



**Incremental less frequent hemodialysis is the optimal way to initiate dialysis
CON**

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The ICDC is funded by Alberta Innovates Health Solutions - CRIO Team Grants Program



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A question from the Executive Director

Does every patient on dialysis need to start with 4 hours regardless of GFR and function? Given recent research that indicates that starting patients early actually does harm, perhaps you should try to determine (predict) which patients require 2, 3 or 4 hours of dialysis or which patients should dialyze twice a week instead of 3.

With the approaching large cohort of baby boomers and lack of funds to build more dialysis units, I'm thinking we need to change something and wondered if we could improve care and secure a few more dialysis spots by triaging patients to differing lengths of dialysis periods. Looking forward to learning from you.

Executive Director



A reply from the Medical Director

- “There is good evidence that High Blood pressure, Heart disease and Fluid overload are very common in this population and short dialysis may be causative”.
- “There is also evidence of higher mortality after the long InterDialytic period even on current 3 times a week 4 Hr. Dialysis.”
- “In the National cooperative study, the 2 groups with short dialysis and high urea paid a very high price.”
- “When symptomatic, you need proper Dialysis”.

“We might have a debate before your formal one at the ASN”.





**Incremental less frequent hemodialysis is the optimal way to initiate dialysis
I mean CON (Thrice weekly is the way to go)**

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Overview

- 1) If you don't need dialysis, then twice weekly hemodialysis is fine
- 2) There is a substantially increased risk of mortality and cardiovascular events on the long (2 day) interdialytic interval
- 3) Underdialysis increases hospitalization
- 4) Over 70% of patients have lost their residual kidney function by one year
- 5) Start with the hemodialysis frequency they will need in the long run



Recommendations:

Don't start dialysis until the patient has a clear indication

Until clinical trials show that twice weekly HD is superior (or equivalent to thrice weekly HD), stay with standard of care





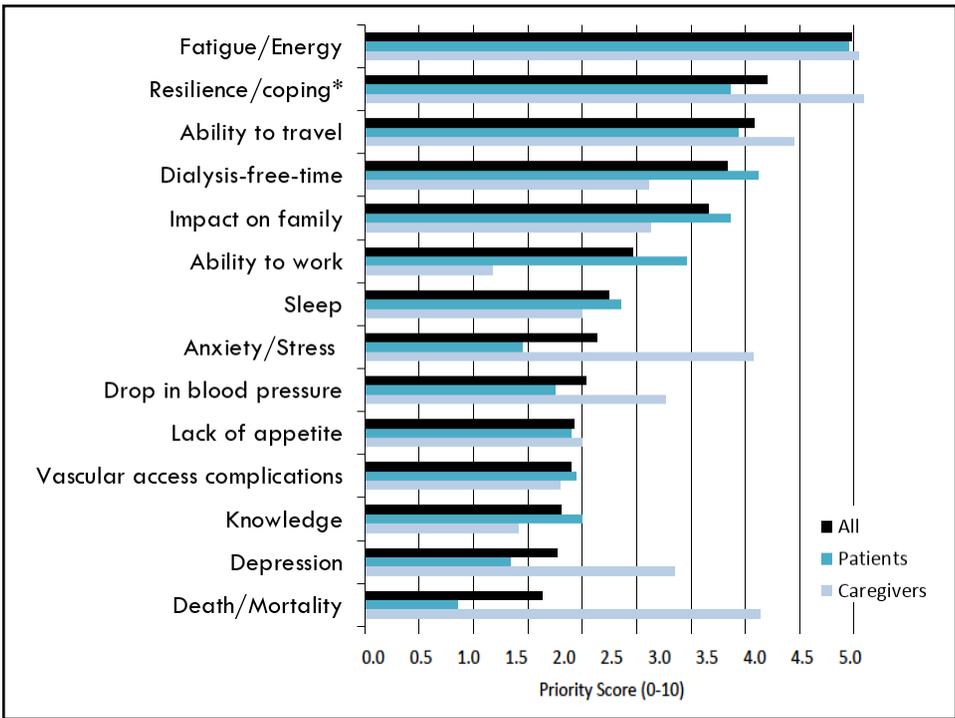
What symptom is most important /
vexing to patients on hemodialysis?

