Proper infection control procedures can significantly reduce the risk of infection. Catheter care and accessing the patient's circulation should be sterile procedures. During catheter connect and disconnect procedures, nurses and patients should wear a surgical mask or face shield. Nurses should also wear gloves during all connect and disconnect procedures, although the evidence for sterile *versus* nonsterile gloves is inconclusive. Use a clean technique for needle cannulation for all cannulation procedures. Ensure that only trained dialysis staff or caregivers change hemodialysis catheter dressings and manipulate catheters that access the patient's bloodstream and minimize contamination.

A randomized control trial of dry gauze dressing with povidone iodine ointment at the catheter exit site, along with sterile dressing technique, resulted in a significant reduction in *Staphylococcal aureus* exit site infections, bacteremia, and catheter tip colonization (37). The beneficial effect was most evident in *S. aureus* carriers. Similar results have recently been reported using mupirocin and polysporin triple ointment (38). In the recent study by Lok *et al.*, polysporin triple ointment was associated with a survival benefit (39).

Routine monitoring for staphylococcal nasal carrier status and its management remains controversial. Although some

studies have shown reduction in *S. aureus* bacteremia in hemodialysis patients with nasal mupirocin ointment, development of antimicrobial resistance remains an important concern.

V. Managing Vascular Access Complications

Recommendations

1. **Use percutaneous angioplasty to treat all hemodynamically significant stenoses in patients with AV fistulae and AV grafts (Grade D); if percutaneous angioplasty is not possible, use surgical revision.**
2. **In the case of AV fistulae aneurysm formation, surgically intervene if the skin overlying the fistula is compromised, the aneurysm is expanding, or available puncture sites are limited. (Grade D)**
3. **In the case of AV grafts, surgically intervene in the presence of graft degeneration and pseudoaneurysm formation. (Grade D)**
4. **Correct thrombosis of an AV graft with pharmacomechanical or mechanical thrombolysis or surgical thrombectomy. (Grade D)**

Background

Angioplasty is the preferred treatment for both fistulae and graft stenosis (21,22,34,40,41). In native vessel AV fistulae, the most common site of stenosis/thrombosis is near AV anastomosis, distal to the insertion of an arterial needle (40,42). Stenosis, as well as the clinical parameters used to detect it, should return to within acceptable limits after the intervention.

Centers should monitor stenosis treatment outcomes on the basis of patency. It is this committee's opinion that reasonable patency goals (for the center as a whole) for angioplasty and surgical revision in the absence of thrombosis are:

- Angioplasty: 50% unassisted patency at 6 mo; for all patients, no more than 30% residual stenosis postprocedure and resolution of physical indicator(s) of stenosis.
- Surgical revision: 50% unassisted patency at 1 yr.

If angioplasty is required >2 times within 3 mo and the patient is a good surgical candidate, referral for surgical revision may be considered. Stents are useful in selected instances (*e.g.*, central venous stenosis, limited residual access sites, surgically inaccessible lesions, contraindication to surgery) when angioplasty fails.

The choice of technique to correct thrombosis should be based on the center's expertise. Treatment should be performed as rapidly as possible (within 24 h) after detection of thrombosis to minimize the need for temporary access. The access should be evaluated by fistulogram for residual stenosis postprocedure. Residual stenosis should be corrected by angioplasty or surgical correction. Outflow venous stenoses are present in >85% of instances of thrombosis of AV grafts. The need for percutaneous transluminal angioplasty or surgical revision is expected in most instances.

Monitoring tests used to screen for venous obstruction should return to normal after the intervention. Centers should monitor outcome results on the basis of patency. It is this committee's opinion that minimum reasonable goals (for the

center as a whole) for percutaneous thrombolysis and surgical revision thrombectomy should be:

- Percutaneous thrombolysis with angioplasty: 40% unassisted patency and functionality at 3 mo.
- Surgical thrombectomy and revision: 50% unassisted patency and functionality at 6 mo and 40% unassisted patency and functionality at 1 yr.
- Immediate patency (patency to next hemodialysis session): 85% for both techniques.

Prophylaxis of access thrombosis has not been extensively studied. A recent, randomized, double-blind, placebo-controlled trial of coumadin *versus* placebo failed to demonstrate a difference in thrombotic events in newly placed AV grafts. Major bleeding was also more common in patients assigned to coumadin therapy (43). There is also some question whether the widespread use of acetylsalicylic acid may be counterproductive (44). Although a small, randomized trial has provided some enthusiasm for the use of fish oil in the prevention of AV graft thrombosis (45), additional trials are required before widespread use of this therapy could be recommended.

5. **Treat hand ischemia from arterial steal with a distal revascularization internal ligation procedure. If this fails or is not feasible, consider ligation of the AV fistula or graft. (Grade D)**
6. **Treat symptomatic central vein stenosis with percutaneous transluminal angioplasty. Place a stent only after failed angioplasty. (Grade D)**
7. **Treat dysfunctional tunneled hemodialysis catheters with instillation/infusion of tPA using a protocol. (Grade D, opinion)**

Background

Significant hand ischemia occurs in 2 to 8% of patients with AV access. Risk factors include female sex, age >60 yr, diabetes, and use of brachial artery as a donor vessel. A 10-yr retrospective review of this complication in Athens, Greece, revealed 28 of 569 patients with proximal AV access developed this complication (46). The Distal Revascularization Interval Ligation procedure, which includes an arterial ligation placed just distal to the AV graft or anastomosis and short bypass from a point 4 to 5 cm proximal to the inflow of the access to a point just distal to the ligation, was performed in 23 of these patients. Immediate relief of symptoms occurred in all and 1-yr patency was 69% (46).

Central vein stenosis can result in significant arm swelling when an AV access is created on the ipsilateral side. When a patient has central vein stenosis and significant arm swelling, percutaneous angioplasty should be performed. Angioplasty can be repeated in case of recurrence. A stent should be placed after more than one recurrence or a failed angioplasty (47).

A protocolized approach is recommended for management of a dysfunctional hemodialysis catheter. Catheter dysfunction is defined as failure, based on catheter-related thrombotic or mechanical factors, to attain and maintain an extracorporeal blood flow sufficient to perform the prescribed hemodialysis

without significantly lengthening or altering the hemodialysis treatment. A common cause for this dysfunction is the development of a fibrin sheath around the catheter, which can develop shortly after insertion. The fibrin sheath acts as a nidus for thrombus and biofilm formation. With the unavailability of urokinase, tissue plasminogen activator (tPA) has been used to restore catheter patency reduced by thrombosis. Instillation of 2 mg tPA in each lumen for a median of 24 h resulted in patency in >80% of cases (48). Given the available information, treatment of a dysfunctional permanent catheter using a protocol for tPA instillation is recommended (Table 3). If adequate flow is not achieved, consideration can be given to the use of low-dose systemic tPA. Although there is no specific trial, this recommendation is based on systemic urokinase use (49). The reader should keep in mind that valid evidence to support the manner of tPA instillation (dwell *versus* advancing *versus* infusion protocols) and the duration of the therapy is lacking. If adequate flow is still not achieved, perform radiographic studies followed by intervention. In patients with contraindications to systemic administration of tPA, fibrin sheath stripping (50) and catheter exchange over a guidewire are alternative options.

8. **Treat extensive infection of a dialysis AV graft with parenteral antibiotics and total graft resection. (Grade D)**
9. **Treat infections of primary AV fistulae as subacute bacterial endocarditis with 6 wk of antibiotic therapy. (Grade D)**

Table 3. Algorithm for malfunctioning central venous catheter

Criteria

- Inability to maintain sustained pump speed >200 ml/min for one hemodialysis run.
- Difficulty aspirating from either lumen of the catheter.
 - Check for kinks beneath catheter clamps.
 - Change patient position.
 - Flush vigorously.
 - Reverse lumens.

tPA Procedure

- tPA instillation for 30 min predialysis (or instill tPA at the end of dialysis in preparation for the next dialysis session).
- Aspirate lumen(s) and attempt dialysis; if flow is established, proceed with dialysis.
- If flow is not established:
 - Infuse 4 mg tPA over 1 h.
 - Reverse lines connecting venous blood line to arterial port.
 - Run infusion *via* pump into venous drip chamber.
 - If both limbs of the catheter have sluggish flows, the lines may be reversed after 30 minutes.
- If flow is still not established, refer to Radiology for management of fibrin sheath, if present.

10. **Treat central venous catheter-related bacteremia with systemic antibiotics and catheter exchange over a wire. (Grade D)**
11. **Treat catheter tunnel infections without bacteremia with parenteral antibiotics and appropriate local measures. Catheter removal is indicated if the infection fails to respond to 2 wk of therapy. (Grade D)**

Background

Use of central venous catheters is associated with a significantly higher risk of bacteremia compared with AV fistulae. With AV grafts, the infection risk is moderate (1,6,51). It may be possible to eradicate a local graft infection with a combination of incision and local resection of the infected portion of the graft and systemic antibiotics (52). However, extensive infection of a graft requires total resection of the graft along with parenteral antibiotics. Tunneled cuffed catheter infection is a serious problem. Appropriate treatment depends on the nature of the infection (53–55).

In patients with cuffed or noncuffed central venous catheters and suspected bacteremias, AV fistulae, or AV graft infections, start treatment with 1 to 2 g cefazolin depending on patient weight, and 1.5 mg/kg gentamycin postdialysis after blood cultures are drawn. In patients with known cephalosporin allergy, or in centers with a predominance of coagulase negative staphylococcal catheter related infections, use 15 mg/kg vancomycin instead of cefazolin. Once blood culture results are available in stable asymptomatic patients without exit site or catheter tunnel tract involvement, the catheter should be changed over a wire and antibiotic treatment continued for 2 to 4 wk as clinically indicated. In all cases, definitive therapy should be based on the organism(s) isolated. For patients with central venous catheters, the catheter should be removed, rather than exchanged, in all instances if the patient is clinically unstable or if the patient remains symptomatic for >36 h (53–55).

In patients with difficult access, clinicians can attempt antibiotic treatment without changing the catheter. However, the success of such catheter salvage is low (54,55). A new, permanent access should not be placed until blood cultures, performed after cessation of antibiotic treatment, have been negative for at least 48 h.

Catheter exit site infections are characterized by redness, crusting, and exudate at the exit site in the absence of systemic symptoms and negative blood cultures. Treatment includes proper local exit site care and oral or parenteral antibiotics based on culture and sensitivity. The catheter typically does not need to be removed. If there is tunnel drainage, treat with parenteral antibiotics (antistaphylococcal or antistreptococcal therapy pending culture report) in addition to following appropriate local measures. Definitive therapy should be based on culture results. Do not remove the catheter unless the infection fails to respond to therapy or the patient is clinically unstable. If the infection fails to respond after 2 wk of therapy, remove the catheter and replace it using a different tunnel and exit site.

For all access-related infections, empiric therapy should be regularly evaluated in conjunction with specialists in infectious

diseases or microbiology so that therapy reflects the changing microbiology and sensitivities that are unique to the local environment.

VI. Quality of Care Standards

Background

Primary AV fistulae should be constructed in all suitable new patients who elect to receive hemodialysis as their initial form of renal replacement therapy. After failure of every dialysis AV access, all patients should be re-evaluated for possible construction of a primary AV fistula. Ultimately, >60% of prevalent patients should have a native AV fistula (1). Each center should establish a database to track the types of accesses created and the complication rates. Centers should work to achieve the following target rates:

- The rate of graft thrombosis should not exceed 0.5 thrombotic episodes per patient year at risk (34).
- After adjusting for initial failures (e.g., failures within the first 2 mo of fistula use), the rate of thrombosis of native AV fistulae should be <0.25 episodes per patient year at risk. Dialysis centers should examine their thrombosis rates and the underlying causes as part of an ongoing Quality Assurance/Continuous Quality Improvement program.
- The rate of infection should not exceed 0.01 episodes per patient year at risk for primary AV fistula and 0.1 episodes per patient year at risk for AV grafts (6).
- For tunneled cuffed catheters, the recommended target rate of systemic infection is <0.5 episodes per patient year at risk (6).
- The primary access failure rates of dialysis AV grafts in the following locations and configurations should not be >15% in forearm straight grafts, 10% in forearm loop grafts, and 5% in upper arm grafts (3,11,56).
- The cumulative patency rate of all dialysis AV grafts should be at least 70% at 1 yr, 60% at 2 yr, and 50% at 3 yr (40,41).

Recommendations for Research

1. To improve the clinicians' ability to monitor and intervene successfully, future research should include a randomized prospective trial on intervention based on access flow measurements in both AV fistulae and PTFE grafts.
2. Randomized trials should be performed to assess the suitability of clinical and vascular studies before AV access creation to improve AV access maturation.
3. Appropriate trials for prevention of venous thrombosis in AV grafts should be performed.
4. Appropriate studies to determine characteristics that would influence/predict the successful creation and maturation of fistulas are required.

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CHAPTER 5: Frequent and Sustained Hemodialysis

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Introduction

There is an emerging body of evidence which suggests that frequent hemodialysis may provide significant clinical advantages for patients with end-stage renal disease (ESRD) over conventional hemodialysis (CvHD). The aim of this chapter is to provide a rational, evidence-based approach for the clinical use of frequent hemodialysis.

For the purpose of this chapter, short daily hemodialysis (SDHD) is defined as hemodialysis prescribed at 5 to 6 sessions per week, 2 to 3 h of treatment per session. Nocturnal hemodialysis (NHD) is defined as hemodialysis prescribed at 5 to 6 sessions per week during sleep, 6 to 8 h treatment per session. The location of renal replacement therapy has not been specified. SDHD is most commonly administered in-center, whereas NHD is usually provided at a home setting but not exclusively.

As there is also ongoing interest in sustained treatment hemodialysis and such practice is showing resiliency, we will provide a rational, evidence-based approach for the clinical use of sustained hemodialysis. Thrice-weekly sustained hemodialysis (TWSHD) is defined as hemodialysis prescribed at 3 sessions per week, >4 h treatment per session.

I. Assessment of Adequacy and Dose of Frequent and Sustained Hemodialysis

Recommendations

1. **Consider control of clinical parameters, including blood pressure (BP), extracellular fluid volume control, anemia, mineral metabolism, and nutritional status when evaluating for dialysis adequacy. (Grade D, opinion)**

Background

SDHD, NHD, and TWSHD deliver enhanced small solute clearance in comparison to conventional therapies. Although multiple dosing constructs based on urea kinetics have been proposed, none have been validated (1–3). Furthermore, the optimal dose of frequent or of sustained hemodialysis has not been defined. Although it is clear that *all forms* of intensive hemodialysis will exceed the current recommended guideline of hemodialysis adequacy, there is no available evidence for a specific target. In addition to urea kinetics, clinicians must consider clinical indicators (*i.e.*, BP, extracellular fluid volume control, anemia management, control of mineral metabolism, nutritional status, and overall cardiovascular health) when using frequent or sustained hemodialysis. Clinicians should consider adjusting duration and frequency of dialysis to provide the best possible clinical outcome while balancing patient burden, quality of life, and costs.

II. Clinical Indications for the Use of Frequent and Sustained Hemodialysis

Recommendations

1. **In patients with poorly controlled BP, consider the use of frequent hemodialysis (Grade D) or sustained hemodialysis. (Grade C)**
2. **In patients with significant left ventricular hypertrophy or impaired left ventricular systolic function, consider the use of frequent hemodialysis as adjunctive therapy. (Grade D)**
3. **In patients who exhibit hemodynamic instability with conventional hemodialysis, the use of frequent hemodialysis should be considered. (Grade D, opinion)**

Background

Hypertension is an adverse prognosticator in patients with ESRD (4). SDHD (5) and NHD (6) have been shown to improve BP control in observational studies. TWSHD has been shown to improve BP control in one randomized study (7) and in numerous observational studies (8–15). Current evidence suggests that SDHD lowers BP by decreasing extracellular fluid volume (3). In contrast, NHD decreases BP in patients with ESRD primarily *via* lowering total peripheral resistance (16). In addition, NHD has been documented to augment flow-mediated dilation (16), which suggests that intensive hemodialysis may have a protective vascular effect. In line with this observation, reduced vascular resistance and phenomena other than volume contraction underlying lower BP have been documented in TWSHD (7,17,18). Further research is required to elucidate the impact of frequent or of sustained dialysis on BP control and clinical outcomes using long-term, prospective, controlled studies.

Left ventricular hypertrophy (LVH) and left ventricular systolic dysfunction are potent cardiovascular risk factors in patients with ESRD (19). To date, numerous medical approaches have been attempted to improve cardiac geometry and systolic function in ESRD patients with limited success (20). NHD and SDHD have been shown in nonrandomized clinical studies to be associated with regression of LVH (5,6,21). NHD was documented in a small clinical series to restore impaired left ventricular systolic function (22). The use of frequent hemodialysis may allow improved control of left ventricular geometry and systolic function. Further research is required to examine the magnitude and impact of both SDHD and NHD on these potent cardiovascular surrogate endpoints. There is no study of LVH regression with TWSHD. Furthermore, there is a high prevalence of LVH in many observational studies of TWSHD (12,13,23).

Hemodynamic instability during conventional hemodialysis

is not uncommonly encountered. Usual manifestations include severe leg cramping and intradialytic hypotension (24). Conversion to frequent hemodialysis has been shown to improve patients' overall sense of well-being (25). Of note, intra- and interdialytic hemodynamic instability were greatly improved upon conversion to frequent hemodialysis (26). In the London Daily/Nocturnal Hemodialysis Study, it was reported that intradialytic symptoms decreased with the use of SDHD or NHD. It is interesting to note that the time required to recover from dialysis therapy was substantially lower with frequent hemodialysis in comparison to conventional hemodialysis. It has been suggested that frequent hemodialysis decreased the potential for intra- and interdialytic hemodynamic instability because of the lack of rapid removal of fluid in excess of interstitial refilling (27). More research is needed to optimally titrate the hemodynamic profile of ESRD patients with the use of frequent hemodialysis. With respect to TWSHD, one randomized crossover study comparing 4-h *versus* 5-h sessions in TW-SHD found less intradialytic and postdialytic hypotension with the longer session, but an increase in other peridialytic symptoms (28).

4. **In patients with refractory hyperphosphatemia and/or secondary hyperparathyroidism, consider the use of NHD as adjunctive therapy. (Grade D, opinion)**
5. **In patients with refractory peripheral vascular disease and ectopic calcification, consider the use of NHD as salvage therapy. (Grade D, opinion)**
6. **In patients who exhibit chronic malnutrition, consider the use of frequent hemodialysis as salvage therapy. (Grade D, opinion)**

Hyperphosphatemia and secondary hyperparathyroidism in conjunction with hypercalcemia have emerged as important contributors to vascular calcification and cardiovascular death in the ESRD population (29–31). Normalization of phosphate balance and superior control of secondary hyperparathyroidism has been shown by NHD in an observational study (32). SDHD has not resulted in a comparable decrease in phosphate level as seen in NHD. The longitudinal impact of enhanced control of phosphate and lowering of parathyroid hormone axis by NHD on vascular biology and renal osteodystrophy remains to be clarified.

Peripheral vascular disease remains a leading cause of cardiovascular morbidity and mortality in the ESRD population. Thus far, medical therapy has not resulted in significant success in the improvement of uremia-associated peripheral vascular disease (33). Improvement in peripheral vascular flow as measured by arterial Doppler was documented in one patient after conversion from CvHD to NHD (34). It is plausible that any improvement in peripheral vascular disease may occur through resolution of ectopic calcification, which has been reported with the use of NHD (35). It is proposed that normalization of phosphate balance in conjunction with augmentation of uremia control facilitates the resorption of ectopic calcification. There is no published data documenting the impact of SDHD on peripheral vascular disease in ESRD.

Impaired nutritional parameters, including lean body mass,

serum albumin, and protein intake, continue to be potent predictors of clinical outcome in ESRD patients (36,37). Observational studies suggest that frequent hemodialysis improves nutritional status of ESRD patients despite a theoretical concern of overdialysis of water-soluble nutrients (38). SDHD has been shown to improve albumin, lipid status, and protein anabolism (39–42). Similarly, NHD improves nitrogen balance, lipid status, and dietary intake in ESRD patients (41,43,44). Current evidence on the impact of frequent hemodialysis on malnutrition is limited by its observational nature and short duration of follow-up. The paucity of long-term or controlled evidence reflects the importance of further research in this domain.

Recommendations for Research

1. There is growing enthusiasm for the routine clinical use of frequent hemodialysis. It is important to note that there has not yet been any randomized controlled data to support the use of SDHD or NHD (45). Thus far, frequent hemodialysis shows early promise in improving clinical outcomes in ESRD patients. Correction of sleep apnea (46), improvement in cardiac autonomic balance (16), and amelioration of homocysteine level (47) continue to suggest that augmentation of uremic clearance is associated with improved surrogate endpoints, especially with NHD. By providing enhanced clearance, frequent hemodialysis represents a unique opportunity for the renal community to gain further insights into the basic science of uremia and its impact on other body systems. The true clinical effect of frequent hemodialysis can only be elucidated by a longitudinal, controlled, clinical study. Finally, the widespread implementation of frequent hemodialysis may only be achieved if barriers in cost, social perception, and hemodialysis training are studied in a systematic manner.
2. Interest in TWSHD stems from sometimes exceptional survival data and BP management in mostly uncontrolled populations. As incremental hemodialysis is gaining popularity and because some patients may accept overnight sustained hemodialysis but not on a daily basis, it is important that such endeavors be explored in a rigorous, prospective manner. NHD provides not only frequent but also sustained hemodialysis compared with CvHD. Dialysis duration is readily recognized as a critical factor for water removal independent of Kt/V urea. The time dependence of uremic toxins other than water, like phosphate, and of surrogate markers of survival, like LVH, needs to be studied.

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Hemodialysis Treatment Time: A Fresh Perspective

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Summary

Historical, clinical, economic, and technological developments have driven a shift in clinical practice from predominantly 6-hour-long hemodialysis treatments to much shorter treatment times that are prevalent today. Patients, physicians, and providers had considered shortening dialysis treatments as a means to decrease the overall burden imposed by this necessary life-saving therapy. However, shorter dialysis is not a panacea and may engender trade-offs in terms of patient morbidity and mortality. We examine the literature with the benefit of hindsight and in light of recent studies that have improved understanding of the complex relationship between dialysis dose and outcome. We touch upon the role of dialysis frequency relative to treatment time. We conclude with the suggestion that a new treatment paradigm should consider a minimum adequate dialysis treatment time of 4 hours for the majority of patients, with anything shorter becoming the exception rather than the rule.

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Introduction

In the over 40 years since hemodialysis has become widely available in the United States, the pendulum has swung from predominantly long (6+ hours) of treatment times toward more efficient, but shorter (<4 hours) and experimentally ultrashort (<2 hours) periods and has now begun to rebound toward longer treatments of 4+ hours, driven by historical, clinical, economic, and technological developments (Figure 1). Patients, physicians, and providers had considered shortening TT as a means to decrease the overall burden imposed by this life-saving therapy. However, shorter TT is not a panacea, and may engender trade-offs in terms of patient morbidity and mortality. We examine dialysis TT within the historical context and evolution of clinical practice, with the benefit of hindsight as well as in light of recent studies that have improved our understanding of the complex relationship between dialysis dose and outcome.

The Kiil and Twin Coil dialyzers commonly used in the 1960s and early 1970s were characterized by small diffusive surface area, impermeate cellulosic membranes, and/or open recirculating dialysate reservoirs and generally necessitated at least 6 hours of therapy three times per week (1–4). The average patient dialyzed for 18 h/wk, extrapolating to 936 hours on dialysis annually (even allowing for 20% missed treatments), which is equivalent to 1 month of every year tethered to the dialysis machine. This estimate ignored patient commute and “wait” times, which were not inconsequential in that era, considering the need to blend individualized dialysate and manually set up equipment, along with a paucity of conveniently located dialysis facilities. Therefore, much of the drive to reduce treatment times (TTs) was related to the desire of patients to spend less time on the dialysis machine.

