

## Incremental Hemodialysis: The University of California Irvine Experience

Mehrdad Ghahremani-Ghajar,\* Vanessa Rojas-Bautista,\* Wei-Ling Lau,\* Madeleine Pahl,\* Miguel Hernandez,\* Anna Jin,† Uffam Reddy,\* Jason Chou,\* Yoshitsugu Obi,\* Kamyar Kalantar-Zadeh,\*† and Connie M. Rhee\*

\*Division of Nephrology and Hypertension, University of California Irvine School of Medicine, Orange, California, and †Nephrology Section, Veterans Affairs Long Beach Health Care System, Long Beach, California

### ABSTRACT

Incremental hemodialysis has been examined as a viable hemodialysis regimen for selected end-stage renal disease (ESRD) patients. Preservation of residual kidney function (RKF) has been the driving impetus for this approach given its benefits upon the survival and quality of life of dialysis patients. While clinical practice guidelines recommend an incremental start of dialysis in peritoneal dialysis patients with substantial RKF, there remains little guidance with respect to incremental hemodialysis as an initial renal replacement therapy regimen. Indeed, several large population-based studies suggest that incremental twice-weekly vs. conventional thrice-weekly hemodialysis has favorable impact upon RKF trajectory and survival among patients with adequate renal urea clearance and/or urine output. In this report, we describe a case series of 13 ambulatory incident ESRD patients enrolled in a

university-based center's Incremental Hemodialysis Program over the period of January 2015 to August 2016 and followed through December 2016. Among five patients who maintained a twice-weekly hemodialysis schedule vs. eight patients who transitioned to thrice-weekly hemodialysis, we describe and compare patients' longitudinal case-mix, laboratory, and dialysis treatment characteristics over time. The University of California Irvine Experience is the first systemically examined twice-weekly hemodialysis practice in North America. While future studies are needed to refine the optimal approaches and the ideal patient population for implementation of incremental hemodialysis, our case-series serves as a first report of this innovative management strategy among incident ESRD patients with substantial RKF, and a template for implementation of this regimen.

In end-stage renal disease (ESRD) patients, preservation of residual kidney function (RKF) and urine output (UOP) has been associated with better solute clearance and fluid balance, as well as greater health-related quality of life and survival (1–11). Indeed, a large proportion of incident ESRD patients will have substantial RKF at the time of dialysis initiation, with 45% and 16% of patients having an estimated glomerular filtration rate (eGFR) of  $\geq 10$  ml/minute/1.73 m<sup>2</sup> and  $\geq 15$  ml/minute/1.73 m<sup>2</sup>, respectively, at the time of dialysis initiation (12). The reasons for high mortality in the

first year on HD are unclear (13,14). Inevitably, these patients will experience loss of RKF over time, which occurs more rapidly amongst hemodialysis (10,11,13,15–17) than peritoneal dialysis patients (18,19), presumably due to episodic renal ischemia from intra-dialytic hypotension and hypovolemia, activation of nephrotoxic inflammatory mediators due to exposure to dialysis tubing and impurities (10,18–21), and reduction in uremic substances that serve as the stimulus for remaining hyperfunctioning nephrons (22).

Recognizing the importance of the preservation of RKF, there has been increasing interest in incremental hemodialysis as an innovative approach for initiating hemodialysis amongst incident ESRD patients (23–28). For example, in a study of 85 incident hemodialysis patients in Shanghai, those who were initiated and maintained on twice-weekly hemodialysis vs. conventional thrice-weekly hemodialysis over the entire study period were less likely to experience loss of RKF (defined as UOP <200 ml/day) over the course of one year (29). In a more recent analysis of 23,645 incident US hemodialysis patients,

*Address correspondence to:* Connie M. Rhee, MD, MSc, Harold Simmons Center for Chronic Disease Research and Epidemiology, University of California Irvine School of Medicine, 101 The City Drive South, City Tower, Suite 400, Orange, CA 92868, Tel.: +714-456-5142, Fax: 714-456-6034, or e-mail: crhee1@uci.edu.

Conflict of interest: None of the authors have any disclosures to report.

*Seminars in Dialysis*—2017

DOI: 10.1111/sdi.12591

© 2017 Wiley Periodicals, Inc.

incremental twice-weekly vs. conventional thrice-weekly hemodialysis was associated with greater preservation of RKF, defined by renal urea clearance and urine volume, after one year (30). An increasing body of data also suggests that incremental hemodialysis is associated with equivalent to better survival, particularly amongst patients with substantial RKF (renal urea clearance  $>3$  ml/minute/ $1.73$  m<sup>2</sup>) (17,30,31).

While the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Peritoneal Dialysis Adequacy Group recommends consideration of an incremental start of dialysis (i.e., less than a “full” dose) in peritoneal dialysis patients with substantial RKF, much less has been written about the practical implementation of incremental hemodialysis (32,33). Although NKF-KDOQI Hemodialysis Adequacy Group guidelines endorse twice-weekly hemodialysis amongst patients with renal urea clearances (KRU) exceeding  $3$  ml/minute/ $1.73$  m<sup>2</sup>, it is not *per se* recommended as an initial treatment strategy amongst such patients (32). Thus, to better inform the field, we describe the largest case series of a university-based single center’s experience in implementing an Incremental Hemodialysis Program among incident ESRD patients.