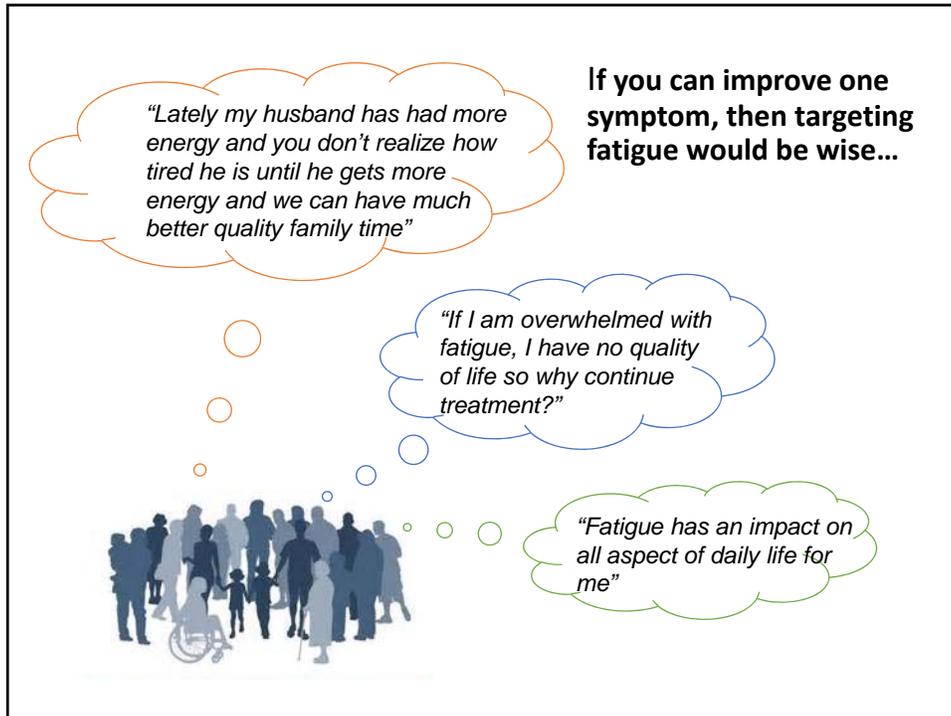
- a) Itching
- b) Fatigue
- c) Restless legs
- d) Cramping



Studies are starting to focus on symptoms

Improving survival is proving to be very difficult. It also does not appear to be what patients on hemodialysis are most interested in







1. If you don't need dialysis, then twice weekly hemodialysis is fine

Dialysis initiation over time

United States:

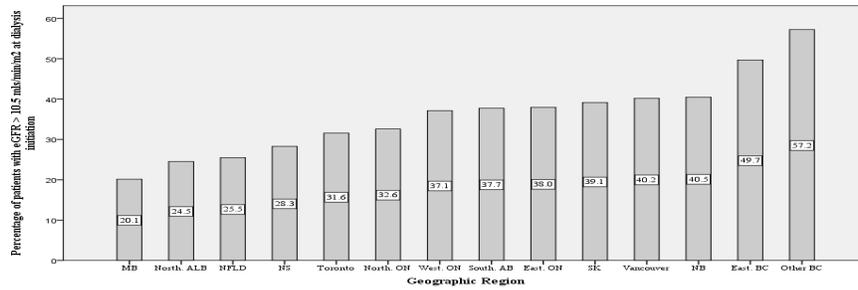
- The proportion of individuals starting dialysis at eGFR > 10mL/min/1.73m² has increased from **19% in 1996** to **45% in 2005** (USRDS)

Canada:

- The proportion of individuals starting dialysis at eGFR > 10mL/min/1.73m² has increased from **28% in 2001** to **36% in 2007** (Clark et al, CMAJ, 2011)