Motivation to reduce TT was also fueled by the belief that providing shorter, more efficient dialysis treatments could be performed safely while being cost-effective. The Medicare entitlement (section 2991 of PL92-603, Social Security Amendments, 1972) was enacted to enable widespread provision of life-saving maintenance dialysis treatments, the costs of which were beyond the means of most Americans. Over its evolution, the program resulted in: (1) more patients on dialysis than initially projected; (2) disproportionately greater allocation of healthcare dollars for one relatively small segment of society; (3) predominantly facility-based outpatient treatment with strategic programmatic cost-shifting toward clinical management to keep costs steady; and (4) a second-order signal to manufacturers and suppliers to compete for market share through cost-reducing technical innovations (5). To maintain financial viability of the program, some degree of cost containment was necessary. This was largely accomplished through composite rate payments (*i.e.*, capitated payment for dialysis treatment and related routine laboratory tests) made to dialysis facilities, which promoted cost-conscious care delivery. In effect, a “cost-shifting” occurred where the onus for keeping cost of dialytic therapy within the capitated composite rate payments fell on dialysis providers. Because there was minimal adjustment of the composite rate over the next two decades, this necessitated improved efficiency just to keep up with inflation.

Shorter TT that met requirements for solute and fluid removal were deemed to be achievable with improved dialysis efficiency. There was a belief that the additional cost of technological advancements required to achieve maximal dialytic efficiency will outweigh the growth of expenses from infrastructure investments and labor that were required as the dial-

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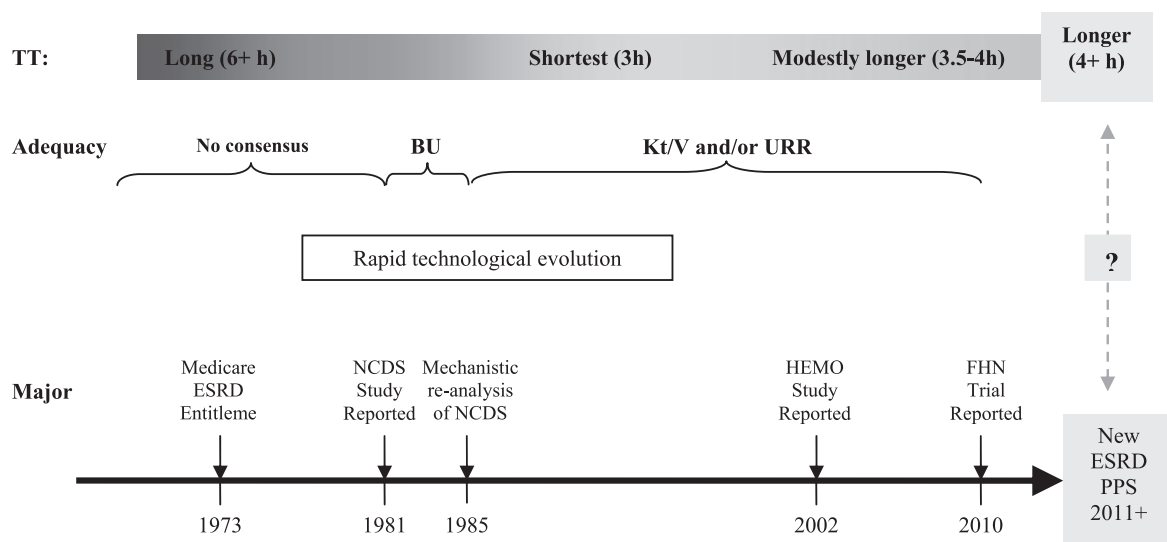


Figure 1. | Timeline of the evolution of dialytic treatment time and associated events. TT, treatment time; BU, blood urea; URR, urea reduction ratio; NCDS, National Cooperative Dialysis Study; FHN, Frequent Hemodialysis Network; PPS, prospective payment system; HEMO Study, Hemodialysis Study.

ysis population expanded. An alignment of objectives emerged between patient interests to decrease the time burden of therapy, physician interests to provide the least burdensome effective therapy, and advantages for more efficient care delivery brought about by shorter dialysis treatments. Therefore, there existed an economic incentive to motivate continued research and development to enhance dialysis efficiency.

Enhancing Dialysis Efficiency

Barriers to shortening TT were overcome one by one through innovative refinements to dialyzer membrane design that enhanced diffusive permeability, improved engineering of dialysis delivery equipment, and made modifications to dialysate composition. The major objective was to increase dialytic capacity for solute clearance (primarily measured in terms of urea removal) so as to maintain the same total clearance over less time. The hollow fiber dialyzer design allowed for a compact, more efficient use of surface area to maximize diffusion (6,7). Membrane materials evolved from basic cellulose into cuprophane and then semisynthetic and fully synthetic fibers that allowed for enhanced diffusive clearance as well as greater convective solute and fluid flux (8). The enhanced capacity for fluid removal necessitated precise control of ultrafiltration rate, spurring the development of blood pumps and volumetric ultrafiltration (4,9).

As the permeability of dialyzers increased, diffusion of dialysate components back into the blood compartment was also enhanced. Serum bicarbonate diffused out to the dialysate, whereas the acetate buffer in dialysate entered the bloodstream at rates that sometimes exceeded patients' metabolic capacity to convert it into bicarbonate, leading to hypoxia and vascular instability (10,11). Thus, transition to bicarbonate-buffered solutions also spurred newer hemodialysis (HD) machines with more sophisticated dialysate proportioning systems, and in parallel, outpatient clinic

design evolved to allow for central delivery of bicarbonate solution (12,13).

Clearance Trumps Time

By the late 1970s, many small short-term, single-center case series reported equivalent metabolic intermediate outcomes between conventional long duration and shorter (<4-hour TT) HD in small patient samples, utilizing increasingly sophisticated technologies (14–18). Nonetheless, some patients did experience hypotension, neuropathy, and difficulties with fluid removal, and some facilities noted the higher costs of the required equipment (19–22). As equipoise was established between proponents of long *versus* short TT, the first multi-center large study of dialysis adequacy was funded by the National Institutes of Health (NIH). The National Cooperative Dialysis Study (NCDS) compared outcomes among patients randomized to one each of two levels of dialysis clearance (*i.e.*, high/low urea level) and TT (short/long) using a 2×2 factorial design. The NCDS concluded that patients with “low time averaged blood urea nitrogen concentrations” experienced fewer treatment withdrawals and hospitalizations than patients with higher levels (23). There was no statistically significant difference between long and short TT; however, longer time approached borderline significance ($P = 0.056$) with regard to reduced hospitalization and complication rates. The study was not powered to examine differences in mortality. On the basis of these findings, many physicians concluded that dialysis dose on the basis of urea removal, not TT, was the important determinant of patient morbidity.

Clinicians in the 1980s subsequently focused on ensuring adequate delivered dialysis dose with respect to urea kinetics, which was formalized into the Kt/V metric (urea clearance time product divided by its volume of distribution) after a kinetic reassessment of the results of the NCDS (24). Confidence in this approach was reinforced by several

survival studies demonstrating similar outcomes between longer TT and short TT using high efficiency and/or high flux membranes (13,25,26).

Then There Was Doubt

Nevertheless, not all clinicians in the United States were convinced that shorter TT was appropriate for all patients. After all, whereas the average TT declined in the United States, the dialysis program in Tassin, France, maintained long, 8-hour overnight dialysis thrice per week with exemplary results that were linked to optimal fluid management and BP control (27). In the United States, improvements in health-related quality of life and biochemical profiles seen during this period were interpreted by some as further justification of the urea-centric paradigm of dialytic titration. In retrospect, however, these improvements may likely have resulted from factors other than dialytic titration, such as trends toward the following: use of biocompatible membranes that decreased immune activation and possibly intradialytic symptoms (28–30), dialysis equipment capable of precise dialysate delivery and tightly controlled fluid removal (4,9), bicarbonate-based in lieu of acetate-based dialysate (10,31), better control of hyperparathyroidism and management of renal osteodystrophy caused by widespread use of activated vitamin D analogs (32–35), and escalating use of erythropoietin (36).

Data from a national cohort from 1986 indicated that TT of <3.5 hours was associated with greater mortality compared with patients treated with longer dialysis (37). Compounding the issue, because the mean TT had fallen to almost 3 hours during 1986 to 1987, 53% of patients were concurrently prescribed an inadequate Kt/V <1.0 (38). More important, critics highlighted that mortality rates in the United States during the period 1982 to 1987 were found to be higher than in Europe and Japan (39). It was further demonstrated that the prescribed dose of dialysis was higher in Europe than the United States (40). These concerns were summarized in a national meeting addressing this issue (Dallas Morbidity, Mortality, and Prescription of Dialysis Symposium) in 1989, which precipitated a re-examination of what constituted adequate dialysis (41). The potential role of TT relative to dialysis adequacy and outcomes formed part of the discussions within the renal community during this period. However, urea kinetics once again took a front seat, and at the close of the decade, there were more reports of single-center experiences with favorable outcomes associated with short but “adequately dosed” dialysis treatments (42–44).

The Next Hemodialysis Outcome Study

In the midst of renewed concern about dialysis adequacy, better relative survival was observed in the subpopulation of American patients whose delivered dialysis dose was above Kt/V of 1.2, further reinforcing interest in urea-based dialytic titration and prompting a renewed search for the minimum standard for “adequate dialysis dose” (45,46). A new equipoise led to the second large NIH-funded randomized clinical trial on HD outcomes, the Hemodialysis (HEMO) Study. This trial used equilibrated Kt/V (eKt/V [47,48]) as the metric by which HD dose was assessed and titrated to account for “urea rebound” (*i.e.*,

increased blood concentration of urea over the succeeding 20 to 30 minutes after dialysis is completed) resulting from solute and fluid movement between tissue compartments and the interstitial and vascular compartments (49–51). The HEMO study compared high urea clearance (eKt/V of 1.45) to conventional clearance (eKt/V of 1.05; analogous to single pool Kt/V of approximately 1.2) and found no significant difference in mortality or hospitalization after a mean follow-up of 2.8 years (52). The 2×2 factorial study design likewise showed no outcome differences between low *versus* high flux dialyzers, except in the subgroup with vintage >3.7 years.

The HEMO study bears relevance on the consideration of the effects on survival in two ways. First, the higher eKt/V group was dialyzed on average for longer than the lower eKt/V group; in this light, an absent effect of greater eKt/V on mortality might be taken to signal no effect of treatment time. Second, the association between treatment time *per se* and mortality was examined in the pooled cohort, again with no association detected. Cautious interpretation is advised, however. Within each eKt/V group, treatment time assigned as “the shortest . . . consistent with the patient’s assigned dose.” Thereby, larger patients would be assigned to longer treatment times than smaller patients, which might have biased estimates in favor of longer treatment times. Conversely, less favorable access types (*e.g.*, catheters, arteriovenous accesses in patients with poor vascular health) would promote longer treatment times, and thereby estimates would favor shorter treatment times. The net effects of these biases cannot be known. However, it is incontrovertible that session length was not assigned randomly (even within the HEMO study), and therefore such confounding cannot be ignored. For this reason, HEMO was not a randomized trial of session length, and analyses of treatment time therein were subject to all of the same biases as in any observational study. In addition, data from the HEMO study likely generalized less to the overall dialysis population considering the stringent inclusion criteria.

Rationale for Renewed Interest in Treatment Time

Among components of the dialysis prescription, TT is likely most influential with regard to middle or larger molecule clearance (53). Although dialyzer flux plays a contributory role in cleansing the vascular fluid, transfer of molecules across from the intracellular fluid to the interstitial fluid and into the vascular fluid plays an important role in total body clearance (54). With contemporary equipment and high flux membranes, one can efficiently cleanse the vascular compartment. However, whole body clearance requires that solutes re-equilibrate from deeper reservoirs, so as to be available for dialytic removal. Intercompartmental (*e.g.*, intracellular to extracellular) redistribution is typically much slower for larger molecules. Thus, despite their efficient dialytic removal from the blood, total body clearance is greatly reduced with shorter TTs (55,56).

The movement of sodium and water across body compartments has been less well studied. This consideration may be important in understanding why recent observational studies have suggested that longer TT is favorably

associated with morbidity and mortality (Table 1) (27,37,57,58). The ability to ultrafilter very large volumes is limited (hemodynamically) by the rate at which salt and water re-equilibrate across body compartments (59). Increased concentrations of sodium in the dialysate ameliorate hypotension by augmenting osmotic attraction of water into the vascular space, which can be a useful adjunct to removing fluid from interstitial compartments within the context of shorter TT (60–62). Unfortunately, such practice can potentially lead to sodium “loading” in some patients (*i.e.*, higher blood sodium concentration after dialysis treatments), promoting thirst, increased fluid intake, and increased predialysis BP (62,63). A cycle of increased fluid gain followed by an increased rate of fluid removal within the same TT, in part to attain BP targets, predisposes patients to suffer from intradialytic hypotension (64–66).

Recently, both intradialytic hypotension and high ultrafiltration rates have been linked to mortality risk in dialysis patients (67–71). It has been demonstrated that longer dialysis with slower ultrafiltration rates allows greater salt and water removal from patients without inducing profound hypotensive episodes (72–74). Long overnight or nocturnal dialysis performed thrice per week for patients with a history of frequent and large interdialytic fluid gains (unresponsive to conventional “short” treatments) improves BP and fluid control (75,76). Thus, longer TT with slower rates of ultrafiltration and with lower dialysate sodium may be an important contributor to both well-being and survival in dialysis patients.

Finally, the highly efficient dialysis prescription requires that a large volume of blood is cleansed within short TTs. By design, rapid blood transport occurs through the dialysis circuit, necessitating that high blood-flow rates be drawn from and subsequently returned through the vascular access. Such demand may take its toll on the arteriovenous vascular access endothelium, which may adversely affect both access maturation and patency. Many Asian and European countries that use slow dialysis (and thereby lower blood-flow rates) have greater utilization of arteriovenous accesses among prevalent and incident patients as well as shorter times to maturation and higher maturation rates than the U.S. (77,78). Notwithstanding that some of these regional differences are likely explained by ambient vascular health and patient behaviors, it is plausible that high blood-flow requirements (with the requisite hemodynamic and shear stress) may contribute to poor vascular access maturation and survival. It is also likely that attempts to perform very rapid HD place unrealistic (or even unnecessary) expectations on what constitutes a “mature” or functional access (79–82). Therefore, speculating further, the short TT dialysis prescriptions may select for circumstances that disadvantageously promote catheter exposure and thereby further compromise patient survival.

Re-evaluating Outcomes Associated with Treatment Time

Despite a relatively narrow range of TT (majority between 3 and 4.5 hours, with the exception of nocturnal dialysis), recent observational studies have demonstrated relative greater comparative survival and less hospitaliza-

tion with longer dialysis three times a week (69,83–86). Data from the United States, Europe, and Japan where the majority of patients dialyzed for <4 hours, indicated that beyond Kt/V, TT of >4 hours was significantly associated with lower adjusted relative risk of death (0.81, $P = 0.0005$) (69). Because Japanese reimbursement policy favors longer (>4 hours) TT in all but the sickest patients, it is important to note that the association between TT and survival was observed within the European and U.S. subgroups. In Australia and New Zealand, where the largest group of patients dialyzed between 4 and 4.4 hours, TT of >4.5 hours was similarly associated with reduced death risk, as TT of 4.5 to 4.9 hours had adjusted hazard ratios (HR) for mortality of 0.80 ($P < 0.05$) (84). In a large prevalent cohort of American patients with mean Kt/V of 1.6, an adjusted HR of 1.12 (with confidence limits of 1.06 and 1.18, inferred from Figure 3 in reference 85) was observed in patients with TT of >2.5 to 3 hours compared with those with TT of 3.5 to <4 hours. In an incident U.S. cohort that survived for at least 30 days, increased death risk was associated with TT of <4 hours (86). Utilizing marginal structural models to account for time-dependent confounding, the adjusted HR was 1.42 ($P < 0.0001$) for TT of <4 hours relative to TT of ≥ 4 hours. Importantly, this association was unchanged in the subgroup of patients whose eKt/V was >1.2, suggesting an influence of TT independent of optimal urea kinetics. It is worth noting that each of the above analyses were adjusted for some index of body size.

Finally, in a cohort of patients dialyzed three times per week, a matched analysis comparing TT of 4 to 8 hours showed the latter group to have better survival (HR = 0.28, $P = 0.02$) along with fewer hospitalizations, regression of left ventricular mass, better cognition, and better biochemical indices (87). Similarly, preliminary data presented by Lacson et al. (88) at the 2010 National Kidney Foundation meeting corroborates better survival with 8 hours of in-center nocturnal HD relative to a propensity score matched control group on conventional HD with mean TT of 3.5 to 4 hours with HR = 0.66 ($P = 0.002$). These observational studies do not prove causation and are all subject to residual confounding. Moreover, comparisons between 3.5 to 4- and 8-hour treatments bear different clinical significance (because of logistical considerations related to implementation) than do comparisons between <4- and ≥ 4 -hour treatments. However, the latter data do provide support for the underlying physiologic principle that longer treatment times may be better.

Hemodialysis Frequency versus Time

Much of the focus of dialysis adequacy after negative results from the HEMO study has been on increasing the frequency of dialysis treatment. The NIH-funded Frequent Hemodialysis Network (FHN) recently published the results of the short daily HD randomized trial demonstrating significantly better composite outcomes (change in left ventricular mass or death and change in physical component score or death) for six *versus* three times per week HD with TT at 2.5 ± 0.3 hours *versus* 3.5 ± 0.6 hours per treatment, respectively (89). The total weekly time for the short daily treatments was ~ 15 hours *versus* approximately 10.5 hours for the controls. It can be argued that

Table 1. Summary of recent observational studies comparing outcomes associated with short and long hemodialysis treatment time (in hours)

Population Studied	Reference or Control Group	Long Treatment Time Group	Results for Longer Hemodialysis Treatment Time (Adjusted Models)
Incident HD patients Australia and New Zealand (84) United States (86)	TT = 4.0 to 4.4 hours (<i>n</i> = 2,091) TT < 4 hours	TT = 4.5 to 4.9 hours (<i>n</i> = 753) TT ≥ 4 hours	20% lower relative risk of death ^a Shorter treatment time has 42% greater death risk (longer time as reference) ^b
Prevalent HD patients International (DOPPS) (69)	TT ≤ 4 hours (<i>n</i> = 14,353)	TT > 4 hours (<i>n</i> = 1980)	19% lower relative risk of death ^c and 16% lower cardiopulmonary death risk ^a
United States (85)	TT = >2.5 to 3.0 hours (<i>n</i> = 4889)	TT = 3.5 to <4.0 hours (<i>n</i> = 29,744)	Shorter treatment time has 12% greater relative death risk (longer time as reference) ^d
United States (76)	TT = 3.7 ± 0.5 hours (<i>n</i> = 15,334)	TT = 7.9 ± 0.5 hours (<i>n</i> = 655)	12% lower hospitalization risk for all causes ^b (31% better death risk before adjustment, not significant after case-mix + lab adjustment)
Turkey (87)	TT = 4 hours (<i>n</i> = 247)	TT = 8 hours (<i>n</i> = 247)	68% lower death risk ^a , fewer hospital days: 5.43 versus 18.78 days/1000 dialysis treatments ^e

HD, hemodialysis; TT, treatment time.

^a*P* < 0.05.^b*P* < 0.0001.^c*P* = 0.0005.^d*P* = not stated, but confidence interval estimated at 1.06, 1.18 from the figure.^e*P* = 0.002.

increasing frequency is just another dimension of increasing total time on dialysis. However, there may be a threshold whereby increasing dialysis frequency even up to five to seven times per week can be offset by ultrashort dialysis time. For example, in one observational study, there was a graded increase in survival among patients undergoing frequent HD to total weekly times of <12, 13 to 15, and >15 hours (90).

Results from the FHN frequent nocturnal hemodialysis trial have not been published. Despite the expectation of even better outcomes because of improvements in the composite outcome of mortality and major morbidity (acute myocardial infarction or stroke) in a recent observational study (91), FHN investigators were unable to meet their original enrolment targets because of unexpected challenges (92). Nevertheless, results of observational studies from home nocturnal HD programs such as that in Toronto, Canada, and Lynchburg, Virginia, indicated significant patient well being with lower requirement for antihypertensive medications, phosphate binders, and erythropoietin in dialysis occurring overnight six to seven times per week (93–96). Preliminary experience from Hong Kong indicates that conversion to every other night long 8-hour dialysis had similar results, with decreased antihypertensive medications, phosphate binder requirements, and erythropoietin dose along with improved well being (97). The Tassin experience already exhibits similar improvements with long thrice weekly HD (27,98). Similarly, favorable changes in well-being and medications can also be achieved with thrice weekly in-center long nocturnal HD (75,99,100).

Differentiating the effect of TT *versus* increasing the frequency of HD beyond three times per week may be a more challenging clinical issue. Furthermore, the cost benefit of longer *versus* more frequent dialysis must be further evaluated. In the past there were limited numbers of dialysis facilities and dialysis stations; thus, rapid turnover of dialysis stations was necessary to accommodate all of the patients with end-stage renal disease. This is no longer a major constraint in the United States and most developed countries in that there are sufficient stations so that patients can potentially have longer dialysis treatments. In-center accommodation of long nocturnal patients still present challenges (101), but they are not insurmountable. Logistically, scheduling patients for more frequent treatments, even during the day, is the greater challenge for providers. In addition, there remains reluctance on the part of patients to increase either TT or frequency of dialysis. Most patients desire to dialyze with the minimum “necessary” frequency and TT (either at home or in center), express fears regarding their ability for self-care, and are lacking critical information toward making informed decisions about their dialytic care. Education for patients with respect to individual skill, resources, technical requirements, and benefits associated with adoption of either longer or more frequent dialysis is essential to overcoming this limitation (92,102,103).

Moving Forward

Although it is becoming clear that better clinical outcomes can be anticipated with longer or more frequent

dialysis, overall costs savings remains speculative until hospitalization rates and days in hospital are included in the economic model of dialysis. The new prospective payment system for dialysis services does not include inpatient costs (104). In the setting of capitation or accountable care organization-type plans, the cost benefit of increased dialysis time and frequency will become more apparent (105–107). Systemic changes associated with these types of patient-centered care systems will include a blurring in the division between reimbursement for outpatient care and for inpatient care, such as the current separation between Medicare Part A and Part B. The hope is for greater emphasis on pre-emptive care that may incur additional expenses upfront but may decrease hospitalization-associated costs down the road. In the interim, inadequate short dialysis treatments likely lead to complications, increased hospitalization, and decreased survival and may have a negative effect on the total cost of therapy. We suggest that in the setting of three-times-per-week HD, a new minimum adequacy prescription target can be established by physicians to include specifications for TT ≥ 4 hours, with anything less becoming the exception rather than the rule.

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Dr. Lacson is a full time employee of Fresenius Medical Care, North America. Dr. Brunelli serves on medical advisory boards to C.B. Fleet Co. and Amgen, and his spouse is an employee at Astra Zeneca.

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Dialysis time: does it matter? A reappraisal of existing literature

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Purpose of review

The length of time (T_d) required for adequate maintenance hemodialysis therapy is perceived as a substantial patient burden. Technological advancements have allowed shortening T_d over the past three decades. However, failure to detect improved outcomes with higher dialysis dose has prompted renewed interest in the potential impact of longer T_d .