## Methods

We conducted a retrospective analysis of 13 incident ESRD patients who initiated incremental twice-weekly hemodialysis in the outpatient setting over the contemporary period of January 2015 to August 2016 at the University of California Irvine Dialysis Center in Orange, California. (The management of the dialysis facility has recently been transferred to Fresenius Medical Care [FMC] under the new designation “FMC University Dialysis Center of Orange.”) Among these patients, eight were transitioned to conventional thrice-weekly hemodialysis, whereas the remaining five patients have continued to receive twice-weekly hemodialysis at the time of this report (December 2016). In the overall cohort and between these two groups, we analyzed socio-demographic characteristics, laboratory parameters, dialysis treatment characteristics, and in-center hemodialysis medications at the *time of dialysis initiation*. We additionally compared laboratory parameters and dialysis treatment characteristics at the *time of dialysis transition* among those who transitioned to thrice-weekly hemodialysis vs. the *most recent values* (i.e., values at the end of the observation period) among those who maintained twice-weekly hemodialysis.

## Results

### Study Population

The baseline characteristics of the 13 enrolled patients are presented in Table 1. Their mean age

( $\pm$ SD) was  $52.7 \pm 18.2$  years; 39% were female; and 23%, 54%, 15%, and 8% were non-Hispanic White, Hispanic, Asian, and Pacific Islander, respectively. The most common causes of ESRD were diabetic nephropathy (31%) and hypertension (15%), and other etiologies included reduced nephron mass due to partial nephrectomy, obstructive nephropathy, glomerulonephritis (e.g., membranoproliferative glomerulonephritis, IgA nephropathy), chronic interstitial nephritis, cystic disease (e.g., tuberous sclerosis), and congenital renal dysplasia (e.g., solitary kidney) (Fig. 1). A large proportion of patients were diagnosed with hypertension (85%), diabetes (54%), and cardiovascular disease (31%). At the time of dialysis initiation, 46% of patients were using an arteriovenous fistula, and 54% patients were using a tunneled dialysis catheter as their primary vascular access. The average initial hemodialysis session length was  $164 \pm 34$  minutes, and 31%, 8%, 46%, and 15% of patients were receiving  $2$ – $< 2.5$  hours,  $2.5$ – $< 3.0$  hours,  $3.0$ – $< 3.5$  hours, and  $3.5$ – $4.0$  hours of treatment per session, respectively.

Among patients who eventually transitioned to thrice-weekly hemodialysis ( $N = 8$ ), the mean  $\pm$  SD, median (IQR), and minimum–maximum duration of their twice-weekly hemodialysis regimens were  $8.0 \pm 3.9$  months, 4.5 (5.0, 9.5) months, and 4.0–15.5 months, respectively. The two primary indications for transitioning to thrice-weekly hemodialysis were problems with (i) excessive interdialytic weight gain ( $N = 4$ ) and (ii) inability to achieve adequate total clearance ( $N = 4$ ) (Fig. 2). Among patients who experienced excessive interdialytic weight gain, one patient developed new onset systolic heart failure and three patients developed frank volume overload. Among patients with inadequate total clearance, the following laboratory aberrancies were observed: hyperkalemia (serum potassium  $>5.3$  mmol/l;  $N = 3$ ), metabolic acidosis (serum bicarbonate  $<20$  mmol/l;  $N = 2$ ), inadequate dialytic clearance per session ( $N = 4$ ), and hyperphosphatemia (serum phosphorus  $>6$  mg/dl;  $N = 2$ ). Among patients who maintained a twice-weekly hemodialysis regimen ( $N = 5$ ), the mean  $\pm$  SD, median (IQR), and minimum-maximum duration of their twice-weekly hemodialysis regimens were  $12.0 \pm 6.3$  months, 5.0 (9.0, 14.0) months, and 5.5–22.0 months, respectively.

### Comparison of Case-Mix Characteristics of Patients Who Maintained Twice-Weekly vs. Transitioned to Thrice-Weekly Hemodialysis Regimens

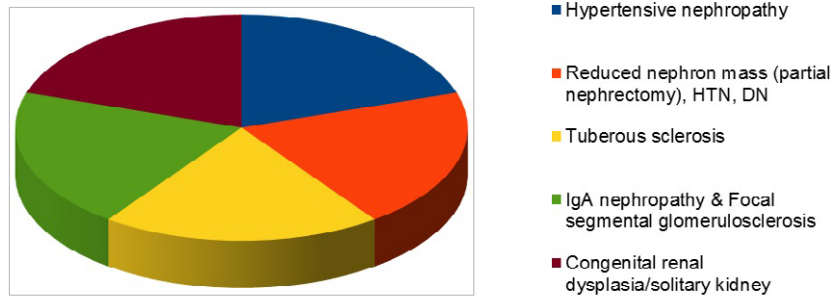
At the time of dialysis initiation, compared to patients who maintained twice-weekly hemodialysis ( $N = 5$ ), those who transitioned to thrice-weekly hemodialysis over the observation period ( $N = 8$ ) tended to be older (mean  $\pm$  SD ages  $54 \pm 17$  vs.  $51 \pm 21$  years, respectively) and had a higher proportion of females (50% vs. 20% respectively). Between the two groups, there were similar

TABLE 1. Baseline characteristics of 13 incident end-stage renal disease (ESRD) patients initiated on twice-weekly hemodialysis schedules