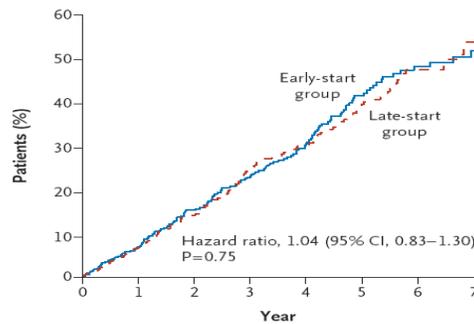


Regional variation in initiation of dialysis with eGFR > 10.5mls/min



IDEAL study

B Time to Death



No. at Risk	0	1	2	3	4	5	6	7
Early start	404	358	305	249	177	99	59	32
Late start	424	385	333	254	187	115	60	32

- No difference in mortality, quality of life, or hospitalization (overall or in subgroups – PD, diabetes)
- Six month delay in initiation of dialysis

Copper et al., NEJM 2010



Canadian Society of Nephrology 2014 Clinical Practice Guideline for Timing the Initiation of Chronic Dialysis

Gihad E. Nesrallah, Reem A. Mustafa, William F. Clark, Adam Bass, Lianne Barnieh, Brenda R Hemmelgarn, Scott Klarenbach, Robert R Quinn, Swapnil Hiremath, Pietro Ravani, Manish M. Sood, Louise M. Moist



For adult patients (>18 years of age) with an eGFR <15 ml/min/1.73m², we recommend an “intent-to-defer” over an “intent-to-start early” approach for the initiation of chronic dialysis. (Strong recommendation; moderate quality evidence)

- With the “intent-to-defer” strategy, patients with eGFR <15 ml/min/1.73m² are monitored closely by a nephrologist, & initiate dialysis with the first onset of a clinical indication or a decline in eGFR \leq 6 ml/min/1.73m², whichever of these should occur first. 19

2. There is a substantially increased risk of mortality and cardiovascular events on the long (2 day) interdialytic interval.

Long Interdialytic Interval and Mortality among Patients Receiving Hemodialysis

Foley et al, NEJM; 2011

- 32,065 participants in the End-Stage Renal Disease Clinical Performance Measures Project, a nationally representative sample of U.S. patients receiving hemodialysis thrice weekly (2004 through 2007) were linked to USRDS data.
- Compared rates of death and cardiovascular-related hospital admissions on the day after the long (2-day) interdialytic interval with rates on other days.



Table 2. Annualized Mortality and Cardiovascular-Hospitalization Rates.

Event	% of Patients with Event	Rate per 100 Person-Yr (95% CI)				P Value
		Overall	Event Occurred on Day after 2-Day Interdialytic Interval			
			Yes	No		
Death						
All causes*	41.1	18.6 (18.3–18.9)	22.1 (21.2–23.0)	18.0 (17.7–18.4)	<0.001	
Cardiac cause	17.4	7.9 (7.7–8.1)	10.2 (9.6–10.8)	7.5 (7.3–7.7)	<0.001	
Vascular cause	2.7	1.2 (1.1–1.3)	1.2 (1.0–1.4)	1.2 (1.1–1.3)	0.9	
Infection	4.8	2.2 (2.1–2.3)	2.5 (2.2–2.9)	2.1 (2.0–2.2)	0.007	
Other cause	16.3	7.4 (7.2–7.6)	8.2 (7.6–8.7)	7.2 (7.0–7.5)	0.001	
Specific causes†						
Cardiac arrest	2.4	1.1 (1.0–1.1)	1.3 (1.1–1.6)	1.0 (0.9–1.1)	0.004	
Dialysis withdrawal	4.3	1.9 (1.8–2.1)	2.0 (1.7–2.3)	1.9 (1.8–2.1)	0.8	
Myocardial infarction	10.3	4.6 (4.5–4.8)	6.3 (5.8–6.8)	4.4 (4.2–4.5)	<0.001	
Septicemia	2.3	1.0 (0.9–1.1)	1.2 (1.0–1.4)	1.0 (0.9–1.1)	0.06	
Stroke	1.5	0.7 (0.6–0.8)	0.7 (0.6–0.9)	0.7 (0.6–0.8)	0.8	
Cardiovascular hospitalization						
Myocardial infarction	9.0	4.2 (4.1–4.4)	6.3 (5.9–6.9)	3.9 (3.7–4.0)	<0.001	
Congestive heart failure	33.1	18.8 (18.4–19.2)	29.9 (28.7–31.1)	16.9 (16.6–17.3)	<0.001	
Stroke	7.1	3.3 (3.2–3.5)	4.7 (4.3–5.1)	3.1 (3.0–3.3)	<0.001	
Dysrhythmia	25.9	13.6 (13.3–13.9)	20.9 (19.9–21.9)	11.0 (10.8–11.3)	<0.001	
Any cardiovascular event	45.8	28.8 (28.3–29.3)	44.2 (42.7–45.8)	19.7 (19.3–20.0)	<0.001	