Recent findings

Ongoing trials are focused on increasing the frequency of treatments, although the feasibility of having most patients agreeing to more than five treatments per week remain doubtful. Furthermore, survival was better in short daily hemodialysis with T_d of 180 vs. 90 min. Within thrice weekly dialysis, several recent epidemiological studies have shown improved survival associated with T_d more than 4 h. Improved outcomes for long in-center nocturnal hemodialysis (6–8 h, 3×/week), similar to what has been performed in Tassin for the last 30 years, have also been reported.

Summary

Compelling rationale and recent outcome data support use of longer T_d . Improved management of salt and water may be the cause for the dissociation of dialysis time and small molecule clearance. In most industrialized countries, hemodialysis care systems in place have the capacity to accommodate it. Until such time that results from prospective randomized trials are available, we believe that physicians should prescribe and exert all efforts to convince thrice weekly hemodialysis patients to accept 4 h as minimum T_d .

Keywords

end-stage renal disease, hemodialysis, mortality, outcomes, quality

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Introduction

During establishment of maintenance hemodialysis for end-stage renal disease in the late 1960s and early 1970s, one of the major burdens for patients, physicians and dialysis providers was thought to be the length of time required for adequate dialysis therapy. In response, clinicians and scientists went on a quest in the decades that followed to attain significant improvement in dialysis clearance in order to alleviate this ‘burden’. We will review and evaluate the literature documenting clinical and technological developments that drove the practice of shortening dialysis time (T_d) and identify current challenges and future needs with regards to T_d .

Treatment time history

In the early years, hemodialysis with Kiil and Twin Coil dialyzers generally required at least 6 h of therapy three times per week [1–3]. Much of the drive to reduce dialysis time was related to the desire of patients to spend less time on dialysis; however, it was also fueled by the belief that providing shorter dialysis would decrease cost

of care. During the late 1970s and 1980s, barriers to shortening T_d were overcome due to improved dialyzer membrane design and function (hollow fiber kidney and synthetic membrane material), improved engineering in dialysis delivery equipment (ultrafiltrate controllers and central dialysate delivery), and modifications to dialysate composition (bicarbonate dialysis) [4–8]. Increasing dialytic efficiency and safety was designed to compensate for reduced time, in effect maintaining the same total solute and fluid clearance.

This experience with shortened T_d led to a number of clinical studies evaluating treatment times of less than 4 h, three times a week. Most of these studies were of short duration and consisted of small numbers of patients with only intermediate outcomes evaluated. Nearly all of the publications espoused the virtues of efficient, short hemodialyses [9–13]. A few indicated potential limitations of the therapy due to hypotension, neuropathy, and potential difficulties in fluid removal, but were mostly tempered by cautious optimism [14–17]. These small studies were controversial and led to the National Institutes of Health (NIH)-funded National Cooperative

Dialysis Study (NCDS), which was the first multicenter large study comparing dialysis clearance (urea level) and dialysis time [18]. This 3-year study concluded that 'low predialysis urea' patients experienced fewer complications and fewer hospitalizations than a group of 'high predialysis urea' patients. There were no statistically significant differences (borderline significance at $P=0.06$) between long and short T_d with regard to reduced hospitalization and complication rates, perhaps because the study was stopped early because safety signals were reached. A 'mechanistic' analysis of the NCDS established a new parameter for measuring dialysis dose, Kt/V (clearance–time product divided by the volume of distribution), derived from the pharmacological formula for first-order kinetics which remains the standard for adequacy measurement today [19].

In the late 1980s, newer studies with longer follow-up evaluated survival but continued to consist of small numbers of patients. Survival with short dialysis using high efficiency membranes was suggested to be equal to that with longer dialysis treatment [8,20,21]. Moreover, during this period improvement in patient symptoms and outcomes were potentially influenced by other factors noted earlier (bicarbonate dialysate, biocompatible membranes, ultrafiltration control with hollow fiber kidneys), as well as improved management of metabolic mineral disorders along with introduction of intravenous vitamin D [22–25], and later in the decade, recombinant human erythropoietin [26,27]. Although there was a secular movement toward shorter thrice weekly dialysis, some programs such as that in Tassin, France, maintained long, 8-h overnight dialysis thrice per week and continued to show exemplary results that were linked to optimal fluid management and blood pressure control [28]. This caused some students of dialysis adequacy to have second thoughts on shortened dialysis.

The end of the 1980s emphasized adequately dosed, albeit short dialysis treatments with single-center experiences reporting good outcomes [29–31]. However, a new study with a wider perspective that examined a national random cohort from 1986 showed worse mortality for patients treated with short T_d less than 3.5 h compared to patients with longer treatments [32]. Furthermore, national data from 1986 to 1987 indicated that the mean T_d had fallen closer to 3 h per week despite a significant proportion of patients not being prescribed an adequate dialysis dose (53% at prescribed $Kt/V < 1.0$) [33]. In the midst of these developments in the USA, comparison of mortality rates with Europe and Japan indicated superior survival during 1982–1987 [34]. Further analyses also showed that the prescribed dose of dialysis was higher in Europe than the USA [35]. Concerns regarding this high mortality rate in long-term dialysis patients were summarized in a national meeting addressing this issue

Key points

- The drive to reduce dialysis time was related to desire of patients to spend less time on dialysis; however, it was also fueled by the belief that providing shorter dialysis would decrease cost of care.
- Survival with short dialysis using high efficiency membranes was suggested to be equal to that with longer dialysis treatment, but symptoms and outcomes were potentially influenced by other factors such as bicarbonate dialysate, biocompatible membranes, ultrafiltrate control with hollow fiber kidneys, improved management of bone or mineral disorders along with introduction of intravenous vitamin D and recombinant human erythropoietin.
- Failure of the HEMO study to show differences in outcome related to urea clearance caused a closer examination of how T_d plays a role in physiologic processes which could impact survival outcomes on dialysis, independent of small molecule clearance.
- Sodium and water physiology during dialysis may be important in understanding why the HEMO study showed no differences in outcomes with high and low urea clearance.
- While awaiting definitive clinical trials, recent evidence supports a practice recommendation for patients on routine thrice weekly hemodialysis to undergo a minimum T_d of 4 h per dialysis treatment.
- Although it is becoming clear that better clinical outcomes result with longer or more frequent dialysis, overall cost savings remains speculative until hospitalization rates and days in hospital are included in the economic model of dialysis.

(Dallas Morbidity, Mortality, and Prescription of Dialysis Symposium) in 1989, which precipitated a re-examination of the adequacy of dialysis [36].

Subsequent observational studies into the 1990s indicated improved survival as dialysis dose was increased to achieve doses beyond Kt/V of 1.2 [37,38]. These observational conclusions led to a second large NIH-funded randomized clinical trial on hemodialysis outcomes – the Hemodialysis (HEMO) study, in which equilibrated dose targets (eKt/V) were utilized (found to be empirically higher than single pool or conventional Kt/V by approximately 0.2 units) [39,40]. The HEMO study compared high urea clearance (eKt/V of 1.45) to low or usual clearance (eKt/V of 1.05). This study demonstrated no significant difference in mortality or hospitalization comparing these two groups after a mean follow-up of 2.8 years [41]. Comparison of outcomes between patients randomized to low vs. high flux dialyzers likewise showed no differences except in patients who had been on dialysis longer than 3.7 years. It is notable that the role of T_d in achieving the eKt/V goals was not specifically evaluated.

Failure of the HEMO study to show any differences in outcome related to urea clearance caused a closer examination of how T_d plays a role in physiologic processes which could impact survival outcomes on dialysis, independent of small molecule clearance. It is important to understand the role of various treatment parameters on small and middle molecule clearance and salt and water management. In addition to T_d , the three components which impact solute clearance are blood flow rate, dialysate flow rate and dialyzer size or membrane surface area. Of these, blood flow rate has a more profound impact on small molecule clearance (hence, urea-based dialysis dose) [42–44]. They were the focus of manipulations in the 1980s and 1990s but the neglected component was a wider range of T_d .

Role of sodium and water in treatment time outcomes

It is apparent that the transfer of smaller molecules across body compartments – that is, from the intracellular to the interstitial to the vascular space is an important consideration in the ability to shorten dialysis time [45]. With current equipment and high flux membranes, one can efficiently cleanse the vascular fluid. However, there is a delay in transfer of such smaller molecules across the various membranes into the different compartments [46,47]. These considerations form the rationale for the need of low intensity, longer dialysis allowing the transfer of molecules from the intracellular space to the vascular space.

The movement of sodium and water across body compartments has been less well studied. However, salt and water physiology may be important in understanding why the HEMO study showed no differences in outcomes with high and low urea clearance, whereas other studies have suggested that longer T_d does impact favorably on mortality and morbidity [28,32,48,49]. The current capabilities of dialysis membranes to remove massive amounts of fluid are similarly constrained by the move-

ment of salt and water across body compartments [50]. Data from a post-hoc analysis of participants in the HEMO study indicated that rapid fluid removal during hemodialysis treatments as represented by the ultrafiltration rate of greater than 13 ml/h/kg had greater associated cardiovascular morbidity and mortality [51**]. It has been demonstrated that longer dialysis with slower ultrafiltration rate allows one to remove greater amounts of salt and water from patients without inducing profound hypotensive episodes [52–54]. Consistent with these findings, data from a multinational study population indicate that lower ultrafiltration rate less than 10 ml/h/kg may be one mechanism for the observed protective effect of longer treatment time on survival [55]. The recent use of nocturnal 8-h dialysis maintaining frequency at thrice per week is a practical demonstration of the ability to manage patients with a history of frequent and large interdialytic fluid gains who in a short dialysis had great difficulty with blood pressure and fluid control [56,57**].

Another consideration is whether T_d may be a more appropriate marker for dialysis adequacy in lieu of or at least in addition to Kt/V or urea reduction ratio (URR) [19,58]. Perhaps T_d should be used as an outcome as well as a process measure. Observational studies summarized in Table 1 have demonstrated relatively greater comparative survival and less hospitalization with longer dialysis three times a week [55,57**,59,60*,61**]. Data from the USA, Europe and Japan where majority of patients dialyzed for less than 4 h, indicated that beyond Kt/V , T_d more than 4 h was significantly associated with lower adjusted relative risk of death (0.81, $P=0.0005$), and T_d remained significant when stratified by region [55]. Separately, data from Australia and New Zealand, where the largest group of patients dialyzed between 4 and 4.4 h, T_d more than 4.5 h was similarly associated with reduced death risk [59]. The group with T_d of 4.5–4.9 h had adjusted hazard ratio for mortality of 0.80 ($P<0.05$). Data from a large prevalent cohort of American patients with mean Kt/V of 1.6 indicated an adjusted hazard ratio of 1.12 (with confidence limits of 1.06 and 1.18, inferred

Table 1 Recent literature indicating improved outcomes with longer dialysis treatment time relative to hemodialysis dose

Reference	No. of patients	Mortality risk	Remarks
Saran <i>et al.</i> 2006 [55]	$T_d > 4$ h $n=1980$ $T_d \leq 4$ h $n=14\,353$	RR = 0.81, $P=0.0005$ for longer time	International cohort (DOPPS) Each additional T_d of 30 min had HR = 0.93, $P<0.0001$
Marshall <i>et al.</i> 2006 [59]	T_d 4.5–4.9 h $n=753$ T_d 4.0–4.4 h $n=2091$	HR = 0.80, $P<0.05$ for longer time	Cohorts from Australia and New Zealand
Miller <i>et al.</i> 2010 [60*]	T_d 2.5–3.0 h $n=4\,889$ T_d 4.35–5.0 h $n=56\,661$	HR = 1.12, CI = 1.06, 1.18 – for shorter time (inferred from Fig. 3)	Large dialysis organization cohort in the USA
Brunelli <i>et al.</i> 2010 [61**]	$n=8\,552$ but the analyses accounted for changes in prescribed dialysis time	HR = 1.42, $P<0.0001$ for $T_d < 4$ h vs. $T_d \geq 4$ h	Marginal structural and time varying association in US incident patients
Lacson <i>et al.</i> 2010 [57**]	T_d 7.9 ± 0.5 h $n=655$ T_d 3.7 ± 0.5 h $n=15\,334$	HR = 0.59, $P<0.0001$ for longer time (adjusted HR = 0.90, $P=0.4$ after case-mix and lab adjustment)	Multicenter US cohort Hospitalization HR = 0.76 and HR = 0.88, $P=0.02$ (after case-mix and lab adjustment)

CI, 95% confidence interval; HR, hazard ratio; RR, relative risk; US, United States (of America).

from Fig. 3 in the manuscript) for patients with T_d more than 2.5–3 h compared to those with T_d 3.5 to less than 5 h [60[•]]. Data from a large US incident cohort ($n=8552$) that survived for at least 30 days showed increased death risk in patients with T_d less than 4 h [61^{••}]. Utilizing marginal structural models to account for time-dependent confounding, the adjusted hazard ratio was 1.42 ($P<0.0001$) for T_d less than 4 h relative to T_d of at least 4 h. Finally, long in-center nocturnal dialysis patients with T_d approximately 8 h exhibited better survival (hazard ratio = 0.59, $P<0.0001$) and hospitalization rates (hazard ratio = 0.76, $P<0.0001$) than patients on conventional hemodialysis with T_d less than 4 h [57^{••}]. The latter remained significant after adjustment for case-mix and access type (hazard ratio = 0.88, $P=0.02$). These observational studies do not prove causation and are all subject to residual confounding – thus would benefit from confirmation in randomized clinical trials. However, we take consolation that the message remains consistent in that within the context of a thrice weekly dialysis regimen, T_d more than 4 h is a reasonable outcome-based clinical target.

Role of dialysis frequency

Much of the focus of dialysis adequacy in recent years has been on increasing the frequency of dialysis treatment. It can be argued that increasing frequency is just another dimension of increasing total time on dialysis. Whether frequency of dialysis more than three times per week has significant impact on survival is yet to be demonstrated in clinical trials. Results of observational studies from home nocturnal hemodialysis programs indicated significant patient well-being with lower requirement for antihypertensive medications, phosphate binders, and erythropoietin in dialysis occurring overnight six to seven times per week [62–65]. Preliminary experience indicates that conversion to every other night-long dialysis had similar results, with decreased antihypertensive medications, phosphate binder requirements, and erythropoietin dose along with improved well-being [66]. Similar benefits are noted with long thrice weekly in-center regimens as well [28,56,67,68[•],69]. The experiences with short daily hemodialyses indicate improved biochemical parameters, well-being, and cardiovascular markers albeit less efficacious than long nocturnal hemodialysis for phosphorus control [62,63,70,71]. Of note, a recent analysis indicated that patient survival within the context of increased dialysis frequency (up to five to seven times per week) is attenuated by opting for ultrashort vs. short daily dialysis [72[•]]. Moreover, frequent nocturnal hemodialysis but not short daily dialysis was shown to be associated with a better composite outcome of mortality and major morbidity (acute myocardial infarction or stroke), in a recent observational study [73]. The value of ‘short’ (2–3 h) daily dialysis as opposed to ‘long’ (6–8 h) nightly dialysis has been debated [74]. In response to this debate, a large multi-

center study is being carried out to compare these two approaches [75]. It is anticipated that results from this study will be available soon. However, differentiating the impact of T_d vs. increasing the frequency of hemodialysis beyond three times per week is a more challenging query, because increased dialysis frequency (rather than increased dialysis time three times a week) is more costly and places greater strain on healthcare resources.

There are certainly barriers to longer and/or more frequent dialysis. A shortage of dialysis facilities and dialysis stations allowing longer or more frequent dialysis is no longer a major constraint. Most dialysis providers appreciate that providing longer dialysis does not change the economics of the dialysis facility and results in better clinical outcomes and is cost saving in the long run. This may not be the case with more frequent treatments. However, the major barrier to increasing either the duration or frequency of dialysis is that of the patient’s desire to spend less time on dialysis, either at home or in center [76–78].

Conclusion

There is a need for prospective studies to investigate various combinations of frequency and time utilizing the concept of a ‘standard’ dialysis treatment period, whether based on a weekly or monthly total clearance. The economics of longer vs. more frequent dialysis (or both) must be further evaluated. Although it is becoming clear that better clinical outcomes result with longer or more frequent dialysis, overall cost savings remains speculative until hospitalization rates and days in hospital are included in the economic model of dialysis. The current ‘bundle’ of dialysis services for dialysis does not include in-patient costs [79]. Study of fully capitated programs or Accountable Care Organization-type plans will be able to better define the cost benefits of increased dialysis time and frequency [80–82]. At present, critical reappraisal of the literature indicates that short T_d within the context of three times weekly dialysis treatments is associated with more complications, increased hospitalization and decreased survival, and in the long run is likely to have a negative impact on the total cost of therapy. Thus, until shown otherwise, we recommend that physicians prescribe and exert all efforts to convince patients to accept a T_d of 4 h, three times per week as minimum hemodialysis therapy.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 206–207).

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Intensity of Care and better Outcomes among Hemodialysis Patients: A Role for the Medical Director

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ABSTRACT

The Medical Director is responsible for all levels of quality patient care in the facility as mandated by the 2008 revision of the Medicare Conditions for Coverage of dialysis facilities. He/she is the leader and primary individual tasked with ensuring that facility processes are in place to meet or exceed key quality goals or adopt new ones and prioritize them appropriately—all to drive improved facility performance, particularly the ultimate outcomes of morbidity and mortality rates. Management of vascular access, dialysis dose, mineral metabolism, acid-base balance, sodium and fluid management, anemia, among other aspects of care, have representative intermediate clinical outcomes that are often called “surrogate” or “process” measures—because they may reflect the quality of care delivery while impacting “primary” outcomes such as death and hospitalization. The proportion of

dialysis patients within a dialysis facility meeting a selected group among these goals has become the standard “care process” metric since the 1990s. Evidence supports its use, in that graded improvements in the facility patients’ primary outcomes have been documented as more patients in a facility achieved a greater number of these “process” goals. A caveat: these process measures do not represent overall quality by themselves because nonclinical processes also influence primary outcomes. Nevertheless, process improvement in meeting facility goals should be led by the Medical Director, particularly those with the strongest links to primary outcomes such as reduction of hemodialysis catheter exposure, forming the cornerstone of quality improvement efforts. Specific recommendations on how to effectively lead a care team to achieve these goals are discussed.

In the context of the current healthcare environment where scarce Medicare dollars are being aggressively managed, a triple aim of enhancing the care experience, improving the care of populations, and reducing cost of care is being pursued (1). For end-stage renal disease (ESRD), healthcare providers in partnership with dialysis facility Medical Directors must adapt to this changing environment by focusing not only on healthcare quality and patient safety but also efficiency in providing care. Moving forward, the revised prospective payment system for ESRD has not only begun redefining reimbursement and quality, but also linked them (2). The dialysis facility Medical Director is primarily responsible for all levels of quality patient care in the facility—no longer just in theory, but as mandated by the 2008 revision of the Medicare Conditions for Coverage of dialysis facilities (3). Although integral to healthcare quality, dimensions of patient safety and care efficiency are momentarily set aside until the end to focus on current concepts of quality healthcare.

Quality of patient care is often measured in terms of patient experience, quality of life, and clinical outcomes, the most prominent being death and hospi-

talization—often referred to as “primary” outcomes. There are intermediate clinical outcomes such as dialysis dose or hemoglobin levels, that are often called “surrogate” or “process” measures that may reflect the quality of care delivery in the facility and impact the “primary” outcomes. Intermediate clinical outcomes by no means encompass the overall quality of care delivery because other unmeasured or nonclinical facility-specific practices likely explain a portion of variability in primary outcomes (4), helpful in defining the concept of a “high performing dialysis facility”. Nevertheless, most of them were derived from patient-based factors that relate to primary outcomes (5) with emphasis on potentially actionable components (6). Not only have they been the subject of clinical practice guidelines and recommendations, but more importantly, achievement of specific thresholds or “goals” for selected measures related to improved patient outcomes not just individually but more so when achieved in combination (7–10).

The proportion of dialysis patients meeting each of the individual patient goals within a dialysis facility has become the standard “care process” metric since the 1990s, when a sampling of national data was publicly reported and compared to drive improvement in outcomes of care (11). We subsequently evaluated three key facility-based process performance measures: dialysis dose, hematocrit, and albumin, and their relationship singly and cumulatively with a facility-specific outcome: the standardized mortality ratio (SMR) during the years 1993 – 1995 at Fresenius Medical Care North America (FMCNA) (12). All three measures were associated with facility SMR, validating their use as process measures that may influence outcomes. However, they explained

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only a small portion of the variability of the SMR; in fact, too small to reliably predict based on facility performance whether the facility will have a significantly high or low SMR. It became apparent that these factors, although important, were insufficient by themselves to drive optimal facility-based quality improvement efforts to better primary outcomes. It implied a need to search for other relevant process measures as well as to continue concurrent monitoring of primary outcomes.

Since then, vascular access, mineral metabolism, acid-base balance, sodium and fluid management, and blood pressure have been considered as areas ripe for process measures. As it turned out, guideline recommended goals for lowering blood pressures (obtained in the dialysis unit) were found to paradoxically associated with worse outcomes (9,13). Immediately after our initial evaluation linking three process measures to SMR, FMCNA initiated an internal facility-based quality improvement program based on a review of available clinical practice guidelines, expert opinions, and a "screening" analysis of available candidate process measures (14). Annual modifications of these goals were determined by the Medical Office (in consultation with our network of Medical Directors, later becoming institutionalized into our national and regional Medical Advisory Boards), with particular attention to trends (annual shifts) in the distribution of facilities that meet these goals, so that we may continuously move the "curve to the right"—i.e., toward more patients in more facilities that satisfy goals over time. We subsequently evaluated the performance of our program (2005–2006) to determine how the expanded process measures impacted mortality and hospitalization risk (15).

The facilities were categorized into meeting < 2 , 2, 3, 4, 5, or > 5 of a total of eight FMCNA goals during the year based on the distribution of the annual mean facility scores, regardless of which quality goal was achieved (15). These scores were matched to contemporaneous facility outcomes for hospital days per patient-year and facility-specific SMR. In addition, we sought to determine if improvement (or deterioration) in the number of facilities' achieved goals from 1 year to the next (i.e., 2005–2006) had any association with the corresponding changes in hospital days per patient-year and crude (unadjusted) mortality rate.

The key finding of this evaluation was: graded improvement in facility outcomes occurred as facilities achieved more quality goals (15). The best primary outcomes were in facilities that met either the catheter and/or albumin goals (incidentally, achieved by the fewest facilities). As in any observational study, results did not "prove" that achievement of at least five of the goals or which combination of five goals would guarantee significant improvement in risk. However, the results supported the notion that increasing intensity of care for each patient to drive more patients within the facility to meet as many quality goals as possible may lead to improvement of both individual patient and aggregated facility outcomes. And thus, we circle back to the role of the Medical Director as the leader and primary individual responsible for directing quality of patient care provided by the dialysis facility care team (3).

Given the dynamic nature of clinical and scientific evidence and the sphere of influence covered by facility care teams, there are certain areas that a Medical Director can focus on in an attempt to improve care quality, but more importantly influence primary outcomes. The FMCNA quality goals have been revisited at least annually and subsequently tiered to improve focus on the top five priorities, with changes incorporated as new evidence came to light. Currently, the Medical Officers have encouraged our Medical Directors that for hemodialysis patients, the most direct benefit is likely gleaned from avoidance of exposure to hemodialysis catheters (16). Hemodialysis catheter use can lead to infections and reactive inflammation that may influence nutritional markers such as albumin (also a main quality indicator) and erythropoietin resistance (that may impact hemoglobin, another quality indicator) (17,18). In addition, lower hospitalization and death risk was observed in patients whose catheters were removed in favor of fistulas or grafts, compared to patients who retained their catheters (19–22). Referral to a predialysis options education program is beneficial not just to encourage kidney transplants and home therapies, but also to initiate vascular access placement (23). Outcomes are best associated with earlier placement of arteriovenous accesses to minimize catheter exposure (24,25), and solutions have been proposed (26,27).