Patient	Age	Gender	Race/Ethnicity	Cause of ESRD	Diabetes (Y/N)	HTN (Y/N)	CVD (Y/N)	Duration on twice-weekly HD (months)	Transition to thrice-weekly HD (Y/N)		Reason for transition from twice-weekly to thrice-weekly HD
									HD (Y/N)	HD (Y/N)	
Patient 1	71	F	Hispanic	Diabetic nephropathy	Y	Y	Y	15.5	Y	Y	IDWG and fluid overload
Patient 2	43	F	Non-Hispanic White	Diabetic nephropathy	Y	Y	N	11	Y	Y	IDWG and new onset HF+rEF
Patient 3	59	M	Non-Hispanic White	Diabetic nephropathy	Y	Y	N	6	Y	Y	IDWG and fluid overload
Patient 4	70	M	Hispanic	Obstructive nephropathy	Y	Y	Y	9	Y	Y	IDWG
Patient 5	20	M	Hispanic	Membranoproliferative glomerulonephritis	N	N	N	5	Y	Y	Adequacy (hyperkalemia)
Patient 6	50	F	Hispanic	Hypertension, NSAID use	N	Y	N	5	Y	Y	Adequacy (acidosis, hyperkalemia, hyperphosphatemia)
Patient 7	68	F	Asian	Diabetic nephropathy	Y	Y	Y	4	Y	Y	Adequacy (hyperkalemia, acidosis, low clearance)
Patient 8	50	M	Asian	Chronic interstitial nephritis	N	Y	N	6	Y	Y	Adequacy
Patient 9	73	M	Asian	Hypertension/Ischemic nephropathy	Y	Y	Y	12	N	N	N/A
Patient 10	66	F	Hispanic	Reduced nephron mass (partial nephrectomy), hypertension, diabetic nephropathy	Y	Y	N	20	N	N	N/A
Patient 11	31	M	Hispanic	Tuberos sclerosis	N	N	N	8	N	N	N/A
Patient 12	59	M	Hispanic	IgA nephropathy & Focal segmental glomerulosclerosis	N	Y	N	7	N	N	N/A
Patient 13	25	M	Non-Hispanic White	Congenital renal dysplasia/solitary kidney	N	Y	N	3.5	N	N	N/A

M, male; F, female; Y, yes; N, no; HTN, hypertension; CVD, cardiovascular disease; HD, hemodialysis; IDWG, interdialytic weight gain; HF+rEF, heart failure with reduced ejection fraction; URR, urea reduction ratio.

**Causes of ESRD in patients who maintained 2x/wk**



**Causes of ESRD in patients who transitioned to 3x/wk**

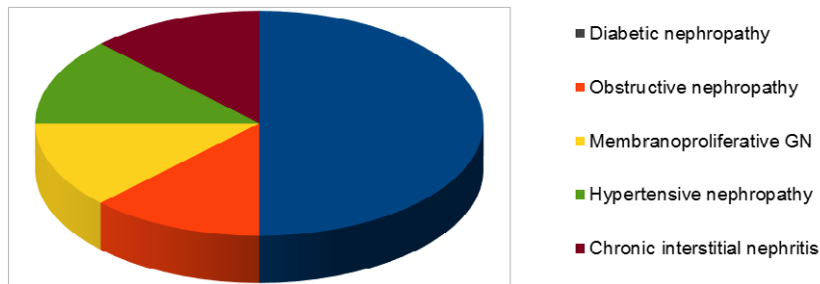


Fig. 1. Causes of end-stage renal disease (ESRD) among patients who remained on twice-weekly hemodialysis ( $N = 5$ ) and those who escalated to thrice-weekly hemodialysis ( $N = 8$ ).

**Patients who Transitioned to Thrice-weekly**

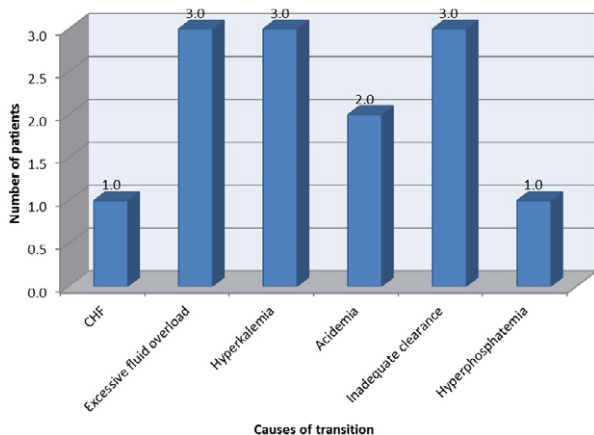


Fig. 2. Indications for escalating to thrice-weekly hemodialysis among eight patients. Note: patients may have had multiple concomitant indications for transition to thrice-weekly hemodialysis.

higher prevalence of diabetes (63% vs. 40%, respectively), hypertension (88% vs. 80%, respectively), and cardiovascular disease (38% vs. 20%, respectively). Fifty percent of the patients who transitioned to thrice-weekly hemodialysis had diabetes as their etiology of ESRD, whereas those who were maintained on twice-weekly dialysis had non-diabetic etiologies of ESRD only (Fig. 1). In comparison to twice-weekly patients, thrice-weekly patients had a higher prevalence of tunneled dialysis catheters as their primary vascular access at the time of dialysis initiation (63% vs. 40%, respectively), an observation that persisted at the time of review of the *most recent* characteristics (37% vs. 20% of thrice-weekly vs. twice-weekly patients, respectively).