3. Underdialysis increases hospitalization

The long and winding road of how much dialysis a person needs...

1. National Cooperative Dialysis Study
2. HEMO Study

Frequent dialysis RCTs - but we are not talking about this

Peritoneal dialysis dose - but we are not talking about this

National Cooperative Dialysis Study

Lowrie et al, NEJM 1981

- 151 chronic hemodialysis patients
- Randomized to
 - short (~3.25 hours) vs longer hemodialysis time (~4.5hours)
 - “low urea” vs “high urea” (predialysis midweek urea of ~110mg/dL)
- Follow-up 1 year
- Outcomes: mortality, hospitalization, early withdrawal

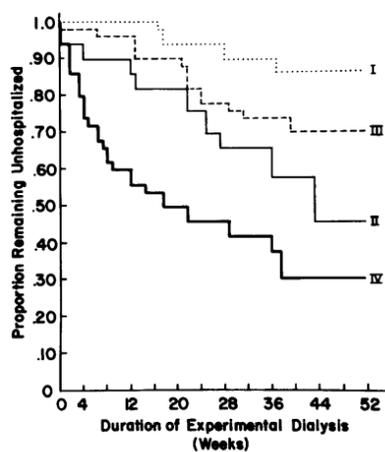


Figure 2. Proportion of Patients Remaining Non-Hospitalized as a Function of Time in the Four Study Groups. The proportion was lower in the high-BUN groups (II and IV) than in the low-BUN groups (I and III).

I: standard time / low urea
III: short time / low urea

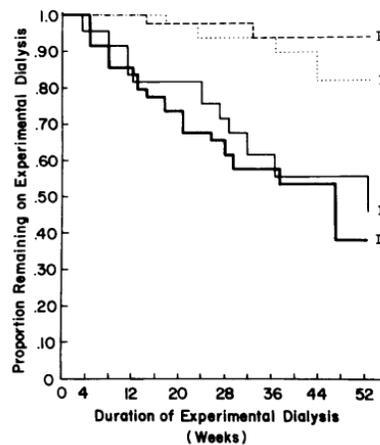


Figure 1. Proportion of Patients Not Withdrawn for Medical Reasons or Death as a Function of Time on Experimental Dialysis in the Four Study Groups.

Loss of patients from the high-BUN groups (II and IV) was greater than loss from the low-BUN groups (I and III). The

II: standard time / high urea
IV: short time / high urea

National Cooperative Dialysis Study

- Nearly half of the patients in the two “high urea” groups were removed from the study early due to uremic symptoms (anorexia, nausea, pericarditis, pleuritis), and significantly more were hospitalized (CHF).
- It has been estimated that the “high urea” groups had \sim Kt/V of 0.6-0.8.
- So we can conclude that some dialysis is truly required to keep hemodialysis patients well, and close attention to volume status is important.
 - At least in people with little residual kidney function