We also believed that improvement in nutritional status, represented in part by albumin (28), may pay potential dividends (29). However, most studies have shown that oral nutrition supplement (ONS) improves albumin levels but few have linked it to mortality (30). The FMCNA ONS program was initiated to provide intradialytic protein supplements for patients with albumin of ≤ 3.5 g/dl until it reaches 4.0 g/dl. We now have data (presented at the ASN 2011 Annual Meeting) that show up to a 33% better mortality risk for patients who were given ONS compared to propensity matched controls ($\sim 27\%$ better with adjustment) (31). We are currently evaluating early results that indicate additional benefit toward decreased hospitalization. Therefore, we strongly recommend that supervised intradialytic ONS is provided for these malnourished patients, even those with accompanying inflammatory state (32,33).

We encourage control of hyperphosphatemia, believing that it drives both hypercalcemia and secondary hyperparathyroidism (6,34,35). It is also a given that hemoglobin and dialysis dose should meet minimum standards which are currently heavily influenced by Medicare's Quality Incentive Program (36). However, we now recommend that adequate dialysis dose should be achieved ideally with initiating treatment times of ≥ 4 hours (37). Realizing the great challenge to extend treatment time in prevalent patients, the process of implementing longer dialysis prescriptions are best initiated in incident patients, with treatment time further extended by 30 minutes for patients starting with a catheter (38). Furthermore, in addition to careful attention to adjusting dry weight, longer treatment time allows for a more gradual ultrafiltration rate, recently recognized as a

TABLE 1. Ten specific recommendations on the role of the Medical Director

1. Review of the medical literature and regulatory context to determine key quality goals
2. Brainstorm with and create consensus among medical attendings and clinical staff regarding processes that:
 - a. Will help achieve key quality goals and are feasible, measurable, and attainable;
 - b. Can be prioritized with a determination of timing of implementation and follow-up; and
 - c. Specific ownership of responsibilities and accountability can be assigned, established and monitored
3. Discuss barriers to achievement of quality outcomes and potential solutions with attendings, such as:
 - a. A need to reduce admissions of patients with a catheter access;
 - b. A need to refer to a treatment options education program prior to requiring dialysis;
 - c. A need to initiate patients to a longer (e.g. 4 or more hours) treatment time;
 - d. Other needs as determined in step #2
4. Discuss with staff the benefits of achieving the goals and encourage a professional and productive interaction with patients
 - a. This process allows for a more effective understanding of the patient population dynamics
 - b. This process allows the Medical Director to inventory gaps in knowledge/experience and objectively provide means to address them
5. Discuss with staff the importance of timely and accurate measurements in order to guide quality improvement efforts and drive improvement of patient outcomes.
 - a. The Medical Director must become proficient at Quality and Process Improvement and the Plan-Do-Study-Act process in order to lead the staff.
 - b. Encourage a culture of excellence by measuring performance and comparing to peers.
6. Discuss patient compliance, such as with scheduled hemodialysis treatments (e.g. avoidance of shortening/skipping treatments) with a root-cause analysis to identify and address specific modifiable factors
7. Discuss with incident patients their difficulties in transition to dialysis and available resources – patients new to dialysis need special attention and encouragement
8. Discuss with attendings concerns regarding quality goals and educate them (or consult experts as necessary) to resolve disagreements
9. Be physically present and actively lead the quality assurance and improvement process in the facility. Staff can easily sense disinterest and inattention, affecting morale and individual efforts to improve
10. Actually set aside time to fulfill leadership role as the Medical Director of the dialysis facility, including time devoted for education, counsel, and administration

risk factor associated with intradialytic complications and mortality (39–41).

Medical Directors are encouraged and expected to be actively engaged with their dialysis operations team, embracing a managerial role and becoming knowledgeable to explore and address modifiable factors that enhance quality, safety, and efficiency in the dialysis facility (42). It may include establishing processes and programs for rapid response to the needs of the sickest patients to get them to achieve the stated process goals, either upon entry into the unit or upon return from the hospital (43,44). Targeted interventions for endemic problems such as peripheral vascular disease and infections may include a foot check with early referral program or an enhanced immunization program against influenza, pneumococcal and hepatitis B (45–49). The key metrics above are a starting point; a set of goals to

build upon, but holistic care and improvement in care is a continuous process.

There is a need for the Medical Director to clearly articulate the facility quality goals so that all facility stakeholders: attending physicians, clinical staff, ancillary staff such as dietitians and social workers, and the patients and caregivers are working together to achieve the desired outcomes. Leadership of this interdisciplinary healthcare team is fundamental to implementing quality improvement programs, particularly those that require changes in behavior, attitude, and established routines (3,42). A systematic process of continuous quality and process improvement is very useful, because QAPI provides a vehicle for change that can be integrated into the workflow. Full Medical Director engagement and understanding of the quality improvement process is necessary to ensure continued focus by the interdisciplinary team—whose members are often adept at sensing inattention and feigned interest.

Where does a Medical Director begin? Specific discussions and key steps need to take place, such as those listed in Table 1. Physicians are the best advocates for their patients but the facility care team implements clinical programs and are often influential with advice offered to our patients. Therefore, establishing ownership and accountability from all stakeholders is essential. Remember too, that patients and caregivers hold a trump card, that the best medical advice requires compliance and adherence to succeed. For the leader of the healthcare team, the Medical Director, it is time to take responsibility for and begin exercising leadership to implement facility processes that may improve patient outcomes.

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EBPG guideline on dialysis strategies

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Outline

Guideline 1. Time and frequency

- 1.1 Minimum length and frequency of sessions.
- 1.2 Cardiovascular instability.
- 1.3 Hypertension.
- 1.4 Hyperphosphataemia.
- 1.5 Malnutrition.

Guideline 2. Flux and convection

- 2.1 High-flux dialysis
- 2.2 Haemodiafiltration.

Guideline 3. Dialysis dose methodology

- 3.1 Frequency of dose estimation.
- 3.2 Reference method.
- 3.3 Renal function.
- 3.4 Standardizing terminology.

Guideline 4. Minimum adequate dialysis dose

- 4.1 Anuric patients treated by thrice weekly dialysis.
- 4.2 Patients with renal function or dialysis schedules other than thrice weekly.

1. Time and frequency

Guideline 1.1

Dialysis should be delivered at least 3 times per week and the total duration should be at least 12 h per week, unless supported by significant renal function. See also Guideline 4.1. (Evidence level III)

Guideline 1.2

An increase in treatment time and/or frequency should be considered in patients with haemodynamic or cardiovascular instability. (Evidence level II)

Guideline 1.3

Dialysis treatment time and/or frequency should be increased in patients who remain hypertensive despite maximum possible fluid removal. (Evidence level III)

Guideline 1.4

An increase of treatment time and/or frequency should be considered in patients with impaired phosphate control. (Evidence level III)

Guideline 1.5

An increase of dialysis time and/or frequency should be considered in malnourished patients. (Opinion)

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Rationale

Definitions of dialysis schedules

Due to high mortality and morbidity rates and, inter and intradialytic symptoms associated with

conventional intermittent HD three times a week, different modalities of HD treatment based on variations in dialysis time and frequency have been developed in the last years:

- Intermittent conventional haemodialysis (HD):
 - A HD session of 3–5 h three times a week.
 - Long intermittent HD: A HD session of more than 5.5 h three times a week.
 - Conventional haemodiafiltration (HDF): A HDF session of 3–5 h three times a week.
- Extended HD > 3 times/week
- Daily (Quotidian) dialysis (at least 6 times/week)
 - Short daily HD 2–3 h/6–7 times a week.
 - Long nocturnal daily HD 6–10 h/6–7 nights a week.
 - Daily haemodiafiltration: 2–2.5 h/6 times a week.

Are there specific indications for increasing the duration of HD?

The ideal length of dialysis is still controversial [1–5]. The length of the dialysis should be individualized according to the requirements of each patient [6]. Adequate randomized controlled trials comparing increased dialysis time with conventional HD are lacking, however, some recommendations may be made:

A dialysis session of 8 h three times a week increases both the dialysis dose and time [7]. Uncontrolled study suggests that it results in better blood pressure control with a significant reduction in antihypertensive drugs, fewer intradialytic complications, improvement of nutritional status and an increased survival [1,8].

Increased treatment time reduces the ultrafiltration rate and may benefit patients with haemodynamic or cardiovascular instability [4]. The incidence of hypotension is significantly reduced in older patients when the length of the dialysis session is increased [6,9].

Increasing treatment time makes it easier to meet the body weight target in unstable haemodialysis patients with high comorbidity [7,9] and may help control blood pressure.

A randomized crossover study reported a significantly lower incidence of hypotension and post-dialysis orthostatic hypotension in 5 h than in 4 h HD sessions, especially in patients over 65 years [9], although some intradialytic symptoms such as headache, nausea, chills, back pain and pruritus were higher with 5 h HD. The main limitation of this trial is the short follow-up of only 2 weeks for each dialysis period.

A randomized study comparing long HD (6–8 h) at home with conventional HD (3.5–4.5 h) in-centre suggests that additional factors to extra-cellular volume may contribute to the superior blood control produced by long HD [10]. On the other hand, a prospective randomized study reported that an increase in the dialysis treatment time without a change in the dry body weight appeared to have a beneficial effect on the blood pressure control in dialysis patients [11]. In addition, preliminary data suggests that an increase of dialysis

time *per se* might have an independent effect on blood pressure control [1,7,8,10–13]. In general, an increase in the length of the dialysis session makes it easier to achieve dry body weight target, improves the tolerance of the dialysis session and allows better control of blood pressure with a marked reduction in the need for antihypertensive therapy [7,12,14]. In summary, longer dialysis is associated with improved fluid volume management [1,15].

An increase in the treatment time improves solute removal [7,16]. This is particularly true for the clearance of middle molecules such as beta 2-microglobulin $\beta 2m$ in comparison with less time and similar Kt/V. Some studies have shown an inverse relationship between weekly treatment duration and pre-dialysis ($\beta 2m$) concentration [17,18].

Treatment time should be increased in patients with poor phosphate control [7]. The effect of increasing the session length on clearance of diffusible small molecular weight solutes (e.g. urea) is minimal. In contrast, the duration of session length is very important for the clearance of small solutes (e.g. phosphorus) that are mainly located in the intracellular compartment [16,19]. Increasing the dialysis time has been reported to increase phosphate removal [19]. Increasing dialysis time and/or frequency are practical and effective options for increasing phosphate removal by HD.

Increasing dialysis time does not seem to improve endothelial function [20]. However, further long-term studies are required.

Impact on mortality. The effect of length of the dialysis sessions on patient mortality is controversial [1,3,4]. Some indirect evidence suggests that a longer dialysis improves the survival of dialysis patients [7,21,22]. Long slow HD 3×8 h a week has been associated with a high survival rate and a reduced cardiovascular mortality, mainly attributed to the adequate control of blood pressure [7]. Increased morbidity and mortality have been associated with shorter HD sessions [3,21–24]. Observational studies of HD session length yielded controversial results [22]. Shorter dialysis seems to be associated with an increased risk of death independent of the adequacy of the dose of dialysis delivered [7,15,21,22]. Difficulties in determining the dialysis time actually delivered, rather than prescribed, limits the value of these retrospective studies [4,22]. Analysis of the Japanese Renal Registry with more than 71 000 patients showed that increased patient survival was associated with the length of treatment sessions up to 5.5 h after accounting for Kt/V [21]. There is no evidence in three times weekly dialysis that session length can be reduced to <4 h without compromising outcome [21].

In summary, results on the effects of haemodialysis length and mortality are inconclusive. Future trials should evaluate haemodialysis length independent of dialysis dose and efficiency.

Can the effects of increased time be separated from increased dose?

Treatment time is probably an independent factor in patient outcome [4,7]. However, it is very difficult to separate the effect of treatment time and dose of dialysis [5]. One study has suggested that an increase in dialysis time, without increasing dialysis dose is associated with improved blood pressure control [10].

An additional problem is that the treatment time actually delivered may not be the same as the time prescribed. In a prospective randomized study, the reduction of the dialysis length (240 vs 150 min) maintaining a constant solute removal, did not show differences in biochemical and haematological measurements, nutritional assessment, nerve conduction studies and morbidity rate. This trial [2] was a short-term study (36 months) with a small number of patients ($n=14$).

The role of time as an independent determinant factor of dialysis adequacy requires further study.

Are there specific indications for increasing frequency?

Increased dialysis frequency constitutes a potential alternative to conventional HD [26–30]. However, it is very difficult to perform randomized trials with a large number of patients during a long period of time to compare three times HD a week with more frequent dialysis sessions [31]. Therefore, there is no available evidence of the potential benefits of these modalities in the treatment of stage 5 renal disease patients [5,18,29]. The majority of reports on frequent HD are based on studies with a small number of selected patients [26,32,33].

Increasing the frequency has theoretical potential advantages that have to be confirmed with adequate trials [29,30,34,35]. The question of what constitutes an adequate dialysis schedule remains unanswered [36]. However, it is interesting to stress that there are several publications reporting the potential benefits of more frequent dialysis treatments and none indicating that this modality is harmful.

An increase in frequency of dialysis results in lower interdialytic weight gains and should benefit patients with haemodynamic instability or large fluid weight gains. An increased frequency has been shown to facilitate the achievement of body weight target in unstable haemodialysis patients with high comorbidity [37,38]. Improved tolerance to dialysis (fewer muscle cramps, headaches and dizziness) and haemodynamic stability with a marked reduction in the number and severity of intra-dialysis hypotensive episodes has been reported [39–42].

High blood pressure is common and difficult to control in HD patients. Daily HD decreases both systolic and diastolic blood pressure with a reduction in the dose and number of anti-hypertensive drugs [32,37,43–50]. This effect is probably due to better fluid volume control [45,46].

The prevalence of left ventricular hypertrophy is greater in HD patients than in the general population and is considered a powerful predictor of poor outcome in maintenance HD. Daily HD has been associated with improved cardiac performance and a reduction in left ventricular hypertrophy [46,49]. This is probably related to a decrease of body fluid volume and better fluid management [44,46]. A prospective crossover study with a small number of patients showed that increased dialysis frequency allows better control of blood pressure with a reduction of left ventricular hypertrophy [49]. These effects seem to be related in part to a reduction of extracellular volume [46]. However, another prospective controlled study reported that the reduction in left ventricular hypertrophy in short daily dialysis occurred even in the absence of blood pressure control [44].

Daily HD seems to improve nutritional status [32,42,51,52]. After switching to daily HD, appetite and nutritional biochemical parameters improve, such as albumin and pre-albumin [52,53]. An increase of dry body weight and lean body mass has also been observed in the majority of patients treated with daily dialysis [32,54]. Daily protein intake [55] and energy intake increased after switching patients from conventional to daily HD [52]. This higher dietary intake was associated with an increase in serum albumin, pre-albumin and total cholesterol [56]. Dry body weight and lean body mass also increased [37,52,53]. Probably increased frequency is more effective than increased dialysis dose to improve nutritional status in HD patients [56].

Daily HD has been considered more physiological than conventional three times a week, with lower peak values of uraemic toxins [17,36,57–62]. Mean pre-dialysis BUN levels are significantly lower in daily HD as compared with conventional HD [40,63].

Improved phosphate control has been reported with nocturnal daily haemodialysis with a reduction in the administration of phosphate-binders [64]. Other studies comparing intermittent conventional and daily dialysis reported conflicting effects on phosphate control [44,65,66]. It is likely that patients on daily HD have more appetite with higher phosphate intake [30], which may counterbalance the higher phosphate removal [53]. Phosphate removal is closely related to the length of the HD session in daily HD [44], a dialysis time longer than 2 h is required to obtain a decrease in phosphorus plasma levels [30].

Daily HD has also been shown to be associated with a decrease in homocysteine levels with daily HD [45]. Non-randomized studies have reported a reduction of C-reactive protein [44] and oxidative stress with daily dialysis [67], however, these findings have not been confirmed in other trials. On the other hand, a better control of circulating AGE protein-bound molecules has been observed on short daily dialysis treatment [46,68,69]. A decrease in the concentration of glycation parameters, both in diabetic and non-diabetic patients,

was observed after shifting from conventional HD to daily HD [69].

There is no clear relationship between correction of anaemia and increases of dialysis frequency [29,37,70]. An increase in the haemoglobin concentration and a decrease in the mean erythropoietin dosage have been reported with quotidian HD [38,71]. However, it is important to note that quotidian dialysis patients received a higher dose of dialysis, even when the weekly dialysis time was unchanged [70,71]. Therefore, it is not possible to differentiate clearly the effects of the dose of dialysis from the increased dialysis frequency. A rise in the haematocrit among patients not treated with erythropoietin after increasing the HD frequency from three to six times per week has been reported [32]. On the other hand, daily dialysis has been associated with a greater quantity of blood loss [70].

An evident improved well-being of the patients is reported with daily HD [58,72–74]. A few studies have evaluated the quality of life of HD patients with different dialysis modalities. The majority of these showed a significant improvement of quality of life on daily HD [42,44]. Once treated by daily HD, patients chose to return to conventional HD three times a week only rarely [39,75]. However, many patients on conventional thrice weekly HD declined to be included in a daily dialysis regimen regardless of the potential benefits of this dialysis modality [76].

Improvement in hospitalization rate has been reported with daily HD compared with conventional HD [38]. More data are needed to corroborate these results. The London Daily/Nocturnal Haemodialysis study [77], a non-randomized prospective trial, did not find significant differences between short daily dialysis ($n=11$), long nocturnal HD ($n=12$) and a control group on conventional HD ($n=22$) in total number of hospital admissions, hospital days or number of emergency visits per patient-year.

There is a high patient survival rate after switching to daily HD, which has been attributed to patient selection [32]. However, daily HD showed potential benefits even when a negative selection of patients was made [38]. In a prospective study, 42 patients with high comorbidity were shifted from conventional HD to short daily HD, maintaining the same total weekly time. There was a significant improvement in the quality of life, blood pressure control and anaemia, a decreased hospitalization rate and no vascular access problems, with a cumulative survival of 35% in patients who remained in daily dialysis for more than 1 year.

Technique survival in daily HD is higher for patients who dialysed at home and lower in patients dialysed in a dialysis unit. Fewer machine alarms and nursing interventions have been reported in daily HD [42].

Potential disadvantages

Potential disadvantages of more frequent HD are related to organization, cost [78,79] and repeated vascular access punctures [80]. Another problem is that most patients did not accept this kind of

treatment regardless of the documented benefits [76]. A daily HD programme requires an appropriate infrastructure and very important logistic changes [79]. Daily HD has an increased cost of disposable materials, treatment preparation time and patient transportation [72,74]. However, the cost analysis should include potential cost reductions, such as less consumption of medications (erythropoietin, anti-hypertensive drugs, phosphate binders, etc.) and a reduction in the hospitalization rate [74,79–82]. An important drawback for the in-centre haemodialysis patient is the time spent in more frequent trips to the dialysis unit [82].

It has been reported that the repeated vascular punctures have no deleterious effect on vascular access survival [32,77,83,84]. However, prospective studies are lacking, and vascular access loss may constitute a late complication of quotidian dialysis [83].

Summary. In summary, it seems that increasing the dialysis frequency improves patient outcome with a favourable effect on blood pressure control, nutrition status, hospitalization rate and quality of life, without influencing anaemia. There is no data on mortality rate. Adequate clinical trials to compare quotidian dialysis regimens with conventional thrice-weekly haemodialysis are required.

Particular advantages of daily long nocturnal HD. Quotidian dialysis schedules, short daily dialysis and long nocturnal HD, have been reported to be more effective than conventional HD in increasing weekly urea clearance measured by single-pool Kt/V, standard Kt/V and equilibrated Kt/V [85]. Increased clearance of middle molecular weight solutes has been also reported with long nocturnal HD. The mass of β_2m removed was significantly higher with long-nocturnal HD [27]. Pre-dialysis serum β_2m levels declined progressively at initiation of long-nocturnal HD and remained stable along the follow-up period [27,86]. Total homocysteine levels in patients undergoing nocturnal HD are significantly lower when compared with conventional HD [45,87].

Improved phosphate control has been reported in nocturnal daily haemodialysis with a marked reduction in the dose of phosphate binders [30,59,88], despite an increase in the dietary phosphate intake [64]. In some patients, phosphate was added to the dialysate to correct hypophosphataemia [89].

Regarding the well-being of patients, a marked decrease of intra-dialysis hypotension episodes and cardiovascular complications has been shown when patients on conventional HD were switched to nocturnal HD [90]. An excellent control of blood pressure with a marked reduction in anti-hypertensive drugs has been reported [29,91]. In observational studies, reductions in blood pressure with nocturnal HD were accompanied by regression of left ventricular hypertrophy [91] and improvement in ejection fraction [90]. It has been suggested that there are several factors involved in the blood pressure control [92]. Recent data suggest that

nocturnal HD reduces peripheral vascular resistance and increases baroreflex sensitivity via greater afferent baroreceptor responsiveness to pulsatile pressure [93].

In a prospective cohort study of 11 patients, triglyceride levels decreased significantly with an increase of high-density lipoprotein, with no changes in total cholesterol and low-density lipoprotein after conversion from conventional to nocturnal HD [94].

In patients with sleep apnoea syndrome, oxygen saturation has been reported to improve with long nocturnal daily dialysis in comparison with conventional three times a week HD [95]. Nocturnal HD decreases the frequency of apnoea, hypopnoea and duration of nocturnal hypoxaemia. The increased heart rate and impaired vagal and augmented sympathetic heart rate modulation during sleep observed in conventional HD is normalized [96,97].

Particular limitations of daily long nocturnal HD

Calcium and phosphate depletion has been reported in long nocturnal HD, due to a high removal [88]. In a study with a small number of patients pre-dialysis phosphate was better controlled with long nocturnal HD than by short daily or conventional HD. In long nocturnal HD patients all phosphate binders were discontinued. However, a decrease in serum calcium levels associated with an increase in PTH was observed. This required an elevated dialysate calcium concentration [88].

A systematic review of the effect of nocturnal HD has been recently published [98]. The main results of this analysis was that of 270 papers identified only 14 were considered relevant, no studies examining the impact of this dialysis modality on mortality were identified, and all reports showed an improved blood pressure control after switching to nocturnal HD. Data regarding left ventricular hypertrophy, anaemia, mineral metabolism and health-related quality of life revealed mixed results. The main conclusion of this analysis is that further randomized clinical trials are required to evaluate the potential benefit of this dialysis regimen on mortality and cardiovascular morbidity.

Daily haemodiafiltration

Daily haemodiafiltration (2–2.5 h with an exchange volume of 13–14 l) six times a week compared with on-line haemodiafiltration (4–5 h) three times a week results in a significant decrease of plasma levels of urea, creatinine, uric acid, β_2 m and homocysteine [99,100]. A reduction in the dose of phosphate binders, better blood pressure control without anti-hypertensive medications, disappearance of post-dialysis fatigue, improvement of nutritional status and a marked decrease of left ventricular mass were also reported [99].

Can the effects of increased frequency be separated from increasing time?

In daily HD, it is difficult to separate the effects of increased frequency from increasing time due to the

high dose of dialysis delivered in most cases of daily HD. Regarding the positive effects of long nocturnal daily dialysis the effect of increased dialysis frequency cannot be separated from increased dose of dialysis.

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2. Flux and convection

Guideline 2.1

The use of synthetic high-flux membranes should be considered to delay long-term complications of haemodialysis therapy. Specific indications include;

- (i) **To reduce dialysis-related amyloidosis (III)**
- (ii) **To improve control of hyperphosphataemia (II)**
- (iii) **To reduce the increased cardiovascular risk (II)**
- (iv) **To improve control of anaemia (III)**

Guideline 2.2

In order to exploit the high permeability of high-flux membranes, on-line haemodiafiltration or haemofiltration should be considered.