**Comparison of Laboratory Characteristics of Patients Who Maintained Twice-Weekly vs. Transitioned to Thrice-Weekly Hemodialysis Regimens**

A comparison of the *initial laboratory characteristics* among patients who remained on a twice-weekly hemodialysis regimen vs. those who eventually transitioned to conventional thrice-weekly hemodialysis showed notable differences (Table 2). Compared to patients who remained on twice-weekly hemodialysis, those who transitioned

proportions of patients who were non-Hispanic White (25% vs. 20%, respectively), Hispanic (50% vs. 60%, respectively), and Asian/Pacific Islander (25% vs. 20%, respectively). Compared to patients who maintained twice-weekly schedules, those who transitioned to thrice-weekly hemodialysis had a

to thrice-weekly hemodialysis tended to have higher serum potassium ( $4.7 \pm 1.0$  vs.  $3.7 \pm 0.6$  mmol/l, respectively) and lower serum sodium levels ( $134 \pm 4$  vs.  $139 \pm 2$  mmol/l, respectively). In terms of mineral bone disease parameters, compared to twice-weekly hemodialysis patients, thrice-weekly patients had higher parathyroid hormone ( $766 \pm 1154$  vs.  $525 \pm 422$  pg/ml, respectively), lower serum phosphorus ( $5.5 \pm 1.5$  vs.  $6.3 \pm 1.6$  mg/dl, respectively), and higher serum calcium levels ( $8.6 \pm 0.7$  vs.  $8.0 \pm 1.1$  mg/dl, respectively). With respect to anemia parameters, they were also observed to have lower hemoglobin ( $8.6 \pm 0.7$  vs.  $9.9 \pm 1.1$  g/dl, respectively), lower iron saturation ( $23 \pm 10$  vs.  $26 \pm 18\%$ , respectively), and higher serum ferritin levels ( $421 \pm 288$  vs.  $233 \pm 226$  ng/ml, respectively). In terms of nutritional markers, they had lower serum albumin ( $3.3 \pm 0.4$  vs.  $3.5 \pm 0.7$  g/dl, respectively) and serum creatinine levels ( $6.6 \pm 2.4$  vs.  $7.2 \pm 1.1$  mg/dl, respectively).

When the *most recent laboratory values* of patients who remained on twice-weekly hemodialysis were compared to those who transitioned to thrice-weekly dialysis *at the time of dialysis transition*, those on thrice-weekly treatment persisted in having higher serum potassium ( $5.3 \pm 0.8$  vs.  $4.3 \pm 0.5$  mmol/l, respectively), higher parathyroid hormone ( $661 \pm 946$  vs.  $526 \pm 414$  pg/ml, respectively), lower hemoglobin ( $9.2 \pm 1.0$  vs.  $10.7 \pm 1.1$  g/dl, respectively), and lower iron saturation levels ( $17 \pm 4\%$  vs.  $37 \pm 23\%$ , respectively) (Table 3).

### Comparison of Dialysis Treatment Characteristics of Patients Who Maintained Twice-Weekly vs. Transitioned to Thrice-Weekly Hemodialysis Regimens

Differences in the *initial* dialysis treatment characteristics between the two groups were also observed (Table 2). Compared to patients who remained on twice-weekly hemodialysis, those who transitioned to thrice-weekly hemodialysis tended to have higher interdialytic weight gain ( $1.2 \pm 0.6$  vs.  $0.9 \pm 0.7$  kg, respectively) and higher predialysis blood pressures ( $156 \pm 18$  vs.  $151 \pm 27$  mmHg, respectively). In terms of dialysis prescriptions, compared to twice-weekly patients, thrice-weekly patients had longer dialysis session lengths ( $173 \pm 27$  vs.  $150 \pm 42$  minutes, respectively) and greater use of dialysate with lower potassium concentrations (i.e., at initiation 75% of thrice-weekly patients were treated with a 2K dialysate bath whereas 100% of twice-weekly patients were treated with a 3K dialysate bath).

Compared to the *most recent values* of the twice-weekly group, the thrice-weekly group's characteristics at the *time of transition* showed similar interdialytic weight gain ( $2.6 \pm 1.8$  vs.  $2.6 \pm 0.9$  kg, respectively), predialysis systolic blood pressures ( $161 \pm 16$  vs.  $156 \pm 17$  mmHg, respectively), and dialysis session lengths (~3.0 hours across both groups) (Table 3).

### Changes in Characteristics over Time among Patients Who Transitioned to Thrice-Weekly Hemodialysis

Among patients who eventually transitioned to thrice-weekly hemodialysis, baseline characteristics at the time of initiation of twice-weekly dialysis vs. those at the time of transition to thrice-weekly hemodialysis are outlined in Tables 2 and 3. Over time, higher serum potassium levels were observed ( $5.3 \pm 0.8$  vs.  $4.7 \pm 1.0$  mmol/l, respectively). In terms of mineral bone disease parameters, they developed higher serum phosphorus ( $6.3 \pm 2.3$  vs.  $5.5 \pm 1.5$  mg/dl, respectively), lower parathyroid hormone ( $661 \pm 946$  vs.  $766 \pm 1154$  pg/ml, respectively), and maintained similar calcium levels ( $8.5 \pm 0.8$  vs.  $8.6 \pm 0.7$  mg/dl, respectively). In terms of anemia parameters, they had higher hemoglobin ( $9.2 \pm 1.0$  vs.  $8.6 \pm 0.7$  g/dl, respectively), lower iron saturation ( $17 \pm 4$  vs.  $23 \pm 10\%$ , respectively), and higher ferritin levels over time ( $535 \pm 431$  vs.  $421 \pm 288$  ng/ml, respectively). In terms of nutritional parameters, they had higher serum albumin ( $3.7 \pm 0.3$  vs.  $3.3 \pm 0.4$  g/dl, respectively) and higher serum creatinine levels over time ( $9.2 \pm 2.5$  vs.  $6.6 \pm 2.4$  mg/dl, respectively). With respect to dialysis treatment characteristics, they had higher interdialytic weight gain ( $2.6 \pm 1.8$  vs.  $1.2 \pm 0.6$  kg, respectively), higher predialysis blood pressure ( $161 \pm 16$  vs.  $156 \pm 18$  mmHg, respectively), longer dialysis session length ( $189 \pm 29$  vs.  $173 \pm 27$  minutes, respectively), and greater use of dialysate with lower potassium concentrations (i.e., 2K dialysate baths) (75% vs. 25%, respectively) over time.