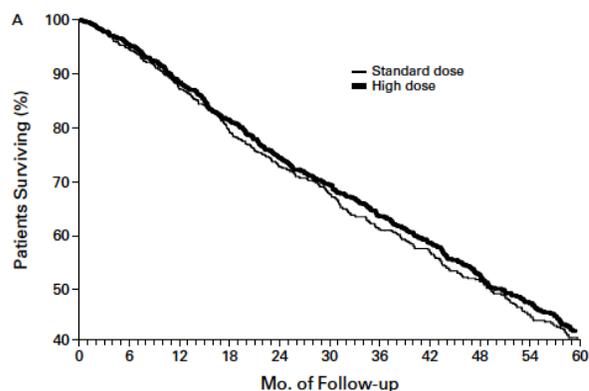
HEMO Study

Eknoyan et al, NEJM 2002

- 1846 chronic hemodialysis patients
- Randomized in a two by two factorial design to
 - standard (Single pool Kt/V 1.25) or high dose of dialysis (Kt/V 1.65); and
 - low-flux or high-flux dialyzer
- Follow-up 4.5 years
- Outcomes: All cause death (primary); quality of life



Impact on survival



No. AT RISK	0	6	12	18	24	30	36	42	48	54	60
Standard dose	854	759	630	524	451	382	315	253	197	149	
High dose	857	753	637	538	470	399	327	266	219	166	



HEMO study – Quality of life

Unruh et al, KI, 2004

Table 3. Effect of dose intervention on health-related quality of life domains^a

Domains	Year 1 BS effect (SE)	Year 2 BS effect (SE)	Year 3 BS effect (SE)	Average effect	P value
Index of Well-Being	0.07 (0.15)	0.31 (0.18)	0.04 (0.23)	0.14 (0.13)	<i>P</i> = 0.29
Physical functioning	0.12 (1.13)	4.33 (1.45)	1.91 (1.87)	2.12 (1.13)	<i>P</i> = 0.061
Role, physical	-1.89 (2.09)	4.72 (2.65)	3.68 (3.18)	2.17 (1.88)	<i>P</i> = 0.248
Bodily pain	3.13 (1.35)	6.21 (1.71)	4.14 (2.05)	4.49 (1.25)	<i>P</i> = 0.0003 ^b
General health	-0.11 (0.96)	2.51 (1.21)	0.22 (1.41)	0.87 (0.90)	<i>P</i> = 0.33
Vitality	0.68 (0.99)	3.07 (1.20)	0.84 (1.41)	1.53 (0.88)	<i>P</i> = 0.082
Social functioning	-0.15 (1.31)	3.15 (1.69)	-1.40 (2.08)	0.53 (1.19)	<i>P</i> = 0.65
Role, emotional	-3.41 (2.17)	2.67 (2.74)	2.28 (3.39)	0.51 (1.91)	<i>P</i> = 0.79
Mental health	-0.54 (0.90)	0.80 (1.14)	-1.29 (1.42)	-0.34 (0.84)	<i>P</i> = 0.68
Physical component summary score	0.19 (0.47)	2.03 (0.60)	1.46 (0.73)	1.23 (0.46)	<i>P</i> = 0.007^b
Mental component summary score	-0.48 (0.55)	0.71 (0.70)	-0.71 (0.86)	-0.16 (0.49)	<i>P</i> = 0.75
Symptom/problem	0.71 (0.59)	1.56 (0.71)	0.61 (0.88)	0.96 (0.54)	<i>P</i> = 0.077
Effects of kidney disease	-0.29 (0.87)	1.43 (1.10)	0.32 (1.31)	0.49 (0.82)	<i>P</i> = 0.55
Burden of kidney disease	-0.10 (1.26)	1.65 (1.56)	-2.80 (1.87)	-0.42 (1.17)	<i>P</i> = 0.72
Cognitive function	1.82 (0.90)	0.28 (1.13)	0.04 (1.36)	0.71 (0.83)	<i>P</i> = 0.39
Sleep	0.81 (1.00)	1.52 (1.35)	3.12 (1.52)	1.81 (0.95)	<i>P</i> = 0.057
Social support	-1.18 (1.00)	0.74 (1.25)	-0.55 (1.58)	-0.33 (0.92)	<i>P</i> = 0.72
Staff encouragement	0.11 (0.83)	2.89 (1.12)	1.21 (1.27)	1.40 (0.76)	<i>P</i> = 0.065
Patient satisfaction	-0.70 (0.98)	-0.95 (1.15)	-4.45 (1.48)	-2.04 (0.87)	<i>P</i> = 0.020

^aShown are estimated mean differences between high and standard dose groups adjusted for baseline covariates (age, albumin, icd, duration of dialysis, race, gender, diabetic status, and baseline quality of life) under the informative censoring model. Domains in **bold** were hypothesized to demonstrate effects by HEMO Committee

^bStatistically significant after adjustment for multiple comparisons.