The exchange volumes should be as high as possible, with consideration of safety. (Evidence level II).

Rationale

Solute removal in high-flux haemodialysis. Compared with low-flux haemodialysis (HD), with either cellulosic or synthetic membranes, high-flux HD has been shown to clear more middle molecular weight solutes. It also clears more of the smaller solutes, which are bound to plasma proteins, mainly albumin, and thus behave kinetically like middle molecules. β 2-microglobulin (β 2-m), a marker of the middle molecular weight uraemic toxins, belongs to the first group. Its enhanced removal in high-flux HD [1,2] results in long-term reductions in plasma levels, as demonstrated in several prospective randomized studies [3–6]. Similar findings have been reported for leptin [7], a middle molecular weight solute, involved in fat metabolism. On the other hand, intradialytic removal or long-term concentrations of smaller protein-bound solutes, retained in uraemia, such as homocysteine and AGEs, is not significantly influenced by high-flux HD [8,9]. Only the unbound fraction of such solutes is shown to be removed by high-flux membranes to a greater extent than low-flux membranes [8,9]. The total concentration in plasma is not reduced by standard high-flux dialysers, but can be reduced by using ‘super-flux’ dialysers which are permeable to albumin [10,11]. Among the favourable effects of high-flux HD, reduced circulating AGE-Apolipoprotein-B level has been described [12], as well as improved lipid profile, with significant reduction in triglyceride and increase in high-density lipoprotein (HDL) concentration and lipoprotein lipase (LPL) activity [13–15]. However, such favourable effects were absent or were not different from that shown with low-flux membranes in other randomized studies [8,16].

Solute removal in haemofiltration/haemodiafiltration. Middle molecular weight solute

removal obtained with highly permeable and biocompatible membranes employed in convective and mixed diffusion/convection strategies is definitely higher than that attainable by ‘internal filtration’ in high-flux HD. Indeed, several randomized trials conducted in the last years have confirmed that haemofiltration (HF) and haemodiafiltration (HDF) achieve a significant enhancement and widening of the molecular spectrum of the removed uraemic compounds compared with both low-flux and high-flux HD. This has been demonstrated for small molecular solutes as urea, creatinine and phosphate [17–22], for middle molecular compounds as β 2-m [17,19,20,22–25], cystatin C [24], leptin [20], retinol-binding protein [24] and for protein-bound solutes as p-cresol [23] and AGEs [26]. Moreover, enhanced removal by convection has been proven in controlled experimental settings for asymmetric dimethyl-arginine (ADMA) [27] complement fractions such as factor D [22,28], and fraction Ba [28], and with a contribution of adsorption onto the membrane, for pro-inflammatory cytokines such as TNF- α and interleukins 1,6, and 8 [29].

Increasing evidence, provided by long-term prospective studies, demonstrates that increased removal obtained by high rates of fluid exchange with HDF and HF results in lower levels of small- and medium-large sized solutes. A prospective randomized study comparing high-flux HD with HDF at a relatively low infusion volume (8–12 l/session) found similar basal β 2-m levels over a period of 24 months [5], but significant differences in basal β 2-m levels emerged from a long-term prospective study in which a mean filtration volume of 21 l was applied [22]. Higher removal in HDF/HD vs high-flux HD was demonstrated in prospective trials for urea [30], phosphate [18,21,30], β 2-m [25,30–35], factor D [22,31], homocysteine [31] and AGEs [26].

The maximum safe filtration rate is determined by the infusion mode, the blood flow rate, hydraulic permeability and surface area of the dialyser membrane and the patient’s characteristics (haematocrit and total protein concentration, coagulability status). These factors, to a different extent, contribute to the establishment of the pressure regimen necessary for the planned filtration. Presently, a feedback control system preventing excessive trans-membrane pressure increase beyond a safe maximum value (i.e. 300 mmHg) by modulating infusion and filtration rate is the most advanced tool to avoid technical and clinical drawbacks of an excessive filtration [19]. In the absence of such equipment, the following general rules can be applied. Post dilution; the filtration rate should be limited to ~40% of plasma water flow rate, corresponding to ~25% of blood flow rate. Pre dilution; the infusion rate should not exceed the plasma water flow rate, to avoid loss of efficiency as a consequence of the excessive dilution of solute concentration. Ultrapure dialysate is mandatory for on-line production of the

infusion fluid. The infusion fluid must be sampled periodically to ensure that it is free of endotoxin and meets the standards of microbial purity described in EBPG 1.

Clinical results of increasing flux. The above middle-molecular compounds have a pathogenic role or are markers of the most frequent long-term complications and causes of death in HD patients such as dialysis-related amyloidosis, cardio-vascular disease, secondary hyperparathyroidism, inflammation and malnutrition. Reduction of the accumulation and lower long-term levels of these compounds may prevent or delay the appearance of such complications. Significant reductions in the incidence of carpal tunnel syndrome and signs of dialysis-related amyloidosis have been reported in two large retrospective studies as a result of high-flux membranes [36] and of convective and mixed dialysis strategies [37] inducing lower chronic β_2 -m levels. These observations have been confirmed by two prospective studies conducted in small groups of patients but with long follow-up (2 and 6 years) [4,38], in which clinical signs of dialysis-related amyloidosis were shown to arrest or ameliorate as an effect of the use of high-flux membranes alone or coupled with β_2 -m adsorption columns. The increased ability of high-flux membranes to remove phosphate [17–21,39] may translate into lower serum phosphate level in the long term, as shown by some prospective studies [3,18,21]. Control of hyper-phosphataemia has been associated with improved patient survival in a large cohort of patients from two special studies of the USRDS [40]. A recent randomized study comparing high-flux and low-flux polysulfone membranes at similar efficiency (Kt/V) suggested that high-flux dialysis was more effective in terms of controlling renal anaemia and reducing the need of erythropoietin therapy [41]. These beneficial effects of high-flux dialysis have been attributed to the improved clearance of middle- and high-molecular weight toxins. Similar findings have been described in other prospective [42,43] and observational studies [44,45] performed in patients on convective and mixed therapies compared with low-flux haemodialysis. However, in patients who are, adequately dialysed, and not iron- and/or vitamin-depleted, this favourable effect was not confirmed in several trials comparing low-flux HD with high flux HD [46,47], acetate-free biofiltration (AFB) [48,49] or HDF [35].

Outcome in high-flux HD and HDF/HF. In the last decade, several observational studies from large databases have reported a reduced death risk in patients undergoing haemodialysis with high-flux membranes [36,50–55]. In some studies, such an effect has been associated with the increased removal of middle-molecular uraemic toxins promoted by these membranes [53,55] independently from the effects related to their high biocompatibility. The association between death risk in dialysis patients and levels of

β_2 -m found in the above studies, was confirmed in the HEMO Study [56], the only randomized prospective study ever performed to assess the effect of high-flux membranes on mortality in haemodialysis patients. On the other hand, overall survival was not influenced significantly by high-flux membranes in an Italian study based on the Lombardy Registry of Dialysis and Transplant [37]. The HEMO Study provided more compelling evidence in this direction: among the 1846 patients enrolled in the study, high-flux membranes did not significantly affect the primary outcome of the all-cause mortality rate or the main secondary composite outcomes, including the rates of first cardiac hospitalization or all-cause mortality [2]. Possibly, the small mean difference in β_2 -m clearance between the low-flux and the high-flux group of the Study (3 ± 7 vs 34 ± 11 ml/min) prevented the achievement of a clearer difference in the overall outcome between groups.

The methodology of the HEMO study has been criticized and the validity of the final results questioned [57–59]. Subgroup analysis of the HEMO study were not in line with its general conclusions, showing that the high-flux intervention was associated with reduced risks of specific cardiac-related events, such as the decreased cardiac mortality and the composite outcome of first cardiac hospitalization or death from cardiac causes [60]. Although high-flux dialysis did not reduce all-cause mortality, it might improve cardiac outcomes. In addition, the effect of high-flux dialysis on all-cause mortality was shown to vary, depending on the duration of prior dialysis. In fact, in the subgroup that had been on dialysis for more than 3.7 years, randomization to high-flux dialysis was associated with significantly lower risk of all-cause mortality compared with low-flux dialysis [60,61]. These data are in favour of the view that patients with different durations of dialysis may be affected differently by high-flux membranes and suggest that their beneficial effect in reducing cardiovascular events may take time to result in a significant reduction of fatal events in chronic patients. In agreement with these findings, a significant effect on mortality has also been described in a subset of patients on HDF with high-flux polysulfone ($n=20$) and on AFB with PAN ($n=20$) [62], 32 patients randomized to pre-dilution HDF (33), and in a larger cohort of 650 selected patients after a two-year extension of a study with a thirty months follow up [63].

However, in spite of the above favourable premises, the positive effect of convective and mixed treatments on patient's survival is still unproven. This may be due to their relatively recent diffusion into routine practice and the scarce number of patients chronically treated with these strategies. Two studies, one registry study [37], and one small 2 years' prospective trial [35], not designed to study mortality of the techniques, did not show a significant difference between HDF and low-flux HD. However, more recently, some evidence has appeared to support the favourable impact of convective therapies: results from the European DOPPS Study [64] in 2165 patients followed from 1998 to 2001 showed that

high-efficiency HDF patients, after adjustment for age, sex, fourteen comorbid conditions and time on dialysis, had a significant 35% lower mortality risk than those receiving low-flux HD (relative risk = 0.65, $P = 0.01$). These observational results suggest that HDF may improve patient survival independently of its higher dialysis dose. Great caution must be used while interpreting these findings, and definite confirmation with large prospective studies is required for their important clinical and economical implications.

Summary of evidence

High-flux membranes employed in convective and mixed diffusion/convection therapies achieve the maximal removal of small- and middle-molecular toxic solutes and, at least in the case of β_2 -m, establish lower long-term concentrations (Evidence II). Prolonged use of such membranes in high efficiency dialysis techniques helps prevent some long-term complications of the uraemic status, such as dialysis-related amyloidosis and hyperphosphataemia, and reduces cardiovascular risk and death (Evidence II).

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3. Dialysis dose methodology

Guideline 3.1

Delivered dialysis dose should be measured at least monthly. (Opinion)

Guideline 3.2

Dialysis dose should be measured using a validated method comparable with the reference method. The reference method is formal urea kinetic modelling using pre- and post-dialysis blood samples and taking ultrafiltration, urea generation and the post-dialysis rebound into account. (Opinion)

Guideline 3.3

Renal function may be taken into account in the dose measurement provided it is measured frequently enough to avoid overestimation as GFR falls, typically every 2 months. (Opinion)

Guideline 3.4

For three times weekly dialysis, dose should be quoted as eKt/V . For schedules other than three times weekly, dose should take frequency into account and be quoted as weekly standard Kt/V ($stdKt/V$), solute removal index (SRI) or equivalent renal clearance (EKR). (Opinion)

Rationale

Frequency of adequacy testing. Numerous studies have shown that low dialysis dose is associated with poor outcome [1–3]. Inadequate dialysis may be difficult to detect clinically or by routine biochemical tests. Faults in the system for delivering dialysis (which includes the fistula, dialysis machine, prescription, schedule and dialyser) may be unpredictable and results in inadequate dialysis [4]. To prevent adverse effects on the patient due to inadequate dialysis, adequacy measurements are customarily taken monthly along with routine biochemical tests [5].

Adequacy measurements may be performed at every treatment without blood sampling using online clearance methods based on dialysate-side measurements [6,7].

Method of adequacy testing, need for a reference method. Various methods have been proposed and are in use for calculating dialysis dose. Dose calculated using many of these methods have been shown to relate to outcome. All methods are based on indirect measurement of mass of urea (or a urea surrogate) removed from the patient over a dialysis session. Differences between methods relate to the extent to which ultrafiltration, urea generation, residual renal function, urea distribution volume and the post-dialysis rebound are taken into account.

As long as a dialysis facility uses a validated method for calculating dose and applies it consistently and properly, it does not matter which method is used for routine surveillance of the patient. The need for a reference method arises when an external standard is applied (such as minimum recommended dose) and when results are to be exported to a registry or used in research. In this case, the relationship between any method in use for calculating dose and the reference method must be known.

The most common method for calculating dose cited in publications is the formal variable-volume, single-pool urea kinetic model of Gotch, returning the single-pool Kt/V ($spKt/V$) [8]. This has become the *de facto* reference method for haemodialysis dose. The Gotch method requires input of pre- and post dialysis weight, height, sex, age, dialyser type, blood flow, dialysate flow, dialysis time, pre- and post-dialysis urea or BUN. The $spKt/V$ returned by the reference method takes urea generation, ultrafiltration and urea distribution volume into account. The $spKt/V$ can be calculated independently from both the dialysis prescription and blood urea measurements to validate the result.

When dialysis is applied intermittently as in haemodialysis, there is always a significant disequilibrium between body water compartments. This results in a significant post-dialysis urea rebound which takes 30–40 min to complete. Unless the post-dialysis sample is taken after the rebound is complete, the Gotch method will significantly overestimate dialysis dose. This overestimation is relatively greater in shorter dialysis, about 25% in a 2 h dialysis compared with 10% in a 5 h dialysis [9]. It has been shown that the Gotch method using an immediate post-dialysis blood sample can easily be corrected for these disequilibrium effects by applying an additional term with input of dialysis session duration (td) [10]. This equilibrated Kt/V (eKt/V) taking the post-dialysis rebound into account, has been validated in the HEMO study [11]. Since td is already required by the Gotch method and since the Gotch method already requires a computer to calculate, rebound correction, returning eKt/V adds no additional cost or logistical complexity.

Trouble shooting and validation. A major advantage of Kt/V is that it can be independently calculated from dialysis session time (t), an estimation of V using body weight and an estimation of K using blood flow, dialysate flow and dialyser urea clearance coefficient. Any discrepancy between the ‘prescribed’ Kt/V calculated in this way and the ‘delivered’ Kt/V calculated using pre- and post-dialysis blood samples can yield valuable diagnostic information. For example, incorrect sampling technique may cause the ‘delivered’ Kt/V to be much higher than ‘prescribed’ Kt/V .

Access recirculation may result in the ‘delivered’ Kt/V being less than ‘prescribed’ Kt/V.

Other methods for calculating adequacy. Other methods used for calculating dialysis dose may be easier to use, with fewer input variables, yet return a result which is a reasonable approximation of the Gotch method. The simplest of these is the urea reduction ratio (URR) which is the fall in blood urea concentration over the dialysis session divided by the pre-dialysis urea. URR can be expressed as Kt/V by the logarithmic transformation [12];

$$\text{Kt/V} = \ln\left(\frac{1}{1 - \text{URR}}\right)$$

This simple method for calculating Kt/V does not take ultrafiltration, urea generation or the post-dialysis rebound into account. For a 4 h dialysis with 2 l of ultrafiltration, these effects approximately cancel out and the result is very close to eKt/V calculated by the reference method. For dialysis sessions shorter than 4 h or with <2 l ultrafiltration, the URR method will significantly overestimate eKt/V. The URR method may be used as an approximation for practical purposes but should not substitute for monthly measurement of eKt/V by the reference method.

Online clearance methods are increasingly used to calculate dialysis dose without blood samples. The equipment is built-in to the dialysis machine and calculates dose from measurements of dialysate conductivity. Online clearance calculates a precise value for Kt. It estimates Kt/V using an estimation of V from inputs of patient weight, height, age and sex. These estimations of V are known to be an overestimate, causing Kt/V to be underestimated [13]. Kt/V calculated by online clearance is not necessarily automatically corrected for rebound, though this could easily be done by the equipment. Online clearance is not currently validated for haemodiafiltration or haemofiltration.

As long as the difference between Kt/V calculated by the online clearance and the reference method is taken into account, online clearance is an acceptable method for calculating haemodialysis on a treatment-by-treatment basis. Online clearance should not substitute for monthly measurements using the reference method.

Dialysis frequency other than three times per week. Three methods have been proposed to quantify dialysis dose in dialysis schedules other than three times per week, taking frequency of dialysis into account, the solute removal index (SRI) [14], standard Kt/V (stdKt/V) [15] and the equivalent renal clearance (EKR) [16].

SRI and stdKt/V are both equivalent to the ‘weekly Kt/V’ in peritoneal dialysis and are approximately equivalent to URR times the number of dialysis sessions per week. They are defined as the mass of

urea removed (or generated) per week divided by the peak mass of urea in the patient in that week. For stdKt/V, the peak is defined as the mean pre-dialysis value, whereas in SRI, the peak is the highest of the pre-dialysis values.

In symmetrical dialysis schedules when the time between dialysis sessions are equal (e.g. daily or alternate day dialysis), SRI and stdKt/V are equal. Where dialyses schedules are asymmetrical, the two measures diverge. In a typical three times weekly dialysis schedule, SRI will be 0.87 times stdKt/V. In an extreme example, with 7 times per week dialysis, the stdKt/V will be the same whether all sessions are performed on the same day or performed daily. SRI will be reduced by 50%, if all dialyses are performed on the same day, influenced by the very high peak concentration after the longest interdialytic interval.

EKR expresses the dialysis dose as the continuous clearance required to achieve the same time averaged concentration. EKR is the urea generation rate divided by the time averaged concentration rate of urea. It uses the familiar units of ml/min.

All three dose measures can be calculated from the urea generation rate (G) and peak urea concentrations (TAC urea in the case of EKR) which can be computed using iterative solution of the Gotch equations with rebound correction. No additional inputs are required apart from frequency of dialysis.

SRI and stdKt/V can also be calculated from dialysate collections, using the same method as for peritoneal dialysis. In this method, a value for urea distribution volume (V) is required but there is no need for a post-dialysis sample or rebound correction.

Where dose is calculated using dialysate and plasma samples, the difference in protein concentrations in the samples will affect the measurement of urea concentration, causing dose to be overestimated unless it is taken into account [17]. V, calculated using anthropometric equations may be an overestimate, causing dialysis dose to be underestimated [13].

To assist in prescribing, stdKt/V can be converted to a ‘per dialysis’ eKt/V using the natural logarithm function (ln) as shown subsequently, where *f* is the frequency of dialysis.

$$\text{eKt/V} = \ln\left(1 - \frac{\text{stdKt/V}}{f}\right)$$

EKR differs from stdKt/V and SRI in that equivalent doses achieve the same time averaged urea concentrations (TAC) rather than peak concentrations (Table 1). This has the effect of giving more ‘weight’ to shorter, more intensive dialysis which reduces TAC more than peak concentrations. EKR is affected by asymmetry of dialysis schedule, but to a lesser extent than SRI. EKR can be corrected for body size as EKRC in ml/min/40 l. EKRC is approximately five times stdKt/V in three times per week dialysis and four times stdKt/V in daily dialysis or if there is significant renal function where TAC is closer to peak concentration.

Table 1. Comparison of dose measures for differing dialysis schedules and renal function

Renal function GFR (ml/min)	Dialysis prescription Frequency (per week)	Time (h)	Dialysis dose (per session)		Total clearance, renal + dialysis (per week)		
			eKt/V	spKt/V	stdKt/V	SRI	EKRc (ml/min)
8	No dialysis	–	0	0	2.0	2.0	8.0
5	2	4	1.2	1.4	2.4	2.3	13.4
3	2	6	1.8	2.2	2.3	2.2	14.4
2	3	3	0.9	1.1	2.3	2.0	12.1
0	3	4	1.2	1.4	2.2	2.0	12.9
0	3	8	2.4	2.9	3.1	2.5	21.2
0	Alternate day	4	1.2	1.4	2.6	2.6	15.2
0	6	2	0.6	0.7	2.8	2.3	13.8
0	7	2	0.6	0.7	3.3	3.3	16.2
0	7	8	2.4	2.9	8.1	8.1	55.1

In each case, V is 40l, and dialyser clearance is 236 ml/min. For the dialytic schedules, fluid weight gain is 1 l/day.

Taking renal function into account. Patients may retain significant renal function for some years after starting haemodialysis [18,19]. It has been shown that the presence of residual renal function is associated with improved outcome in peritoneal dialysis and haemodialysis [20–22]. In peritoneal dialysis, current guidelines specify that, where there is significant renal function, it is measured every 2–4 months. In peritoneal dialysis, residual renal function may be quantified as the urea clearance and is expressed as ‘weekly Kt/V’ which is identical to the weekly SRI or stdKt/V. Current PD guidelines specify that ‘weekly Kt/V’ is calculated from mass of urea, in dialysate and urine. Since urea is absorbed by the renal tubules, urea clearance underestimates GFR by about 40%. Most software in current use actually calculates the renal component of ‘weekly Kt/V’ from the mean of urea and creatinine clearance, which has been shown to closely approximate GFR [23].

To be consistent with peritoneal dialysis practice and CKD guidelines, renal function may be quantified as GFR, calculated from the mass of urea and creatinine in an interdialytic urine collection and average concentrations of urea and creatinine in blood during the collection as described in the EBPG part 1 [24]. For reasons outlined in the EBPG part 1, we recommend using GFR rather than renal urea clearance when adding to the weekly dialysis dose measures EKR, stdKt/V or SRI. In this case, GFR may be added to the dialytic component of EKR to give a total (dialysis and renal) EKR. GFR in ml/min can be converted to a renal component of stdKt/V or SRI as follows;

$$\text{stdKt/V(renal)} = \frac{\text{GFR} \times 10080}{V}$$

Since a body surface area of 1.73 m² equates to a urea distribution volume of ~35.5l, the renal component of stdKt/V or SRI is ~0.28 times GFR in ml/min/1.73 m². Table 1 shows how different levels of GFR can be combined with varying HD schedules to achieve the same stdKt/V.

If the patient has a reduced dialysis prescription, relying on residual renal function to make up to the recommended minimum dose, there is a risk of inadequate dialysis if the renal function were to fail unexpectedly. For this reason, unless renal function has been shown to be exceptionally stable in an individual patient, renal function should be measured at least twice monthly or whenever a change is suspected. Where renal function is questionable, there are no recent results available or the results are suspect in any way, renal function should be assumed to be zero.

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4. Minimum adequate dialysis

Guideline 4.1

In anuric patients, treated by three times per week dialysis, the prescribed target eKt/V should be at least 1.2. Higher doses, up to 1.4 should be considered in females and those patients with high comorbidity. (Evidence level III)

Guideline 4.2

For patients with renal function or those with dialysis schedules other than three times per week, weekly dialysis dose should be at least equivalent to an SRI of 2. (Evidence level IV)

Rationale

Three times per week dialysis. The evidence guiding the minimum dose of dialysis has been challenged in the last few years.

A typical dialysis in Europe delivers an eKt/V of around 1.2 three times per week [1]. Numerous older studies have shown a relationship between outcome and dialysis dose, with eKt/V less than around 1 associated with worse outcome [2–4]. The recent HEMO study [5] failed to show any difference in outcome on an intention-to-treat basis between an eKt/V of 1.05 and 1.45. The same study showed that there was a very strong relationship between achieved dialysis dose and outcome within each arm [6]. This has been taken to demonstrate a strong dose-targeting bias effect in the study. It seems that the success or failure to achieve adequacy targets is more important than the target level. Since the HEMO study is the only large randomized controlled study designed to investigate dialysis dose, there is the possibility that the association between mortality and dose seen in most other studies could be the effect of this dose-targeting bias.

Subanalysis of the HEMO study demonstrated a significantly reduced mortality in females in the high-dose group (and corresponding non-significant increased mortality of males in the high-dose group). The DOPPS study also suggested that the optimal Kt/V might be higher for females than males. It showed a reducing mortality with eKt/V increasing to 1.2 in males and 1.3 in females.