### Changes in Characteristics over Time among Patients Who Maintained Twice-Weekly Hemodialysis

Baseline characteristics at the time of initiation compared to the most recent values among patients maintained on a twice-weekly hemodialysis regimen are shown in Tables 2 and 3. Similar to those converted to thrice-weekly dialysis, serum potassium concentrations rose albeit to lower levels ( $4.3 \pm 0.5$  vs.  $3.7 \pm 0.6$  mmol/l respectively). In terms of mineral bone disease parameters, they developed higher serum phosphorus ( $6.3 \pm 2.3$  vs.  $5.5 \pm 1.5$  mg/dl, respectively), lower parathyroid hormone ( $661 \pm 946$  vs.  $766 \pm 1154$  pg/ml, respectively), and maintained similar calcium levels ( $8.5 \pm 0.8$  vs.  $8.6 \pm 0.7$  mg/dl respectively). In terms of anemia parameters, they had higher hemoglobin ( $9.2 \pm 1.0$  vs.  $8.6 \pm 0.7$  g/dl, respectively), lower iron saturation ( $17 \pm 4$  vs.  $23 \pm 10\%$ , respectively), and higher ferritin levels over time ( $535 \pm 431$  vs.  $421 \pm 288$  ng/ml respectively). In terms of nutritional parameters, they had higher serum albumin ( $3.7 \pm 0.3$  vs.  $3.3 \pm 0.4$  g/dl, respectively) and higher serum creatinine levels over time ( $9.2 \pm 2.5$  vs.  $6.6 \pm 2.4$  mg/dl respectively). With respect to

TABLE 2. Dialysis treatment and laboratory characteristics at the initiation of twice-weekly hemodialysis

Patient	IDWG <sup>a</sup> (kg)	Serum K (mmol/l)	Phos (mg/dl)	PTH (pg/ml)	Hb (mg/dl)	ESA <sup>a</sup> (units)	Serum bicarbonate (mmol/l)	BMI (kg/m <sup>2</sup> )	Pre-HD SBP (mmHg)	HD time (min)	Dialysate K (meq/l)	Vascular access type	Calcitriol (µg) <sup>b</sup>	Serum albumin (mg/dl)	Serum creatinine (mg/dl)	Ca (mg/dl)	Tsat (%)	Ferritin (ng/ml)	Na (mmol/l)
Patient 1	1.3	3.7	3.7	7	8.4	2200	23	33.1	151	180	3	TC	0.25 qd	3.1	3.4	9.9	16	430	124
Patient 2	1.4	4.4	7.9	92	8.8	2200	17	37.0	190	120	3	AVF	none	2.8	8.5	8.3	18	65	140
Patient 3	2.0	4.7	5.7	272	9.7	0	18	27.1	167	210	2	TC	None	3.0	4.1	8.4	38	552	137
Patient 4	1.0	4.6	3.9	244	8.8	2200	27	27.6	166	180	3	TC	None	2.9	6.4	9.2	30	204	134
Patient 5	0.4	7.1	4.5	895	7.3	4400	19	19.9	147	180	1	AVF	0.25/HD	3.8	5.4	8.8	13	916	138
Patient 6	0.2	4.4	6.9	3475	8.1	2000	22	22.6	135	150	3	TC	0.25/HD	3.7	7.8	8.3	17	322	137
Patient 7	1.5	4.3	5.1	156	8.7	3000	16	23.5	155	180	3	AVF	0.25/HD	3.8	10.7	8.4	14	697	136
Patient 8	1.7	4.4	6.5	990	8.8	2000	16	23.7	140	180	2	TC	0.25/HD	3.6	6.5	7.5	35	181	136
Patient 9	1.6	4.4	7.5	311	9.3	4400	25	33.2	179	120	3	AVF	0.25 qd	3.9	8.0	8.2	22	306	138
Patient 10	0.3	3.3	7.3	71	10.2	0	23	24.8	138	120	3	AVF	None	3.4	6.3	8.7	12	46	140
Patient 11	1.2	3.0	3.8	779	9.9	0	18	18.4	113	180	3	TC	0.25/HD	2.5	7.4	6.1	57	72	139
Patient 12	1.5	4.2	7.4	339	11.6	0	10	35.0	149	120	3	AVF	0.5 qd	4.3	8.3	8.3	20	145	138
Patient 13	0.1	3.5	5.7	1125	8.6	5000	24	29.9	174	210	3	TC	None	3.5	5.8	8.8	21	594	135

K, serum potassium; Phos, serum phosphorus; HTN, hypertension; PTH, parathyroid hormone; Hg, hemoglobin; ESA, erythropoietin stimulating agent; BMI, body mass index; HD, hemodialysis; IDWG, interdialytic weight gain; Ca, serum calcium; Tsat, transferrin saturation; Na, serum sodium; TC, tunneled catheter; qd, daily.

<sup>a</sup>Equivalent ESA dose among patients receiving varying ESA formulations.