HEMO Study

- No impact on mortality
- Statistically significant changes in physical composite summary scores
- Also noted reduction in pain score (not predicted in advance)
- Neither change was large enough to be “clinically detectable”



Guidelines on hemodialysis adequacy

Canadian Society of Nephrology Hemodialysis adequacy guidelines (2006):

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)



4. Over 70% of patients have lost their residual kidney function by one year

Over 70% of patients have lost their residual kidney function by one year

Residual kidney function is important

- Observational studies - strong and consistent association between higher levels of residual kidney function and better outcomes on PD
 - ?due to improved volume control, better BP control, and improved larger solute clearance (or healthier patient)
- Urinary volume and residual renal clearances of urea and creatinine both appear important

CANUSA study – a re-analysis

Bargman et al JASN 2001

- A prospective cohort study of 680 incident PD patients in 14 Canadian and US centers noting a significant association between adequacy and outcomes
 - specifically an increase of 0.1 unit of Kt/V (total (renal and peritoneal) solute clearance) per week was associated with a 5% decrease in the RR of death
- 1999 CSN guidelines recommended aiming for a weekly Kt/V of >2.0 based on the results of the CanUSA study – assuming an equivalence between clearance of small molecules by the native kidneys and by the peritoneal membrane.



CANUSA study: a re-analysis

Bargman et al JASN 2001

- For each 5 L/wk per 1.73 m² increment in GFR (residual kidney function), there was a 12% decrease in the relative risk (RR) of death (RR, 0.88; 95% confidence interval [CI], 0.83 to 0.94) but no association with peritoneal creatinine clearance (RR, 1.00; 95% CI, 0.90 to 1.10).
- With respect to urine volume, for a 250-ml (1 cup) increment in urine volume, there was a 36% decrease in the RR of death (RR, 0.64; 95% CI, 0.51 to 0.80).



CHOICE study:

- Prospective cohort study of 734 incident hemodialysis participants treated in 81 clinics; enrollment, 1995-1998, follow-up until December 2004
- Measured the impact of urine output, defined as producing at least 250 mL (1 cup) of urine daily, at baseline and year 1.
- 617/734 (84%) participants reported urine output at baseline and 163/579 (28%) at year 1.



CHOICE study:

- Baseline urine output was not associated with survival.
- Urine output at year 1, indicating preserved RKF, was independently associated with lower all-cause mortality (Hazard Ratio [HR], 0.70; 95% Confidence Interval [CI], 0.52-0.93; $p=0.02$) and a trend towards lower CVD mortality (HR, 0.69; 95% CI, 0.45-1.05; $p=0.09$).
 - Strongest association was noted comparing those with residual urine output at one year, compared to those who had lost urine output



4. Over 70% of patients have lost their residual kidney function by one year

- Measuring residual kidney function is not routinely done
- Measuring uremic symptoms is not routinely done
 - Though these are very important to patients



5. Start with the hemodialysis frequency they will need in the long run

Start with the hemodialysis frequency they will need in the long run

- Uremic symptoms are subjective
- People don't like change
- (it is reasonable to try to maintain residual kidney function)



Overview

1. If you don't need dialysis, then twice weekly hemodialysis is fine
2. There is a substantially increased risk of mortality and cardiovascular events on the long (2 day) interdialytic interval
3. Underdialysis increases hospitalization
4. Over 70% of patients have lost their residual kidney function by one year
5. Start with the hemodialysis frequency they will need in the long run



Recommendation

Don't start dialysis until the patient has a clinical indication:

- Fluid overload
- Symptoms of uremia
- Refractory hyperkalemia or acidemia
- Other conditions or symptoms likely to be ameliorated by dialysis



Recommendation

Until clinical trials show that twice weekly HD is superior (or equivalent to thrice weekly HD), stay with standard of care

Ensure the studies measure symptoms that are important to patients



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