The EBPg group interprets the available evidence to date for three times weekly dialysis as demonstrating that eKt/V <1 is almost certainly harmful. On the other hand, there is no benefit to increasing eKt/V above 1.2, at least in males. In routine clinical practice, dialysis dose is likely to be less well controlled than in clinical studies. Most errors of dialysis prescription or delivery tend to reduce delivered dialysis dose to value below expected. Therefore, it seems sensible to allow a 20% safety margin and recommend a minimum eKt/V of 1.2.

More frequent dialysis than three times per week. There is limited data from studies investigating outcome as a function of dialysis dose in schedules greater than three times weekly. Most daily or 6 times weekly dialysis schedules deliver a weekly SRI of much >2.0 (equivalent to eKt/V >1.2 three times weekly). A theoretical advantage of more frequent dialysis is that it is easier to increase SRI to levels >2.5 (3 is the maximum possible for three times weekly dialysis, unless very long times are employed).

Twice weekly dialysis. There is no published evidence supporting the safety of twice weekly dialysis. Some centres in Europe treat patients with residual renal function by twice weekly dialysis as part of an incremental or early start programme [7]. The maximum SRI practically achievable with twice weekly dialysis without renal function is <2. Therefore, the recommended minimum SRI of 2 would only be possible with demonstrated significant residual renal function.

Higher doses of dialysis. There is no evidence supporting the safety of dialysis dose exceeding 1.5 in three times weekly dialysis <15 h per week. The HEMO study failed to show any benefit from increasing dose above eKt/V of 1.05 [5].

Observational studies show a relatively high mortality associated with eKt/V >1.5 [8]. This is thought to be related to low body mass and high comorbidity in patients treated with high dose but a directly harmful effect of high dialysis dose cannot be excluded [9]. It is quite hard to achieve an eKt/V >1.5 with standard three times weekly schedules unless long session durations (>5 h) are employed.

The EBPg group interpret this evidence as indicating that there is no benefit to eKt/V >1.5 in standard three times weekly dialysis and there is the possibility that high dose may be harmful in this setting. On the other hand, more frequent or longer dialysis allows higher eKt/V to be delivered relatively easily. There are theoretical advantages to high eKt/V in combination with long or more frequent dialysis which deserve further study.

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Shorter dialysis times are associated with higher mortality among incident hemodialysis patients

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There is an association between hemodialysis session length and mortality independent of the effects of session duration on urea clearance. However, previous studies did not consider changes in session length over time nor did they control for the influence of time-dependent confounding. Using data from a national cohort of 8552 incident patients on thrice-weekly, in-center hemodialysis, we applied marginal structural analysis to determine the association between session length and mortality. Exposure was based on prescribed session length with the outcome being death from any cause. On the 31st day after initiating dialysis, the patients were considered at-risk and remained so until death, censoring, or completion of 1 year on dialysis. On primary marginal structural analysis, session lengths <4 h were associated with a 42% increase in mortality. Sensitivity analyses showed a dose-response relationship between session duration and mortality, and a consistency of findings across prespecified subgroups. Our study suggests that shorter hemodialysis sessions are associated with higher mortality when marginal structural analysis was used to adjust for time-dependent confounding. Further studies are needed to confirm these findings and determine causality.

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Over the past several decades, dialysis dose has been measured in terms of, and titrated with respect to, urea kinetics. In 1985, Gotch and Sargent¹ introduced the concept of single pool Kt/V , a measure of dialysis adequacy that attempts to match the degree of urea clearance to metabolic needs. In the intervening years, single pool Kt/V , and the related equilibrated Kt/V (eKt/V), have been largely adopted as the primary indices of dialysis adequacy.²

Over the past decade, the validity of Kt/V (single pool and/or equilibrated) as an outcome measure has been debated. Lowrie *et al.* have argued that since both greater urea clearance (K^*t) and greater volume of distribution (V) are each associated with improved survival,³ dividing the two (that is, placing V in the denominator) is counter-intuitive, and guiding therapy by the Kt/V metric may therefore lead to disadvantageously low levels of urea removal in patients with already poor projected survival on the basis of small body size.⁴ In addition, in the present era of high-efficiency dialyzers (which enable rapid urea removal), the singular focus on urea kinetics may result in session lengths that are too short to enable adequate clearance of larger, charged, or protein-bound molecules, and moderate, well-tolerated rates of fluid removal for many patients.^{5,6}

Several studies have examined the association between dialysis session length and mortality independent of (that is, adjusted for) Kt/V .^{5,7,8} Although many results lent credence to an association between shorter session length and mortality, these studies were beset by methodological shortcomings. Specifically, all studies considered session length as of a baseline value, which does not reflect the commonplace clinical practice of titration in response to clinical and biochemical circumstances. Moreover, none of the studies accounted for the potential of time-dependent confounding of the session length–mortality association. Time-dependent confounders are variables that are influenced by previous exposure, that then influence subsequent exposure, and are also associated with the outcome.^{9–12} It has been shown that in the presence of time-dependent confounding, standard methods of statistical adjustment (as used by the previous studies cited above) yield biased (that is, inaccurate) estimates of causal association, even when covariates are time-updated in the statistical model. Fortunately, novel statistical methods

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have been developed that enable more accurate estimation of causal associations in the presence of time-dependent confounding, among them marginal structural analysis.^{11,12}

To determine whether shorter session length is associated with higher mortality while considering time-dependent confounding, we undertook a series of marginal structural analyses in which we examined the associations between session length and mortality, considering the former as a time-varying exposure. For comparative purposes, we also present the results of standard analyses—those in which session length was considered as of baseline levels, and those in which it was considered as a time-varying exposure using standard methods of statistical adjustment—to emphasize the potential advantages of marginal structural analysis as a means of more accurately quantifying associations when exposures are titrated over time.

RESULTS

The source cohort contained data on 10,044 patients who initiated incenter maintenance hemodialysis at any Fresenius Medical Care North America facility between June 2004 and August 2005. After excluding minors ($n = 14$), patients who did not survive until the start of at-risk time (dialysis day 31; $n = 603$) and those with insufficient covariate data for analysis ($n = 875$), 8552 subjects qualified for inclusion in the study. The mean age was 62.3 ± 15.4 years, 54.8% were male and 40.5% were of nonwhite race (Table 1). Excluded patients were significantly more likely than study participants to be older, nonwhite, dialyze through a catheter, have lower blood pressure, serum albumin, and creatinine, be prescribed

shorter session lengths, and less likely to have congestive heart failure (CHF) (Table 1).

The distribution of baseline session length (that is, the last observed over dialysis days 0–30) is shown in Figure 1a. Given the discrete pattern observed, session length was categorized as shorter (< 240 min) or longer (≥ 240 min) in primary analyses; secondary analyses considered session length categorized as ≤ 180 , 181–239, or ≥ 240 min and as a continuous variable. Representative changes in session length during at-risk time are depicted in Figure 1b. For clarity, the figure shows transitions occurring between months 0, 3, and 6; analytically, session length was updated with each new order (time-updated analyses) or at monthly intervals (marginal structural analyses). Overall, 1698 subjects (19.9%) transitioned at least once between shorter (< 240 min) and longer (≥ 240 min) session length; 2478 (29.0%) transitioned at least once among ≤ 180 , 181–239, and ≥ 240 min session length strata.

At-risk time began on dialysis day 31 and continued until each subject died, was censored, or completed 1 year on dialysis (the last day of complete follow-up). Censoring criteria included transfer of care ($n = 851$), recovery of kidney function ($n = 236$), withdrawal from dialysis ($n = 336$), and receipt of a kidney transplant ($n = 213$). Overall 8552 subjects contributed 78,798 patient-months of at-risk time, during which 1047 died; 5869 subjects remained alive and on dialysis as of the end of study.

Baseline and Time-updated Analyses

In baseline analyses, exposure and covariates were defined as the last value observed during the baseline exposure period

Table 1 | Baseline description of study participants and excluded patients

Variable	Study cohort ($n=8552$)	Excluded ($n=1492^a$)	P^b
Age (years)	62.3 ± 15.4	65.0 ± 16.1	< 0.001
Male	4686 (54.8%)	815 (54.6%)	> 0.9
Nonwhite race	3461 (40.5%)	467 (31.3%)	< 0.001
BMI (kg/m^2)	26.3 (22.5–31.2)	26.2 (22.3–31.4) ($n=1388$)	0.8
Vascular access			< 0.001
Fistula	2347 (27.4%)	126 (11.4%)	
Graft	1031 (12.1%)	64 (5.8%)	
Catheter	5174 (61.5%)	915 (82.8%) ($n=1105$)	
CHF ^c	1642 (19.2%)	234 (15.7%)	0.01
eKt/V	1.35 ± 0.32	1.35 ± 0.35 ($n=688$)	> 0.9
Blood pressure (mm Hg)			
Systolic	147.8 ± 28.2	138.8 ± 30.0	< 0.001
Diastolic	76.1 ± 16.9	71.7 ± 17.5 ($n=1491$)	< 0.001
Albumin (g/dl)	3.7 ± 0.5	3.4 ± 0.6 ($n=1490$)	< 0.001
Creatinine (mg/dl)	7.4 ± 3.1	6.1 ± 3.0 ($n=1403$)	< 0.001
Session length (min)	225 (210–240)	210 (210–240) ($n=1483$)	< 0.001
Deaths	1047	222	
Mortality rate (deaths per 1000 pt-years)	161.7 (152.2–171.8)	509.5 (446.7–581.2)	< 0.001

Abbreviations: BMI, body mass index; CHF, congestive heart failure; CI, confidence interval; pt-years, patient years.

Continuous data expressed as mean $\pm$ s.d. or median (inter-quartile range) as appropriate. Categorical data presented as n (%). Mortality rates expressed as point estimate (95% CI).

^aExcept where noted.

^bComparing study participants to excluded patients. Continuous variables compared using Student's t -test or Wilcoxon rank-sum test as appropriate, categorical variables compared using χ^2 test, survival data compared using log rank test.

^cCHF defined as diagnosis code on Medical Evidence Form 2728 or attributed hospitalization during the baseline period.

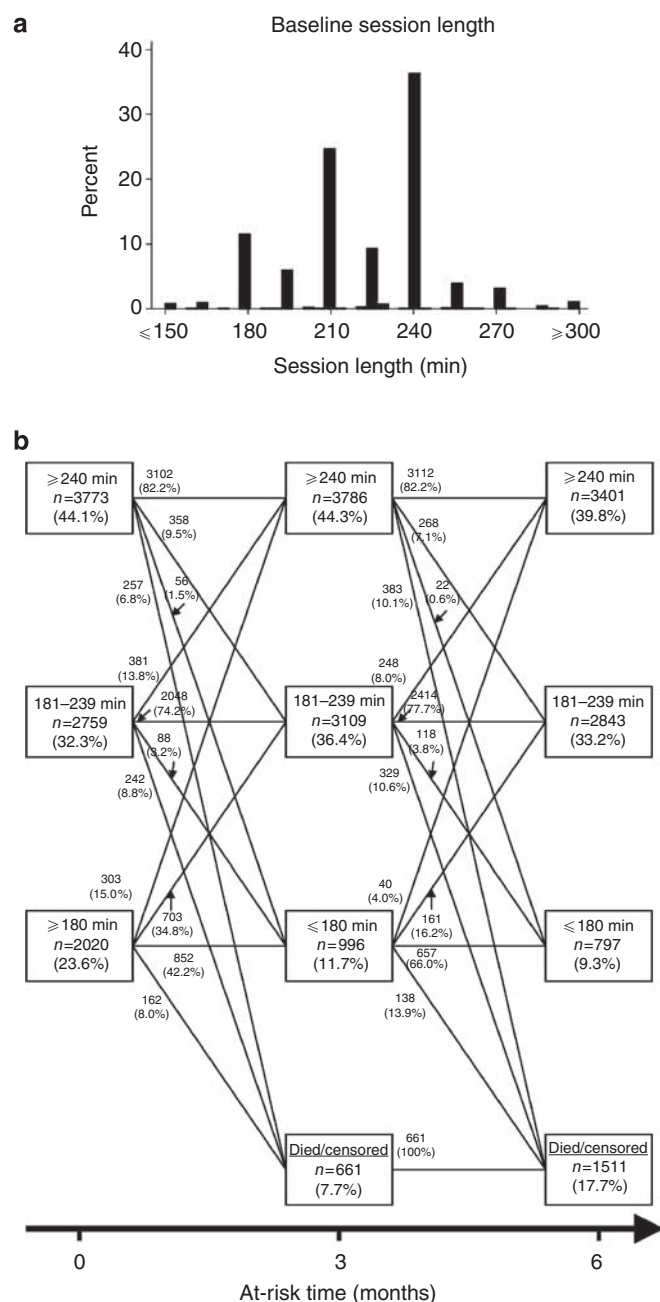


Figure 1 | Observed hemodialysis session lengths among study cohort. (a) Distribution of observed session length at baseline ($n = 8552$). (b) Representative transitions among strata of session length at baseline, months 3 and 6. At the start of at-risk time (at-risk day 0, corresponding to dialysis day 31), 2020 (23.6%) patients had session length ≤ 180 min; of these 303 (15.0%), 703 (34.8%), and 852 (42.2%) had session length of ≥ 240 , 181–239, and ≤ 180 min, respectively, at the start of month 3; the remaining 162 (8.0%) had died or were censored by that time. Interpretation is analogous for other session-length strata and time intervals.

(dialysis days 0–30), and used to predict survival in the subsequent at-risk period. Over the baseline exposure period, last observed session length was highly correlated with mean session length ($r = 0.94$), suggesting that classification of exposure in terms of the former was reflective of the cumulative exposure to dialysis during this interval. Shorter session length (< 240 min) was observed for 54.7% of subjects.

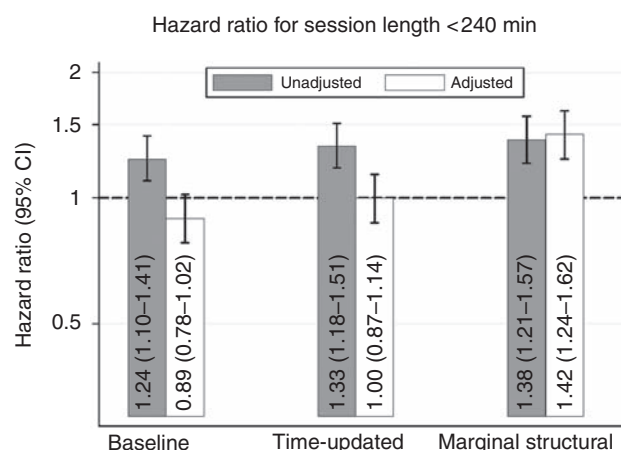


Figure 2 | Hazard ratios (95% CIs) for all-cause mortality for shorter session length (< 240 min) in baseline, time-updated, and marginal structural analyses. The referent category is session length ≥ 240 min (hazard ratio = 1 by definition; not shown). Gray bars represent unadjusted estimates. White bars represent estimates adjusted for age, sex, race (white versus nonwhite), vascular access (fistula, graft, catheter), body mass index (≤ 20 , 20–25, 25–30, and > 30 kg/m²), congestive heart failure, eKt/V (≤ 1.0 , 1.0–1.2, 1.2–1.4, 1.4–1.6, > 1.6), systolic blood pressure, serum albumin, and creatinine. CI, confidence interval.

On unadjusted analysis, shorter session length was significantly associated with higher mortality: HR (95% CI) 1.24 (1.10–1.41; $P = 0.001$) (Figure 2). On multivariable adjustment, the association between shorter session length and mortality was attenuated and no longer statistically significant: HR (95% CI) 0.89 (0.78–1.02; $P = 0.09$) (Figure 2).

As session length is not static, but rather, typically titrated in response to clinical circumstances, we fit time-updated proportional hazards models to estimate the association between session length and mortality. In these models, we updated session length with each new order, along with blood pressure, eKt/V , presence or absence of CHF, serum albumin, and creatinine (as described in Materials and Methods). Shorter session length (< 240 min) was observed in 52.9% of all patient-time.

On unadjusted analysis, shorter session length was significantly associated with higher mortality: HR (95% CI) 1.33 (1.18–1.51; $P < 0.001$) (Figure 2). On multivariable adjustment, the association between shorter session length and mortality was attenuated and no longer statistically significant: HR (95% CI) 1.00 (0.87–1.14; $P > 0.9$) (Figure 2).

Marginal Structural Analysis

To better account for the influence of time-dependent confounding on the session length–mortality association, we applied marginal structural analyses. In these analyses, session length and time-varying covariates were updated at each month of study. Overall, shorter session length (< 240 min) was observed in 52.4% of all patient-months.

In the unweighted (that is, unadjusted) model, there was a significant association between shorter session length and death similar to that seen in the unadjusted time-updated

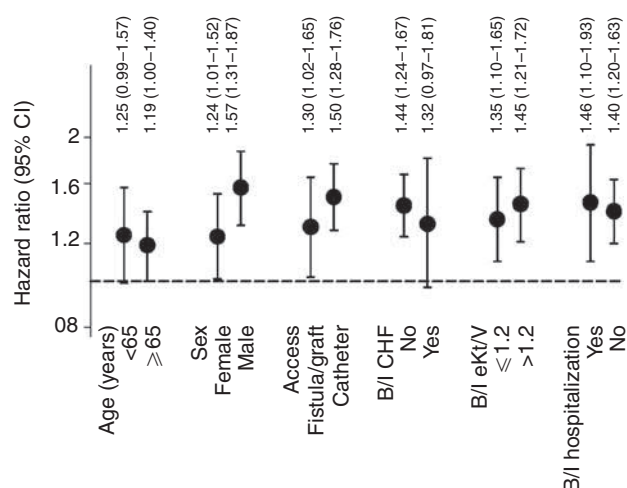


Figure 3 | Adjusted hazard ratios (95% CIs) for all-cause mortality for shorter session length (<240 min) in prespecified subgroups. The referent category was session length ≥ 240 min. Estimates were adjusted through marginal structural analysis in an analogous manner to that used in the primary analysis; stabilized weights were reestimated for each subgroup. Baseline (B/I) eKt/V and congestive heart failure (CHF) refer to those values updated through dialysis day 30; baseline hospitalization refers to any hospitalization occurring between dialysis days 0–30.

model: HR (95% CI) 1.38 (1.21–1.57; $P < 0.001$) (Figure 2). However, unlike with baseline and time-updated models, on multivariable adjustment (through application of stabilized weights), the association between shorter session length and mortality was not attenuated, and remained highly statistically significant: HR (95% CI) 1.42 (1.24–1.62; $P < 0.001$) (Figure 2).

To examine the robustness of this finding, we examined the association between shorter session length and mortality in prespecified subgroups of study patients using marginal structural models analogous to those above. In each model, weights were reestimated in the restricted population using models otherwise analogous to those from the full population. Adjusted estimates of association between shorter session length and mortality were qualitatively similar in all 12 subgroups, and reached conventional levels of statistical significance in 10 of 12 (Figure 3).

To assess for a potential dose response, we fit models in which session length was categorized as ≤ 180 , 181–239, or ≥ 240 min (observed in 12.2, 40.2, and 47.6% of patient-months, respectively). In both the unadjusted (unweighted) and multivariable adjusted (weighted) models, incremental decrements in session length corresponded to incrementally higher risks of mortality; all values were statistically significant relative to the referent group receiving session length ≥ 240 min (Figure 4). In addition, we fit a model in which session length was considered as a continuous variable. On marginal structural adjustment, each 15 min decrement in session length was associated with a hazard ratio (95% CI) for all-cause mortality of 1.12 (1.08–1.16; $P < 0.001$).

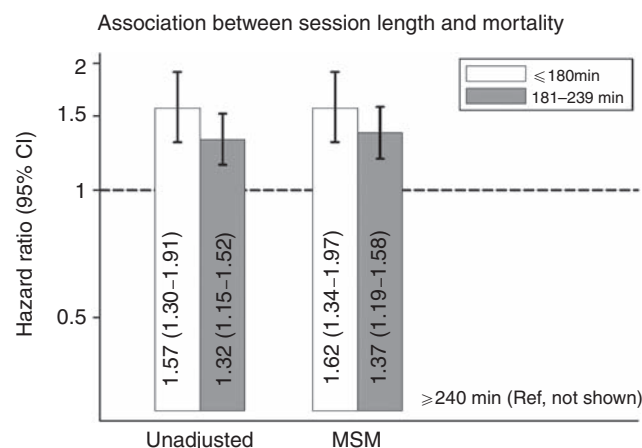


Figure 4 | Association between incremental decrements in session length and all-cause mortality. White bars represent session length ≤ 180 min, gray bars 181–239 min; the referent category was session length ≥ 240 min (hazard ratio = 1 by definition; not shown). Marginal structural analyses were adjusted for age, sex, race (white versus nonwhite), vascular access (fistula, graft, catheter), body mass index (≤ 20 , 20–25, 25–30, > 30 kg/m²), congestive heart failure, eKt/V (≤ 1.0 , 1.0–1.2, 1.2–1.4, 1.4–1.6, > 1.6), systolic blood pressure, serum albumin, and creatinine. MSM, marginal structural model.

DISCUSSION

In this study, we sought to determine whether hemodialysis session length was associated with mortality under a thrice-weekly paradigm. The primary finding was that shorter session length was associated with higher mortality. Our findings differed depending on the analytic strategy adopted; using marginal structural modeling, we were better able to adjust for time-dependent confounding on the basis of eKt/V and markers of nutritional (serum albumin and creatinine), hemodynamic status (blood pressure and CHF), and case-mix. Findings seemed robust on sensitivity analyses in which prespecified subgroups of patients were considered.

Numerous observational studies have examined the relation between hemodialysis session length and mortality, with conflicting results. In a sample of prevalent hemodialysis patients from Australia and New Zealand, Marshall *et al.*⁸ showed that shorter session length (therein defined as < 3.5 h) was associated with significantly higher mortality (HR 1.75; 95% CI 1.27–2.40) compared with a referent group receiving 4–4.4 h treatments. Similarly, in a multinational sample of prevalent hemodialysis patients from the Dialysis Outcomes and Practice Patterns Study (DOPPS), Saran *et al.*⁵ showed that session lengths < 211 and 211–240 min were associated with significantly higher mortality (HR 1.34, $P < 0.001$ and 1.19, $P = 0.01$, respectively) compared with a referent group receiving > 240 -min treatments. In a national sample of prevalent Fresenius Medical Care patients from 2002, Lowrie *et al.*⁷ showed a near linear association between shorter session length and a greater log-hazard for all-cause mortality. Conversely, several studies failed to show a session length and mortality,^{13,14} however these studies were based

on data from the late 1980's and early 1990's—an era when shorter treatment times, non-volumetric ultrafiltration and acetate-based buffers were the norm—and their applicability to contemporary hemodialysis patients remains uncertain.

Our study differed from previous studies in several important ways. First, unlike previous studies, which considered session length at baseline only, our study examined session length as a time-varying exposure, which minimizes the potential for exposure misclassification bias stemming from manipulation of session length, as is commonplace in clinical practice. Second, our study considered a cohort of strictly incident hemodialysis patients, thereby minimizing the potential for survivor bias (that is, depletion of susceptibles), and informing decisions regarding session length at a time when dialysis-associated mortality is highest and consideration of session length most acute. Most importantly, we used marginal structural analysis to appropriately adjust for the influence of time-dependent confounding. Time-dependent confounders are variables that (like typical confounders) are associated with future exposure and outcome, but (unlike typical confounders) are influenced by previous exposure. It has been proven that in the presence of time-dependent confounding, conventional statistical methods yield biased (that is, incorrect) estimates of causal association.^{11,12} To understand this, consider the example of eKt/V . Measured eKt/V in month 2 will influence session length in month 3, and will also be associated with future survival. In this sense, eKt/V functions as a typical *confounder*, and necessitates statistical adjustment lest estimates be biased. However eKt/V in month 2 will be influenced by session length in month 1, and this pathway (session length $\rightarrow eKt/V \rightarrow$ mortality) is one means by which session length might influence mortality. In this sense, eKt/V functions as a causal *pathway intermediate*, and any statistical adjustment for it will lead to biased (toward the null) estimates of the session length–mortality association. Conventional statistical methods cannot selectively adjust for the *confounding* effects of eKt/V without simultaneously (and inappropriately) adjusting for its *pathway-intermediate* effects, thus ensuring that results will be biased. Though presented in the context of eKt/V , these considerations are true for time-dependent confounders in general.