<sup>b</sup>Equivalent calcitriol dose among patients receiving varying activated vitamin D/vitamin D analog formulations.

TABLE 3. Dialysis treatment and laboratory characteristics immediately prior to transition to thrice-weekly hemodialysis and most recent values among those who maintained twice-weekly hemodialysis

Patient	IDWG <sup>a</sup> (kg)	Serum K (mmol/l)	Phos (mg/dl)	PTH (pg/ml)	Hb (mg/dl)	ESA <sup>a</sup> (units)	Serum bicarbonate (mmol/l)	BMI (kg/m <sup>2</sup> )	Pre-HD SBP (mmHg)	HD time (min)	Dialysate K (meq/l)	Vascular access type	Calcitriol (µg) <sup>b</sup>	Serum albumin (mg/dl)	Serum creatinine (mg/dl)	Ca (mg/dl)	Tsat (%)	Ferritin (ng/ml)	Na (mmol/L)
Patient 1	2.9	5.3	4.5	129	9.8	3000	26	3.5	175	180	3	AVF	0.25 qd	3.7	6.4	9.7	24	1210	128
Patient 2	2.7	4	5.2	61	10.1	3000	25	34.3	194	180	2	AVF	None	3.4	7	9	18	598	128
Patient 3	5.8	5.1	4.5	321	8	2000	20	28.5	160	240	2	TC	None	3.1	7.24	8.4	18	416	133
Patient 4	3.6	5.4	5.7	415	8.3	3000	23	26.8	153	180	2	TC	0.25/HD	3.5	8.1	7.2	16	348	137
Patient 5	3.4	6.5	9.1	1125	7.8	3000	17	21.5	152	225	2	AVF	0.75	4	12.9	8.3	10	1164	134
Patient 6	0.5	6.4	10.6	2846	9.6	4600	13	25.6	161	150	3	AVF	0.5/HD	3.8	11	7.6	13	129	135
Patient 7	0.3	5.3	5.6	296	10	3000	23	23.7	154	180	2	AVF	0.5/HD	4	8.7	8.8	20	296	134
Patient 8	1.7	4.5	5	93	10	6000	25	22.9	141	180	2	TC	0.75/HD	4	12.1	9.2	14	120	140
Patient 9	2.83	4.5	8.3	504	11	4400	20	31.6	177	210	3	AVF	None	3.6	7.9	7.7	29	288	141
Patient 10	1.7	4.9	5	17	9.3	3000	27	23.4	149	180	3	AVF	None	4.2	11.9	9.5	25	1168	138
Patient 11	1.6	4.1	3.6	1154	10	4000	23	21.4	136	180	3	AVF	4.5/HD	3.9	8.7	8.1	77	262	139
Patient 12	3.2	3.6	6.5	361	11.1	0	22	3.6	146	210	3	AVF	None	4.1	9.7	7.6	21	65	137
Patient 13	3.6	4.2	6.2	595	12.2	7500	27	26.8	171	200	3	TC	0.25/HD	3.3	4.7	9.1	32	774	138

K, serum potassium; Phos, serum phosphorus; HTN, hypertension; PTH, parathyroid hormone; Hg, hemoglobin; ESA, erythropoietin stimulating agent; BMI, body mass index; HD, hemodialysis; IDWG, interdialytic weight gain; Ca, serum calcium; Tsat, transferrin saturation; Na, serum sodium; TC, tunneled catheter; qd, daily.

<sup>a</sup>Equivalent ESA dose among patients receiving varying ESA formulations.

<sup>b</sup>Equivalent calcitriol dose among patients receiving varying activated vitamin D/vitamin D analog formulations.

dialysis treatment characteristics, they had higher interdialytic weight gain ( $2.6 \pm 1.8$  vs.  $1.2 \pm 0.6$  kg, respectively), higher predialysis systolic blood pressure ( $161 \pm 16$  vs.  $156 \pm 18$  mmHg, respectively), longer dialysis session length ( $189 \pm 29$  vs.  $173 \pm 27$  minutes, respectively), and greater use of dialysate with lower potassium concentrations (i.e., 2K dialysate baths) (75% v. 25%, respectively) over time.

## Discussion

In this report, we describe the largest case series of ambulatory incident ESRD patients enrolled in a university-based Incremental Hemodialysis Program. Over a 23-month follow-up period, 13 patients initiated incremental hemodialysis, among whom eight patients eventually transitioned to thrice-weekly hemodialysis and five patients have continued on twice-weekly hemodialysis regimens.

In this descriptive evaluation, we observed that patients who transitioned to conventional thrice-weekly hemodialysis had a higher comorbidity burden (e.g., diabetes, hypertension, cardiovascular disease) compared to their counterparts who maintained twice-weekly hemodialysis. Notably, half of the patients who transitioned to thrice-weekly hemodialysis had diabetic nephropathy as the underlying cause of their ESRD compared to none of those who were maintained on a twice weekly regimen. This is consistent with observations in predialysis chronic kidney disease patients and incident hemodialysis patients in whom diabetic nephropathy is associated with faster kidney function decline vs. nondiabetic etiologies (34,35).

Those who eventually transitioned to thrice-weekly hemodialysis had slightly worse metabolic status (e.g., hyperkalemia, hyponatremia), mineral bone disease parameters (e.g., higher parathyroid hormone levels), hematologic values (e.g., lower hemoglobin, lower iron saturation), malnutrition-inflammation-complex characteristics (e.g., lower serum albumin, lower serum creatinine, higher serum ferritin), and fluid balance (e.g., higher interdialytic weight gain, higher predialysis systolic pressure) than those remaining on twice-weekly hemodialysis.

We did not have access to data on serial renal urea clearance and urine output measurements over time. While it is possible that, compared to the twice-weekly group, the thrice-weekly patients may have had lower baseline RKF and faster decline over time, behavioral factors such as compliance with diet, medications, and dialysis treatments may also have contributed to these initial differences and eventual transition to more frequent hemodialysis. Longitudinal follow-up of these patients also showed that, compared to the twice-weekly group's most recent values, the thrice-weekly group's values at the time of transition continued to show worse metabolic (e.g. hyperkalemia), mineral bone disease

(e.g., higher parathyroid hormone), and anemia parameters (e.g., lower hemoglobin and iron saturation). Although updated fluid status parameters showed that average interdialytic weight gain and predialysis systolic pressures were similar across the two groups, excessive fluid gain was cited as an indication for transitioning to more frequent hemodialysis among 50% of the thrice-weekly patients.

Beyond the NKF-KDOQI's recommendations regarding a requisite amount of RKF (i.e., renal urea clearance of  $>3$  ml/minute/1.73 m<sup>2</sup>), there are limited data on the optimal subpopulations and patient characteristics for the implementation of incremental hemodialysis (25). Experts have proposed criteria that can be used to select appropriate patients for the incremental hemodialysis regimen (25), including those with (i) renal urea clearance  $>3$  ml/minute/1.73 m<sup>2</sup> AND (ii) urine output  $>500$  ml/day, as well as five additional criteria: (a) limited fluid retention between two consecutive hemodialysis treatments with an interdialytic weight gain  $<2.5$  kg, or  $<5\%$  of the ideal dry weight without hemodialysis for 3–4 days; (b) limited or readily manageable cardiovascular or pulmonary symptoms without excessive fluid overload; (c) infrequent or readily manageable hyperphosphatemia; (d) ESA-responsiveness and an absence of profound anemia (hemoglobin  $<8$  g/dl); (e) suitable body size, particularly if not hypercatabolic; (f) infrequent or readily manageable hyperkalemia; (g) adequate nutritional status without hypercatabolism; (h) infrequent hospitalization and easily manageable comorbidities; and (i) adequate health-related quality of life.

At this time, there remain multiple questions with respect to the practical implementation of incremental hemodialysis among incident ESRD patients, such as (i) What is the optimal dialysis prescription for incremental hemodialysis?; (ii) Beyond assessing quarterly renal urea clearance as per the NKF-KDOQI Hemodialysis Adequacy Group guidelines, are there additional accurate and efficient tools that can be used to serially monitor patients' RKF?; (iii) What adjunctive management strategies (i.e., medications, diet, physical activity) can be concurrently implemented with incremental hemodialysis to best preserve RKF?; (iv) What characteristics predict patients who will be able to maintain incremental hemodialysis vs. eventually transition to thrice-weekly hemodialysis?; (v) What are the optimal transition points for escalation from twice- to thrice-weekly hemodialysis?; and (vi) Does the incremental hemodialysis regimen provide a more cost-effective management strategy than conventional hemodialysis?

Our report has several limitations which bear acknowledgment. First, we lacked data on baseline and longitudinal renal urea clearance and urine output data that could be correlated with patients' characteristics and trajectories toward escalation to thrice-weekly vs. continuation of twice-weekly hemodialysis. Second, due to data limitations, we

were unable to examine and compare relevant outcomes such as health-related quality of life, hospitalization, and mortality risk amongst patients in the Incremental Hemodialysis Program; they are being examined in corollary studies. Third, given that our case-series was restricted to a single university-based center with experience in the implementation of incremental hemodialysis, our findings may not be generalizable to other patient populations. However, we aspire for our experience to serve as a template for the broader implementation of incremental hemodialysis across other medical centers.

In conclusion, we describe a novel strategy for initiating hemodialysis among incident ESRD patients as a means to preserve RKF in this population. Future studies are needed to refine the optimal approaches for implementation of the incremental twice-weekly hemodialysis regimen, as well as the ideal patient populations for this management strategy.

### Funding

The authors are supported by research grants from the NIH/NIDDK including K23-DK102903 (CMR), K24-DK091419 (KKZ), R01-DK096920 (KKZ), U01-DK102163 (KKZ), and philanthropist grants from Mr. Harold Simmons, Mr. Louis Chang, and Dr. Joseph Lee.