Marginal structural modeling is one statistical technique capable of adjusting for *confounding* by time-dependent confounders without inappropriately adjusting for their *pathway-intermediate* effects;^{11,12} its use in this regard has become increasingly common in the nephrology literature.^{15–18} Under the untestable assumption that all time-dependent confounders are included and appropriately specified in the statistical model (an assumption no different from that implicit in standard multivariable adjustment), marginal structural models render estimates that approximate randomized controlled trials.¹¹ In these analyses, use of standard proportional hazards analyses suggested no association between shorter session length and mortality, which likely resulted from the inappropriate ‘adjusting away’ of the

effects of session length on mortality mediated through improvements in nutritional status, small molecule clearance and hemodynamics. Conversely, on marginal structural analysis, it seemed that shorter session length was potentially associated with higher mortality.

Ultimately, the best strategy to eliminate the influence of time-dependent confounding is through randomization of subjects to fixed treatment protocols. To date, only two large randomized trials of the effect of dialysis dose on patient outcomes have been conducted. The National Cooperative Dialysis Study randomized patients in a 2×2 factorial design to high or low blood urea nitrogen levels and shorter or longer session lengths.¹⁹ Findings suggested a near-significant association between shorter session lengths and increased morbidity ($P=0.056$), but no effect on mortality. However, the National Cooperative Dialysis Study was underpowered to examine mortality as an endpoint, in part due to early termination at the time of interim analysis. The Mortality and Morbidity in Hemodialysis (HEMO) study randomized subjects to high or standard equilibrated Kt/V_{urea} (and high versus low flux dialysis membranes), and found no association between either intervention and mortality.²⁰ It is important to note that subjects in the HEMO study were not randomized to various levels of session length *per se* (rather to levels of Kt/V_{urea} , which can be manipulated through multiple means); thus the study does not constitute a true randomized trial of session length.²¹ As such, conclusions with respect to the influence specifically of session length are subject to some of the same limitations (for example, bias, confounding) as would accompany an observational study.

The precise mechanism through which session length might influence mortality is not clear. It has been shown that longer session lengths result in improved removal of urea, creatinine, phosphorous, and beta-2 microglobulin even when Kt/V_{urea} is held constant.⁶ Therefore, it is possible that some of the true effects of longer session length stem from enhanced solute clearance beyond what is reflected by Kt/V_{urea} . In addition, longer session length enables ultrafiltration to proceed at a slower rate, which may improve blood pressure control and facilitate more consistent attainment of dry weight.^{22,23} These effects may, in turn, attenuate left ventricular hypertrophy, fibrosis, and diastolic dysfunction, all of which are associated with mortality in patients on maintenance dialysis.^{24–27} Some have argued that, given the inherent inter-relatedness of session length and Kt/V , that the association between session length and mortality may stem from inappropriately low Kt/V among patients receiving shorter session lengths.²⁸ Nonetheless, that the association between session length and mortality remained potent and statistically significant among the subgroup of patients with $eKt/V > 1.2$ (Figure 3) is evidence that session length may influence mortality even when eKt/V conforms to the current standard of care.²

Several limitations of this study bear mention. Most notably, our study was designed to measure the association

between session length and mortality within the context of conventional thrice-weekly, incenter hemodialysis. Specifically, we did not include patients receiving short-daily or extended dialysis (incenter/at home, diurnal/nocturnal), and therefore, we cannot determine the associations of session length or changes in session length among patients on more frequent or more intensive hemodialysis schedules. Although our findings support the hypothesis that more dialysis might reduce mortality and/or morbidity, definitive conclusions must await the results of dedicated clinical trials, such as the ongoing Frequent Hemodialysis Network trials.²⁹ Studies such as ours cannot replace clinical trials (which may fall short in power and generalizability) but can and should contribute to the evidence based on which clinical decisions are made in practice.

As with any observational study, our study is subject to the potential influence of residual confounding. To minimize this concern, we adjusted estimates for many factors that may confound the association between session length and mortality such as demographics, anthropometrics, and indices of small molecule clearance, hemodynamics and nutrition. Of note, we lacked data on interdialytic weight gain, which may influence decisions on session length and may also be directly related to mortality and morbidity. However, inasmuch as patients with larger interdialytic weight gains are more likely to have longer session lengths and are more likely to die,^{30–33} any bias would be toward the null and would not explain our findings. In addition, we tracked *prescribed* (not *delivered*) session length. This approach, though necessitated by the available data, is consistent with intention-to-treat principles, and residual confounding on this basis would be expected to bias estimates toward the null assuming either that early termination of dialysis sessions was unrelated to prescribed duration, or (as might be more likely) that patients prescribed longer session lengths were more likely to terminate prematurely. Again, this would not explain the observed association between shorter session length and mortality, and may have rendered our findings conservative. Finally, exclusion of some patients may limit generalizability of findings to certain patient groups, most notably those who have extremely limited survival on dialysis. Nonetheless, given the modest (30 day) survival requirement, and our large and diverse study population, we believe that our results do generalize to the vast majority of chronic dialysis patients for whom consideration of session length is of issue.

In conclusion, when applied to data from this large cohort of incident hemodialysis patients, marginal structural analysis suggests that shorter prescribed hemodialysis session length is potently and independently associated with higher all-cause mortality at 1 year. Differences in findings between marginal structural and proportional hazards analyses may point to the ability of the former to appropriately adjust for time-dependent confounding. Further studies are needed to confirm and extend these findings.

MATERIALS AND METHODS

Study Population

This protocol was deemed exempt by the Partners Health Care Institutional Review Board. We conducted a nonconcurrent cohort study of patients in the ArMORR cohort. Details of the source cohort have been previously published.^{15,34} Briefly, the Accelerated Mortality on Renal Replacement (ArMORR) cohort contains data on 10,044 patients who initiated incenter maintenance hemodialysis at any Fresenius Medical Care Unit in North America (FMC-NA) between June 2004 and August 2005. Of these, we excluded minors (age <18 years), patients who did not survive until the start of at-risk time (dialysis day 31), and those with insufficient covariate data for analysis.

Study Data

All study data were collected prospectively. Demographic and comorbid disease characteristics were recorded as of dialysis initiation. Time-updated data were available for session length (updated with each new order), seated pre-dialysis blood pressure (updated at each treatment), and laboratory data (updated with each measurement, typically at intervals of 2–4 weeks). All serum and urine tests were performed in a centralized laboratory (Spectra Laboratories, Rockleigh, NJ, USA). Equilibrated Kt/V was calculated by formal urea kinetic modeling. Presence of pre-existing CHF was assessed at dialysis initiation, and patients' status were updated (where necessary) at the time of attributed hospitalization (International Classification of Disease-9 codes 276.6, 402.x1, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 425.xx, 428.xx); all hospitalization data were rigorously collected and reconciled by dialysis unit personnel as previously described.¹⁵

Statistical Analysis

All analyses were conducted using STATA 10.0MP (College Station, TX, USA). Continuous variables were examined graphically, described in terms of their means and standard deviations or medians and inter-quartile ranges, and compared across groups using Student's t -test or the Wilcoxon rank-sum test as appropriate. Categorical variables were described by frequency distribution and compared across groups using contingency tables and χ^2 testing.

Unadjusted associations between predictors and outcome were explored using Kaplan Meier methods, log rank testing, and unadjusted proportional hazards models. Adjusted associations between predictors and outcome were estimated by fitting multivariable proportional hazards models. Covariates were selected on the basis of biological plausibility and clinical precedent; all were forced into multivariable models. For continuous covariates the linearity assumption was tested graphically (by Martingale residuals) and by comparison of model fit (by Akaike's Information Criterion) between non-nested models in which the covariate was specified as a linear and categorical term. Those variables demonstrating gross violation of the linearity assumption were entered as categorical terms in the final multivariable models. The overall covariate vector in the primary analysis consisted of the following: age, sex, race (white, nonwhite), vascular access (fistula, graft, catheter), body mass index (≤ 20 , 20–25, 25–30, > 30 kg/m²), CHF, eKt/V (≤ 1.0 , 1.0–1.2, 1.2–1.4, 1.4–1.6, > 1.6), systolic blood pressure, serum albumin, and creatinine. Results of all analyses were nearly identical when body mass index and eKt/V were specified as linear terms, when diastolic blood pressure was substituted for systolic (strong collinearity precluded inclusion of both simultaneously; $r = 0.72$), and when height and weight were substituted for body mass index (data not shown).

We estimated the parameters of a marginal structural proportional hazards model using a pooled logistic regression model as previously described.^{11,12} In these analyses, each patient's experience was decomposed into individual patient-months. For each patient-month, the probability of survival was estimated as a function of the patient's session length measured at month's start, and the month of dialysis (to allow for differential baseline probability of survival according to time on dialysis); robust variance estimates were used to account for nonindependence of observations within patient.

Marginal structural models were adjusted by application of stabilized weights based on the probability that a patient had his/her observed session length and on the probability of censoring.^{11,12} Stabilized probability of exposure weights were defined as the ratio of two terms: the numerator the probability that each subject had his/her observed session length based on previous session length and baseline covariates; the denominator the probability that each subject has his/her observed session length based on previous session length, and covariates considered both at baseline and as of the previous month. In the primary marginal structural analyses, each was estimated using a separate pooled logistic regression model in which session length was categorized as <240 or ≥240 min. Secondary analyses considered session length as ≤180, 181–239 or ≥240 min; multinomial logistic regression models were used to estimate the probability of exposure. Stabilized probability of censoring weights was estimated in a completely analogous manner except that no term was included for the previous month's session length. Fuller detail regarding specification of marginal structural models is given in online supplemental materials.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/ki>

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Original Article

Independent effect of haemodialysis session frequency and duration on survival in non-indigenous Australians on haemodialysis

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KEY WORDS:

Australian and New Zealand Data Registry, end-stage kidney disease, haemodialysis, dialysis prescription, renal replacement therapy.

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ABSTRACT:

Background: End-stage kidney disease patients have increased mortality compared to the general population. Haemodialysis (HD) of more frequent and of longer duration has been proposed to improve survival but it remains unclear if this is attributed to increased frequency, duration, or both. We aimed to examine the independent effects of session frequency and duration on mortality in incident HD patients.

Methods: A retrospective cohort study was performed using data from the Australian and New Zealand Dialysis and Transplant Registry examining non-Indigenous patients aged ≥ 18 years who initiated HD of ≥ 3 sessions/week in Australia from 2001 to 2015. Initial dialysis prescription was categorized as session duration >5 h/session compared to ≤ 5 h/session and session frequency as >3 sessions/week compared to 3 sessions/week. Survival analysis was performed using Cox regression analysis, with multi-variable analysis controlling for available covariates.

Results: We examined 16 944 patients of whom 757 (4.5%) received >3 sessions/week and 518 (3.1%) received >5 h/session. After controlling for frequency, patients initiated on HD sessions >5 h had a significantly reduced risk of mortality compared with patients with HD session ≤ 5 h (adjusted hazard ratio (HR) = 0.57; 95% confidence interval (CI) = 0.44–0.74). In contrast, patients initiated on >3 sessions/week of HD had a similar risk of death when compared with patients on 3 sessions/week of HD (adjusted HR = 0.97; 95% CI = 0.84–1.13), after controlling for duration. Limitations include potential residual confounding and changes in exposure over time.

Conclusion: Longer duration rather than increased frequency of treatment appears to reduce mortality in HD patients. This has implications for management and requires further study.

SUMMARY AT A GLANCE

This Australian and New Zealand Dialysis and Transplant Registry study assessed the interaction between haemodialysis sessions duration and frequency and their outcome on mortality. Of 16 944 patients, 757 received >3 sessions/week and 518 received >5 h/session. Patients initiated on HD with sessions >5 h had lower mortality than patients with HD session = 5 h (adjusted hazard ratio = 0.57; 95% confidence interval = 0.44–0.74). There was no statistically significant association between session frequency and mortality.

End-stage kidney disease (ESKD) is a significant and growing problem globally, with an estimated 2.6 million people worldwide treated in 2010.¹ Haemodialysis (HD) is the most common renal replacement therapy (RRT) for patients with ESKD both worldwide and in Australia.² The most common prescription of HD is 3–5 h, 3 times/week, referred to as conventional dialysis.¹ This prescription arose as a result of a pragmatic set of economic, technical, patient, provider and

political factors in the 1970s when US government legislation provided the framework to provide life-sustaining HD to patients through subsidy. This encouraged providers to develop more efficient dialysis machines and practices to keep up with demand and to be cost-effective. Coupled with observational data that thrice weekly dialysis of increasingly shorter durations was at least adequate, this prescription became mainstay of treatment.³ Despite improvements in

mortality rates in both the general and ESKD populations, mortality rates remain high among dialysis patients in Australia compared to the general population.⁴

Consequently, discussion as to whether the conventional HD prescription may be associated with sub-optimal survival when compared with alternative prescriptions in the ESKD population have occurred. Intensive HD prescriptions of more frequent and longer duration have been investigated. Multiple observational studies,^{5–8} as well as the Frequent Haemodialysis Network (FHN) randomized clinical trials^{9,10} report on survival in patients receiving various frequent HD prescriptions, including short daily and nocturnal regimens. However, comparison across studies is hindered by varying definitions for ‘frequent’ or ‘intensive’, and ‘extended duration’ HD. The FHN short daily trial¹⁰ reported a benefit of frequent (6 sessions/week) over conventional (3 sessions/week) based on their composite outcome over 12 months. Benefit was found to persist in the extended follow-up report.¹¹ Interestingly no such benefit was found in the nocturnal study which compared extended duration sessions up to 6 times/week to conventional HD.⁹ However, this study was significantly underpowered limiting the reliability of the results. Furthermore, the extended follow-up found a survival disadvantage for the nocturnal group.¹²

Observational studies have consistently shown improved outcomes in patients receiving longer session durations compared with shorter durations in patients receiving 3 sessions/week.^{13–19} Consequently, it is unclear whether the improved survival observed in frequent or intensive HD patients may be attributed to increased frequency, increased duration, or both.

This analysis of Australian registry data aimed to assess the independent effects of session frequency and session duration in incident ESKD patients receiving HD on mortality.

METHODS

Study design and data source

We performed a retrospective cohort study of incident Australian ESKD patients initiated on HD as their initial RRT over a 15-year period from 2001 to 2015. Data was extracted from the Australia and New Zealand dialysis and transplant registry (ANZDATA), which collects information annually on all patients receiving maintenance RRT throughout Australia and New Zealand.

Participants

The cohort was defined as all non-Indigenous adults (aged over 18 years old at the time of RRT commencement) commencing HD as their first RRT for ESKD in Australia from 1 January 2001 to 31 December 2015. Patients contributed to the cohort from the date of HD commencement until the

date of death, transplant, change of dialysis modality or recovery of native kidney function, or the end of the study duration, whichever came first. Exclusion criteria included prevalent cases as of 1 January 2001, patients receiving less than three sessions of dialysis per week, Indigenous identity and those who received less than 90 days of HD. In line with similar studies, patients with missing data on any of the primary variables or co-variables were removed prior to analysis.^{13,20}

Primary exposure and outcome variables

The primary exposure variables were dialysis frequency and session duration taken as first recorded. ANZDATA collect data annually through cross-sectional surveys conducted on the 31st December each year, including, for dialysis patients, data on the type of dialysis, prescription and comorbidities. Session frequency was grouped into conventional frequency HD (3 sessions/week) and compared to frequent HD (>3 sessions/week). This definition was based on the current standard practice of conventional HD in Australia.²

Session duration (in hours/session) was categorized as conventional duration (≤ 5 h/session) and extended duration (> 5 h/session). This definition was created to compare what is considered the conventional standard practice in Australia of ≤ 5 h with session durations that are longer.² A further exposure variable of total weekly hours per week derived from the weekly frequency and session duration was also examined.

The primary outcome measures were time to death and all-cause mortality. The number of deaths in each of the two groups for session duration and session frequency was determined and proportions calculated as percentage.

Data measurement and covariates

Data collected by ANZDATA were included for baseline characteristics and multivariable-adjusted models. These included: sex, ethnicity (non-Caucasian and Caucasian), age at commencement of treatment, body mass index (BMI; derived from recorded height and weight), smoking status (current/former and never), primary renal disease (glomerulonephropathies, renovascular, diabetes, polycystic, analgesic, reflux and other/uncertain, as grouped by ANZDATA classification), presence of medical comorbidities (chronic lung disease, ischemic heart disease, peripheral vascular disease, cerebral vascular disease, diabetes and cancer), late referral (< 90 days before initiation of HD) and first vascular access. First vascular access data was missing for a large proportion of patients and therefore this group was included as a separate category. Comorbidities were mutually exclusive and taken as first recorded.

Continuous variables including age and BMI were also categorized. Age was grouped into patients aged ≥ 18 and ≤ 40 years, > 40 and ≤ 65 years, and > 65 years for

purposes of baseline characteristics. BMI was categorized as ≤ 20 kg/m², >20 and ≤ 25 kg/m², >25 and ≤ 30 kg/m² and >30 kg/m².

Statistical analyses

Baseline characteristics were examined according to session frequency and duration. Frequency and percentages were calculated and presented for categorical variables. Mean and standard deviation (SD) were calculated for normally distributed continuous variables and median and interquartile ranges were provided for non-normally distributed continuous variables.²¹ χ^2 tests were performed for categorical variables and Student's *t*-tests, or one-sided analysis of variance tests were performed for continuous variables depending on the number of comparators, to test for differences in characteristics between the primary exposure subgroups. Significance was set at $P < 0.05$ and 95% confidence intervals (CI) were provided where appropriate.

All-cause mortality (deaths/100 person-years) was derived by dividing the total number of deaths during the follow-up period by the combined follow-up time of the cohort, for the whole cohort and by primary exposure variables. Univariate Cox analysis was performed for the effect of session frequency and duration, as well each covariate, on survival.

Multivariable Cox regression analysis was then used to identify independent factors associated with patient survival. All clinically appropriate available demographic and treatment variables, as well as patient comorbidities were considered in the Cox regression analysis. Variables shown to be associated with survival based on univariate analysis were initially included in the regression model. A backwards selection procedure was implemented to determine the final regression model that included the review of nested models and analysis of likelihood ratio tests, and residual plots. This approach was based on clinical and research evidence and discussion with experts in the field, and used in similar studies using ANZDATA.⁸ The final regression model included an interaction term between session frequency and session length.

Analysis was completed using R (v. 3.4.0).²²

Ethics

ANZDATA is based at the South Australian Health and Medical Research Institute and the activities of the registry have been granted full ethics approval by the Royal Adelaide Hospital Human Research Ethics Committee (reference number: HREC/17/RAH/408 R20170927, approval date: 28/11/2017). Permission to analyse the data was granted by ANZDATA Executive. The need for informed consent was waived because all data were deidentified and authors did not have access to patient-identifying information as part of this analysis.

RESULTS

Participants

A total of 28 247 patients initiated HD between 1 January 2001 to 31 December 2015. After removing patients based on inclusion and exclusion criteria, a final cohort of 16 944 patients was available for analysis with a total follow-up time of 54478.2 person-years. Mean follow-up time was 3.2 person-years. Median survival on HD for the cohort was 4.6 years (95% CI = 4.50–4.72).

Baseline characteristics

Table 1 displays the baseline characteristics for the cohort. Nearly all patients were initiated on 3 sessions/week (95.5%) and on ≤ 5 h/session (96.9%). There was significant overlap between frequency and duration with 94.0% of patients commenced on 3 sessions/week of ≤ 5 h/session.

Baseline characteristics for respective cohorts based on frequency and duration of HD are displayed in Table 1. In general, patients commenced on frequent, or longer duration dialysis were younger, more likely to be male, have a higher BMI and to have fewer comorbidities compared with their respective conventional subgroup.

Almost all (99.5%) patients received their initial HD treatment prescription in-centre. Patients receiving frequent (3.6%) or extended duration (2.1%) HD were proportionally more likely to receive their treatment in the home compared with the conventional groups, but these numbers were small.

Mortality

There were 8488 deaths over the follow-up period, with an all-cause mortality rate of 15.6 deaths/100 person-years. Table 2 shows the mortality rate and median survival for the cohort and respective subgroups. Compared with the conventional group, patients receiving >3 sessions/week had lower mortality while receiving HD (8.77 deaths/100-person-years vs 15.89 deaths/100-person-years, $P < 0.001$) and their median survival on HD was 2.5 years longer (7.0 years vs 4.5 years, $P < 0.001$). Figures 1 and 2 show unadjusted Kaplan–Meier survival curves with corresponding *P* values and 95% CI.

Similarly, patients commenced on >5 h/session had lower mortality (5.08 deaths/100-person-years vs 15.95 deaths/100-person-years, $P < 0.001$) and had a median survival 6.0 years longer than their respective conventional group (10.5 years vs 4.5 years, $P < 0.001$).