### References

- Bargman JM, Thorpe KE, Churchill DN; CANUSA Peritoneal Dialysis Study Group: Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J Am Soc Nephrol* 12(10):2158–2162, 2001
- Canaud B: Residual renal function: the delicate balance between benefits and risks. *Nephrol Dial Transplant* 23(6):1801–1805, 2008
- Chandna SM, Farrington K: Residual renal function: considerations on its importance and preservation in dialysis patients. *Semin Dial* 17(3):196–201, 2004
- Morduchowicz G, Winkler J, Zabłudowki JR, Boner G: Effects of residual renal function in haemodialysis patients. *Int Urol Nephrol* 26(1):125–131, 1994
- Obi Y, Rhee CM, Mathew AT, Shah G, Streja E, Brunelli SM, et al.: Residual kidney function decline and mortality in incident hemodialysis patients. *J Am Soc Nephrol* 27(12):3758–3768, 2016
- Paniagua R, Amata D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, et al.: Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol* 13(5):1307–1320, 2002
- Shafi T, Jaar BG, Plantinga LC, Fink NE, Sadler JH, Parekh RS, et al.: Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. *Am J Kidney Dis* 56(2):348–358, 2010
- Termorshuizen F, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT, et al.: Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *J Am Soc Nephrol* 15(4):1061–1070, 2004
- van der Wal WM, Noordzij M, Dekker FW, Boeschoten EW, Krediet RT, Korevaar JC, et al.: Full loss of residual renal function causes higher mortality in dialysis patients; findings from a marginal structural model. *Nephrol Dial Transplant* 26(9):2978–2983, 2011
- Vilar E, Farrington K: Emerging importance of residual renal function in end-stage renal failure. *Semin Dial* 24(5):487–494, 2011
- Vilar E, Wellsted D, Chandna SM, Greenwood RN, Farrington K, et al.: Residual renal function improves outcome in incremental haemodialysis despite reduced dialysis dose. *Nephrol Dial Transplant* 24(8):2502–2510, 2009
- US Renal Data System, USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, 2011:10.
- Bradbury BD, Fissell RB, Albert JM, Anthony MS, Crichtlow CW, Pisoni RL, et al.: Predictors of early mortality among incident US hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol* 2(1):89–99, 2007
- Lukowsky LR, Kheifets L, Arah OA, Nissenson AR, Kalantar-Zadeh K: Patterns and predictors of early mortality in incident hemodialysis patients: new insights. *Am J Nephrol* 35(6):548–558, 2012
- Daugirdas JT, Greene T, Rocco MV, Kaysen GA, Depner TA, Levin NW, et al.: Effect of frequent hemodialysis on residual kidney function. *Kidney Int* 83(5):949–958, 2013
- Diao Z, Zhang D, Dai W, Ding J, Zhang A, Liu W: Preservation of residual renal function with limited water removal in hemodialysis patients. *Ren Fail* 33(9):875–877, 2011
- Lin YF, Huang JW, Wu MS, Chu TS, Lin SL, Chen YM, et al.: Comparison of residual renal function in patients undergoing twice-weekly versus three-times-weekly haemodialysis. *Nephrology* 14(1):59–64, 2009
- Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT, et al.: Predictors of the rate of decline of residual renal function in incident dialysis patients. *Kidney Int* 62(3):1046–1053, 2002
- Lysaght MJ, Vonesh E, Gotch F, Ibels L, Keen M, Lindholm B, et al.: The influence of dialysis treatment modality on the decline of remaining renal function. *ASAIO Trans* 37(4):598–604, 1991
- Burton JO, Jefferies HJ, Selby NM, McIntyre CW: Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol* 4(5):914–920, 2009
- Hyodo T, Koutoku N: Preservation of residual renal function with HDF. *Contrib Nephrol* 168:204–212, 2011
- Bricker NS, Morrin PA, Kime SW Jr: The pathologic physiology of chronic Bright's disease. An exposition of the "intact nephron hypothesis". *Am J Med* 28:77–98, 1960
- Agrawal A, Saran R, Nolph KD: Continuum and integration of pre-dialysis care and dialysis modalities. *Perit Dial Int* 19(Suppl 2):S276–S280, 1999
- Daugirdas JT, Kjellstrand C: Chronic hemodialysis prescription: a urea kinetic approach. *Handbook Dial* 4:146–170, 1994
- Kalantar-Zadeh K, Unruh M, Zager PG, Kovesdy CP, Bargman JM, Chen J, et al.: Twice-weekly and incremental hemodialysis treatment for initiation of kidney replacement therapy. *Am J Kidney Dis* 64(2):181–186, 2014
- Keshaviah PR, Emerson PF, Nolph KD: Timely initiation of dialysis: a urea kinetic approach. *Am J Kidney Dis* 33(2):344–348, 1999
- Mehrotra R, Nolph KD, Gotch F: Early initiation of chronic dialysis: role of incremental dialysis. *Perit Dial Int* 17(5):426–430, 1997
- Rosansky SJ, Cancarini G, Clark WF, Eggers P, Germaine M, Glascock R, et al.: Dialysis initiation: what's the rush? *Semin Dial* 26(6):650–657, 2013
- Lin X, Yan Y, Ni Z, Gu L, Zhu M, Dai H, et al.: Clinical outcome of twice-weekly hemodialysis patients in shanghai. *Blood Purif* 33(1–3):66–72, 2012
- Obi Y, Streja E, Rhee CM, Ravel V, Amin AN, Cupisti A, et al.: Incremental hemodialysis, residual kidney function, and mortality risk in incident dialysis patients: a cohort study. *Am J Kidney Dis* 68(2):256–265, 2016
- Hanson JA, Hulbert-Shearon TE, Ojo AO, Port FK, Wolfe RA, Agodoa LY, et al.: Prescription of twice-weekly hemodialysis in the USA. *Am J Nephrol* 19(6):625–633, 1999
- Hemodialysis Adequacy Work Group: Clinical practice guidelines for hemodialysis adequacy, update 2006. *Am J Kidney Dis* 48(Suppl 1):S2–S90, 2006
- NKF-DOQI clinical practice guidelines for hemodialysis adequacy. *Am J Kidney Dis* 30(3):S17–S63, 1997
- Jones C, Roderick P, Harris S, Rogerson M: Decline in kidney function before and after nephrology referral and the effect on survival in moderate to advanced chronic kidney disease. *Nephrol Dial Transplant* 21(8):2133–2143, 2006
- Moist LM, Port FK, Orzol SM, Young EW, Ostbye T, Wolfe RA, et al.: Predictors of loss of residual renal function among new dialysis patients. *J Am Soc Nephrol* 11(3):556–564, 2000