Survival analysis

Patients initiated on >3 sessions/week had an unadjusted 44% reduced mortality risk compared with 3 sessions/week

Table 1 Summary statistics for the cohort, by session frequency and by session duration

Characteristic	Total <i>n</i> = 16 944	3 sessions/week <i>n</i> = 16 187	>3 sessions/week <i>n</i> = 757	<i>P</i>	≤5 h/session <i>n</i> = 16 426	>5 h/session <i>n</i> = 518	<i>P</i>
Male, <i>n</i> (Pct.)	10 989 (64.9)	10 426 (64.4)	563 (74.4)	<0.001	10 564 (64.3)	425 (82.0)	<0.001
Ethnicity: Caucasian, <i>n</i> (Pct.)	14 889 (87.9)	14 208 (87.8)	681 (90.0)	0.081	14 454 (88.0)	435 (84.0)	0.007
Age, mean (SD)	62.73 (14.88)	63.16 (14.75)	53.53 (14.71)	<0.001	63.10 (14.79)	50.83 (12.83)	<0.001
Age, <i>n</i> (Pct.)							
≤18 and ≤ 40 years	1420 (8.4)	1289 (8.0)	131 (17.3)		1329 (8.1)	91 (17.6)	
>40 and ≤ 65 years	7191 (42.4)	6724 (41.5)	467 (61.7)		6832 (41.6)	359 (69.3)	
>65 years	8333 (49.2)	8174 (50.5)	159 (21.0)	<0.001	8265 (50.3)	68 (13.1)	<0.001
BMI kg/m ² , mean (SD)	28.50 (7.04)	28.43 (7.02)	30.04 (7.39)	<0.001	28.39 (6.97)	31.94 (8.26)	<0.001
BMI, <i>n</i> (Pct.)							
≤20 kg/m ²	1143 (6.7)	1107 (6.8)	36 (4.8)		1131 (6.9)	12 (2.3)	
>20 and ≤ 25 kg/m ²	4647 (27.4)	4482 (27.7)	165 (21.8)		4553 (27.7)	94 (18.1)	
>25 and ≤ 30 kg/m ²	5403 (31.9)	5171 (31.9)	232 (30.6)		5257 (32.0)	146 (28.2)	
>30 kg/m ²	5751 (33.9)	5427 (33.5)	324 (42.8)	<0.001	5485 (33.4)	266 (51.4)	<0.001
Smoking history (current/former), <i>n</i> (Pct.)	9357 (55.2)	8970 (55.4)	387 (51.1)	0.022	9083 (55.3)	274 (52.9)	0.300
Primary disease, <i>n</i> (Pct.)							
Glomerulonephropathies	3827 (22.6)	3601 (22.2)	226 (29.9)		3660 (22.3)	167 (32.2)	
Analgesic	382 (2.3)	373 (2.3)	9 (1.2)		381 (2.3)	1 (0.2)	
Hypertension or renovascular	2674 (15.8)	2581 (15.9)	93 (12.3)		2620 (16.0)	54 (10.4)	
Polycystic	1187 (7.0)	1065 (6.6)	122 (16.1)		1106 (6.7)	81 (15.6)	
Diabetes	5258 (31.0)	5092 (31.5)	166 (21.9)		5126 (31.2)	132 (25.5)	
Reflux	419 (2.5)	382 (2.4)	37 (4.9)		399 (2.4)	20 (3.9)	
Uncertain	995 (5.9)	962 (5.9)	33 (4.4)		979 (6.0)	16 (3.1)	
Other	2202 (13.0)	2131 (13.2)	71 (9.4)	<0.001	2155 (13.1)	47 (9.1)	<0.001
Comorbidities, <i>n</i> (Pct.)							
Chronic lung disease	2891 (17.1)	2808 (17.3)	83 (11.0)	<0.001	2836 (17.3)	55 (10.6)	<0.001
Ischemic heart disease	7299 (43.1)	7088 (43.8)	211 (27.9)	<0.001	7171 (43.7)	128 (24.7)	<0.001
Peripheral vascular disease	4556 (26.9)	4424 (27.3)	132 (17.4)	<0.001	4477 (27.3)	79 (15.3)	<0.001
Cerebral vascular disease	2652 (15.7)	2597 (16.0)	55 (7.3)	<0.001	2617 (15.9)	35 (6.8)	<0.001
Diabetes	7298 (43.1)	7057 (43.6)	241 (31.8)	<0.001	7114 (43.3)	184 (35.5)	<0.001
Ever diagnosed cancer	4747 (28.0)	4570 (28.2)	177 (23.4)	0.004	4636 (28.2)	111 (21.4)	0.001
Late referral, <i>n</i> (Pct.)	4037 (23.8)	3933 (24.3)	104 (13.7)	<0.001	3972 (24.2)	65 (12.5)	<0.001
First access, <i>n</i> (Pct.)							
Native	6395 (37.7)	5911 (36.5)	484 (63.9)		6062 (36.9)	333 (64.3)	
Non-tunnel CV catheter	2261 (13.3)	2207 (13.6)	54 (7.1)		2215 (13.5)	46 (8.9)	
Tunnel CV catheter	5388 (31.8)	5250 (32.4)	138 (18.2)		5309 (32.3)	79 (15.3)	
Synthetic	360 (2.1)	344 (2.1)	16 (2.1)		342 (2.1)	18 (3.5)	
Missing	2540 (15.0)	2475 (15.3)	65 (8.6)	<0.001	2498 (15.2)	42 (8.1)	<0.001
Hours/session, median (IQR)	4 (4–5)	4 (4–5)	5 (4–6)		4 (4–5)	6 (6–8)	
Sessions/week, median (IQR)	3 (3–3)	3 (3–3)	4 (3.5–4)		3 (3–3)	3 (3–3.5)	
Location, <i>n</i> (Pct.)							
In-centre, <i>n</i> (Pct.)	16 851 (99.5)	16 121 (99.6)	730 (96.4)		16 344 (99.5)	507 (97.9)	
Home, <i>n</i> (Pct.)	93 (0.5)	66 (0.4)	27 (3.6)	<0.001	82 (0.5)	11 (2.1)	<0.001

BMI, body mass index, CV, central venous, IQR, interquartile range; *n*, number of patients; Pct., percent; SD, standard deviation.

(HR = 0.56, 95% CI = 0.48–0.64) irrespective of session duration. Extended duration (>5 h/session) was associated with an unadjusted survival benefit of 68% (HR = 0.32, 95% CI = 0.26–0.39) irrespective of session frequency. Older age, low BMI (≤20 kg/m²), smoking, late referral, medical comorbidities and non-native first vascular access were all associated with increased risk of mortality in univariate Cox regression analysis. In contrast, BMI categories >25–≤30 and > 30 kg/m² as well as non-Caucasian background were associated with reduced mortality. Gender was not a significant predictor of survival in univariate analysis. Unadjusted and adjusted regression model results are shown in Table 3.

The effect of extended duration of dialysis (>5 h/session) was qualified with an interaction with session frequency, with a 43% reduction in the hazard of death after adjustment (HR = 0.57, 95% CI = 0.44–0.74). However, after adjustment, more than 3 sessions/week was no longer associated with improved survival (HR = 0.97, 95% CI = 0.84–1.13), with the effect of session frequency dependent on the patient's session duration. Figures 3 and 4 show adjusted survival curves based on these models. In this multivariable model, age, ethnicity, smoking history, primary disease, vascular access, low BMI, late referral and presence of comorbidities

Table 2 Summary of cause of death and survival of the cohort, by session frequency and by session duration

Characteristic	Total <i>n</i> = 16 944	3 sessions/week <i>n</i> = 16 187	>3 sessions/week <i>n</i> = 757	<i>P</i>	≤5 h/session <i>n</i> = 16 426	>5 h/session <i>n</i> = 518	<i>P</i>
Deaths, <i>n</i> (Pct)	8488 (50.1)	8282 (51.2)	206 (27.2)	<0.001	8395 (51.1)	93 (18.0)	<0.001
Transplanted, <i>n</i> (Pct)	3435 (20.3)	3119 (19.3)	316 (41.7)	<0.001	3199 (19.5)	236 (45.6)	<0.001
Changed to PD, <i>n</i> (Pct)	1402 (8.3)	1370 (8.5)	32 (4.2)	<0.001	1390 (8.5)	12 (2.3)	<0.001
Recovery, <i>n</i> (Pct)	264 (1.6)	259 (1.6)	5 (0.7)	0.059	262 (1.6)	2 (0.4)	0.045
Cause of death, <i>n</i> (Pct)							
Cardiac	2662 (31.4)	2588 (31.2)	74 (35.9)		2617 (31.2)	45 (48.4)	
Vascular	669 (7.9)	656 (7.9)	13 (6.3)		663 (7.9)	6 (6.5)	
Infection	769 (9.1)	758 (9.2)	11 (5.3)		761 (9.1)	8 (8.6)	
Social/withdrawal	3205 (37.8)	3130 (37.8)	75 (36.4)		3185 (37.9)	20 (21.5)	
Malignancy	589 (6.9)	577 (7.0)	12 (5.8)		581 (6.9)	8 (8.6)	
Other	595 (7.0)	573 (6.9)	21 (10.2)	<0.001	588 (7.0)	6 (6.5)	<0.001
Mortality, deaths/100 person-years	15.58	15.89	8.77	<0.001	15.95	5.08	<0.001
Median survival, years (CI)	4.62 (4.50–4.72)	4.53 (4.42–4.65)	7.00 (6.47–8.73)		4.5 (1.40–4.63)	10.5 (7.82 - infinite)	

CI, confidence interval, *n*, number of patients; PD, peritoneal dialysis; Pct., percent..

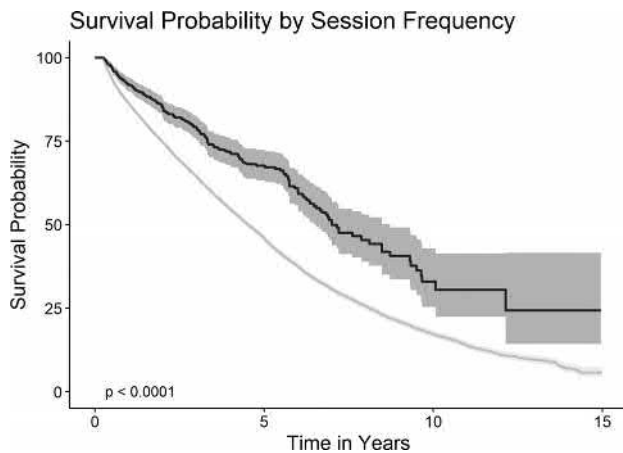


Fig. 1 Un-adjusted survival curve for session frequency, including *P* value derived from log-rank tests, and 95% confidence interval. Sessions/week (—) three sessions, (---) more than three sessions.

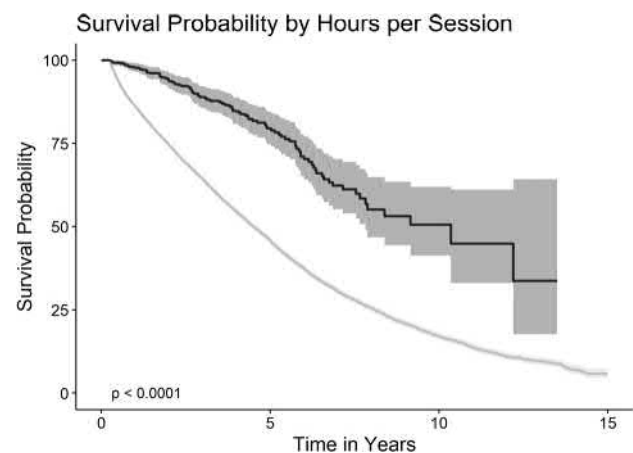


Fig. 2 Un-adjusted survival curve for session duration, including *P* value derived from log-rank tests, and 95% confidence interval. Hours/session (—) five or less hours, (---) more than five sessions.

(excluding cancer) all continued to be significantly associated with increased risk of death.

With respect to interaction between session frequency and duration, the use of the interaction term of session length * session frequency significantly fit the data better than without. Therefore, the interaction term was included, even though the interaction term was itself statistically non-significant.²³

Finally, there appeared to be a dose response relationship with total weekly hours on survival. Compared to patients receiving <15 h/week, 15–20 h was associated with an 18% reduced risk of death, and 20 or more hours associated with a 29% lower risk of death (Table 4).

DISCUSSION

This study has found that non-Indigenous incident HD patients in Australia commenced on more than 5 h of HD

per session had a 43% reduced mortality when compared with patients on conventional duration HD of up to 5 h/session independent of session frequency. However, increased frequency of HD beyond 3 sessions/week had similar survival compared with 3 sessions/week, independent of session duration. Furthermore, increasing total weekly hours was also associated with reduced mortality, with >20 h/week being associated with 29% reduced mortality. It is unlikely that patients could achieve 20 or more hours of HD by increasing frequency alone (at a minimum this would require 6 session of at least 3.5 h or daily dialysis of nearly 3 h), therefore, this finding further supports the benefit of increased session duration on mortality.

These findings suggest that more frequent HD prescriptions do not translate into a survival benefit independent of session duration. Rather it is the increased session duration that may provide a survival benefit. Previous studies have shown improved survival with longer session durations only

Table 3 Univariable and adjusted hazard ratios on survival

Variable	Univariate analysis Hazard ratio (95% CI)	Adjusted model Hazard ratio (95% CI)	P value
Session frequency			
3 sessions/week	Reference	Reference	
>3 sessions/week	0.56 (0.48–0.64)	0.97 (0.84–1.13)	0.78
Hours per session			
≤5 h/session	Reference	Reference	
>5 h/session	0.32 (0.26–0.39)	0.57 (0.44–0.74)	0.0001
Gender			
Women	Reference	Reference	
Men	0.99 (0.95–1.04)	0.96 (0.91–1.01)	0.09
Age (years, continuous)	1.03 (1.03–1.03) 4)	1.02 (1.02–1.02)	<0.001
BMI			
≤20 kg/m ²	1.17 (1.08–1.28)	1.22 (1.12–1.33)	<0.001
>20 and ≤ 25 kg/m ²	Reference	Reference	
>25 and ≤ 30 kg/m ²	0.90 (0.85–0.95)	0.89 (0.84–0.94)	<0.001
>30 kg/m ²	0.74 (0.69–0.78)	0.78 (0.74–0.83)	<0.001
Smoking history yes (current/former)			
Never smoked	Reference	Reference	
Ever smoked	1.20 (1.15–1.25)	1.06 (1.01–1.11)	0.01
Primary disease categories			
Glomerulonephropathies	Reference	Reference	
Analgesic	1.64 (1.44–1.87)	1.07 (0.93–1.22)	0.35
Hypertension or renovascular	1.86 (1.74–2.00)	1.24 (1.15–1.33)	<0.001
Polycystic	0.69 (0.61–0.78)	0.81 (0.72–0.92)	0.001
Diabetes	1.55 (1.45–1.65)	1.23 (1.13–1.33)	<0.001
Reflux	0.64 (0.52–0.77)	0.81 (0.67–0.99)	0.041
Other/Uncertain	1.79 (1.67–1.92)	1.46 (1.36–1.56)	<0.001
Late referral			
No	Reference	Reference	
Yes	1.33 (1.27–1.40)	1.10 (1.04–1.16)	<0.001
Ethnicity			
Caucasian	Reference	Reference	
Non-Caucasian	0.57 (0.53–0.62)	0.62 (0.57–0.68)	<0.001
Comorbidities (present vs absent)			
Chronic lung disease	1.62 (1.54–1.70)	1.25 (1.18–1.32)	<0.001
Ischemic heart disease	1.79 (1.71–1.87)	1.25 (1.19–1.31)	<0.001
Peripheral vascular disease	1.65 (1.58–1.72)	1.19 (1.13–1.25)	<0.001
Cerebral vascular disease	1.65 (1.57–1.74)	1.16 (1.10–1.23)	<0.001
Diabetes	1.27 (1.21–1.32)	1.22 (1.14–1.30)	<0.001
Cancer	1.20 (1.14–1.25)	1.04 (1.00–1.09)	0.08
First access			
Native	Reference	Reference	
Non-tunnel CV Catheter	1.83 (1.71–1.96)	1.58 (1.47–1.70)	<0.001
Tunnel CV catheter	1.69 (1.60–1.79)	1.47 (1.39–1.56)	<0.001
Synthetic	1.12 (0.96–1.31)	1.06 (0.91–1.24)	0.46
Missing	1.55 (1.46–1.65)	1.54 (1.45–1.64)	<0.001

BMI, body mass index; CI, confidence interval.

in patients receiving conventional 3 sessions/week.^{13–19,24} Whereas studies on the effect of increased session frequency, including the FHN trials, have compared frequent regimens that have varying session durations, including short duration, longer nocturnal sessions and more broadly intensive regimens that are some combination of more frequent or longer duration.^{5–10,25–28} This study separates the independent effects of increased session frequency and

session durations to determine whether it is session frequency, session duration or both that is associated with improved survival in patients receiving more intensive HD regimens.

Previous analysis of ANZDATA cohorts have suggested that it is the location of dialysis (home vs in-centre) that has been the main mediator of improved survival.²⁷ However, more recent analysis of a more current cohort did not find

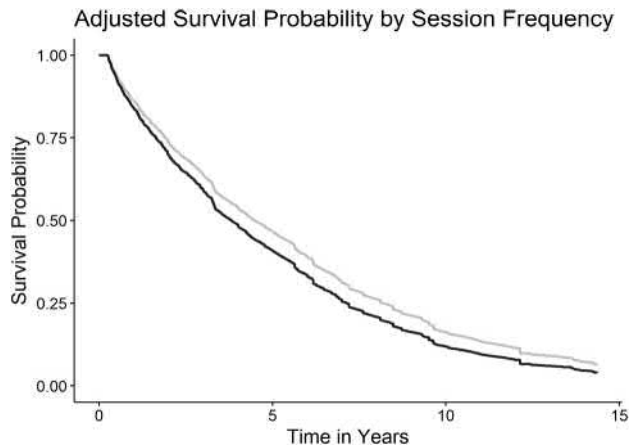


Fig. 3 Adjusted survival curve for session frequency based on multivariable survival analysis model. Sessions/week (—) three sessions, (---) more than three sessions.

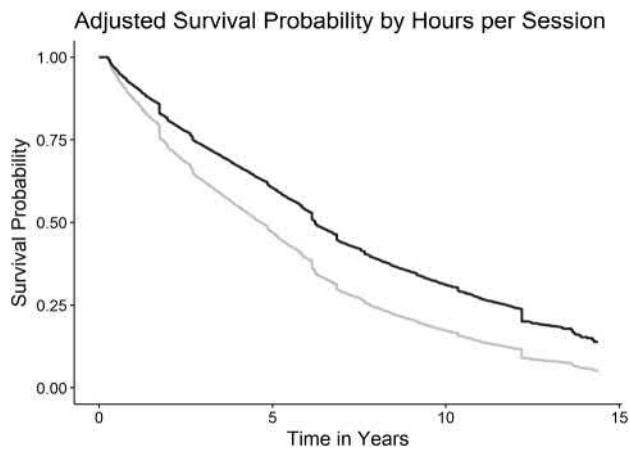


Fig. 4 Adjusted survival curve for session duration based on multivariable survival analysis model. Hours/session (—) five or less hours, (---) more than five sessions.

location to be as strong a contributor when compared to intensity.⁸ Our cohort included only a small number of patients receiving HD at home at the time that initial prescription was recorded, and hence, we cannot comment on the effect of HD location on survival. The findings of improved survival with increasing total weekly hours, however, appears to be consistent with the dose relationship of dialysis in these studies. The secondary analysis of the ACTIVE trial which is examining survival according to total weekly hours are awaited.²⁹ Most of the participants who comprise the extended hours group are receiving longer session durations 3 times/week.³⁰ The primary analysis in the ACTIVE trial examining the effect of increased total weekly hours on quality of life, found no significant difference between the two groups after 12 months.³⁰

Haemodialysis adequacy has conventionally been measured by urea clearance (Kt/V), which is a measure of small

Table 4 Results of multivariable survival analysis for total hours per week

Variable	Adjusted hazard ratio (95% CI)	P value
Total weekly hours		
<15 h/week	Reference	
≥15–<20 h/week	0.82 (0.78–0.87)	<0.001
≥20 h/week	0.71 (0.57–0.89)	<0.002
Gender		
Women	Reference	
Men	0.97 (0.92–1.02)	0.20
Age (years, continuous)	1.02 (1.02–1.02)	<0.001
BMI categories		
≤20 kg/m ²	1.21 (1.11–1.32)	<0.001
>20 and ≤ 25 kg/m ²	Reference	
>25 and ≤ 30 kg/m ²	0.89 (0.84–0.94)	<0.001
>30 kg/m ²	0.8 (0.75–0.84)	<0.001
Smoking history		
Never smoked	Reference	
Ever smoked	1.07 (1.02–1.12)	0.004
Primary disease categories		
Glomerulonephropathies	Reference	
Analgesic	1.07 (0.93–1.22)	0.341
Hypertension or renovascular	1.23 (1.14–1.33)	<0.001
Polycystic	0.82 (0.72–0.93)	0.002
Diabetes	1.22 (1.13–1.33)	<0.001
Reflux	0.81 (0.67–0.99)	0.04
Other/uncertain	1.26 (1.15–1.39)	<0.001
Late referral		
No	Reference	
Yes	1.10 (1.05–1.16)	<0.001
Ethnicity		
Caucasian	Reference	
Non-Caucasian	0.63 (0.58–0.69)	<0.001
Comorbidities (present vs absent)		
Chronic lung disease	1.24 (1.18–1.31)	<0.001
Ischaemic heart disease	1.25 (1.20–1.32)	<0.001
Peripheral vascular disease	1.20 (1.14–1.26)	<0.001
Cerebral vascular disease	1.17 (1.10–1.23)	<0.001
Diabetes	1.22 (1.15–1.31)	<0.001
Cancer	1.04 (0.99–1.09)	0.132
First access		
Native	Reference	
Non tunnel CV catheter	1.59 (1.45–1.71)	<0.001
Tunnel CV catheter	1.47 (1.39–1.56)	<0.001
Synthetic	1.07 (0.92–1.25)	0.362
Missing	1.54 (1.45–1.64)	<0.001

BMI, body mass index; CI, confidence Interval.

molecule clearance and has little to no emphasis on session duration.³¹ The National Cooperative Dialysis Study³² is often cited as being the origin of this approach. The authors found a higher ratio of observed to expected hospitalizations in the short session groups receiving both high and low urea clearance compared with the respective long session groups however, they rejected a significant effect of time on morbidity based on the *P* value being 0.06, above their 0.05 cut-off. Instead, favouring the effect of urea clearance which was significant (*P* < 0.0001). Focus on small molecule

clearance has since resulted, at the expense of session duration. To compensate for shorter session duration and achieve adequate urea clearance as measured by the Kt/V, high ultrafiltration requiring increased blood flows have been used. Despite achieving adequate biochemical targets, higher mortality rates have been reported with this approach, and dialysis length has since been increasing.¹ This phenomenon suggests that the Kt/V measure and merely targeting urea clearance has been at the expense of other important, un-measured, effects of longer session durations that affect survival. Potential mechanisms may include the removal of larger toxic molecules that are not removed with short durations, slower ultra-filtration, better fluid balance and reduced inter-dialytic weight gain which result in less hypotensive episodes and reduced post-dialysis recovery time, with overall improved patient tolerance.³¹

Our study did not control for HD dose (Kt/V) and therefore cannot examine whether session duration improved survival independent of dose. However, previous studies, including those carried out on Australian patients, have shown that increased session duration improved survival independent of HD dose, and that HD dose and session length act independently as well as synergistically to affect survival.^{13,14} Results from these studies, and supported by the finding in our study, suggest that longer session durations improve survival by exerting effects other than simply achieving adequate small molecule clearance.

This retrospective study can only conclude associations, not causation. Common limitations inherent in cohort studies using registry data include the accuracy of data collection and limits on which variables have data collected. This national cohort using ANZDATA has a high degree of external validity, but the possibility of residual confounding remains. Measures including physical and cognitive function, severity of comorbid disease, the degree of independence and social supports are not readily captured in the ANZDATA survey. Alternative statistical methods including inverse probability and competing risks could have been used, we acknowledge that patients on frequent or extended HD prescriptions are likely healthier based on the findings in Table 2, however, further analyses accounting for this would be limited based on the available data.

Patients receiving fewer than 3 sessions/week were excluded as this group are likely to be different to patients on 3 sessions/week and may confound the results. Indigenous patients were excluded since this patient population has a significantly different disease and treatment profile compared to the non-Indigenous population and experience persistently poorer outcomes that would not be able to be fully adjusted for in this analysis using available covariate data.³³ Separate analysis for the optimal HD prescription in this population would be warranted. Patients receiving <90 days of treatment were removed to avoid bias by attributing the outcome of mortality to the treatment in this early period. Future studies examining the optimum number of

sessions per week or hours per session within the dichotomous groups used in this study would be of value, however was beyond the scope of this analysis.

Furthermore, exposure was based on initial HD prescription in line with similar studies.^{13,19} Patients may have altered their prescription over time, whether from conventional dialysis to frequent/extended duration or vice versa. Although this approach avoids the effect of differences in patients who crossover between treatments, the reason for initiating a particular prescription regimen was unknown and therefore, may have contributed to differences in the treatment cohorts. We included incident patients only to minimize the effect of previous RRT, or longevity effect of prevalent patients as well as minimise the effect of variable residual renal function as a potential confounder. The results of this study are therefore generalizable to the adult, non-Indigenous Australian population who initiated HD as their initial RRT.

In summary, this study separates the independent effects of increased frequency and session duration that have variably been termed intensive dialysis. The results suggest that initial longer session durations greater than 5 h/week, but not necessarily more frequent HD, are associated with improved survival on dialysis in non-Indigenous Australian adult ESKD patients initiating HD. This would suggest that it is the increased duration of intensive dialysis rather than the increased frequency that has the greatest effect on survival in patients. Further analyses would provide valuable information that would both strengthen these findings and provide potential causal mechanisms for the observed result.

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