Nocturnal Hemodialysis: A new *sexy* dialysis treatment and implications for pharmacists

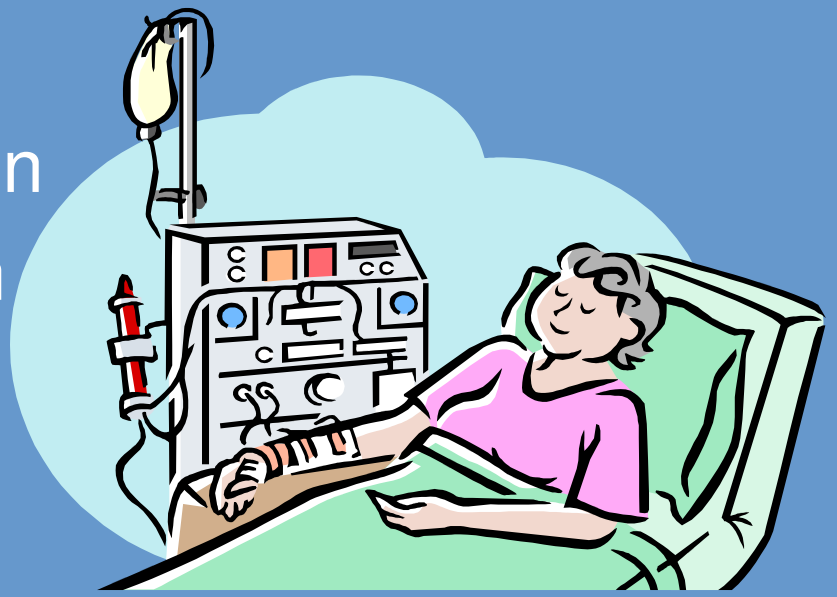
Marisa Battistella, Pharm D
Clinical Pharmacist - Hemodialysis
University Health Network, Toronto General Hospital

Objectives

1. Compare and Contrast the different modes of Hemodialysis: conventional vs nocturnal
2. Outline how ESRD affects the different organ systems.
3. Describe the impact of Nocturnal Hemodialysis on the different organ systems
4. Discuss the implications of Nocturnal Hemodialysis on medication use and the implications for pharmacists.

Nocturnal home hemodialysis (NHD)

- Form of home hemodialysis
  - Done by patient or partner
- Occurs 5-6 times/week for 8 hours at night during sleep
- Low pump speeds
  - Blood flow at 300mL/min
  - Dialysate at 300mL/min



Comparison of NHD vs CHD

Nocturnal HD

- 5 - 6 sessions / week
- 8 hrs / treatment
- 3 x normal dialysis dose
- Enhanced middle molecule clearance
- Moderate fluctuations in volume and biochemical status

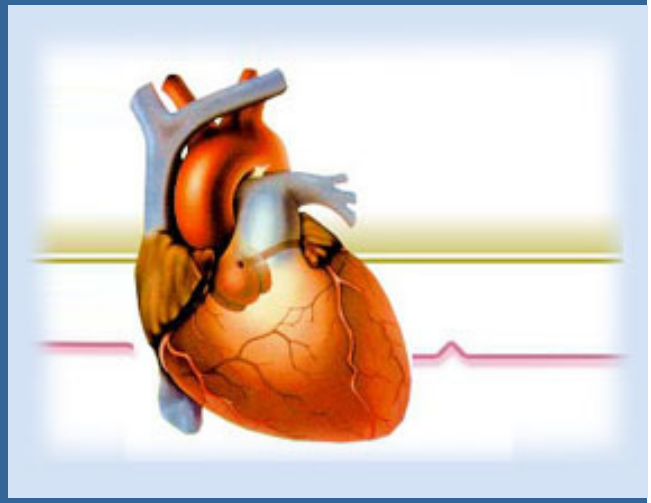
Conventional HD

- 3 sessions / week
- 3 – 4 hrs / treatment
- Less solute clearance
- Less middle molecule clearance
- Large fluctuations in volume and biochemical status

ESRD affects every organ system!

- CVS (leading cause of death)
  - Hypertension – abnormal LV geometry and function
  - Autonomic dysfunction
  - Elevated arterial stiffness – impaired vascular responsiveness
  - PTH/Ca/Pi
  - Inflammation
- Anemia
- Endocrinopathies
  - Vitamin D
  - Lipid
  - Bone/Osteoporosis
  - Reproduction
- Social
  - Cognition
  - Mortality

Cardiovascular System



Impact of long term NHD on LVMI, blood pressure, and anti-hypertensive therapy

Measurements	CHD (n=13)		NHD (n=28)	
	Initial	Final	Initial	Final
LVMI (g/m^2)	142 ± 33	150 ±56	147 ± 42	114 ± 40*
SBP (mmHg)	136 ± 25	131 ± 20	146 ± 20	122 ±13*
DBP (mmHg)	82 ± 13	80 ± 15	84 ± 15	74 ± 12*
PP (mmHg)	54 ± 22	51 ± 17	61 ± 12	49 ± 12*
Anti-BP Meds	1.5	1.5	1.8	0.3*

* $p < 0.05$

Chan CT et al, *KI 2002;* 61:2235-2239.

Effect of Frequent Nocturnal Hemodialysis vs Conventional Hemodialysis on LV mass and QoL

Table 2. Outcomes for LV Mass, Blood Pressure, Anemia, and Mineral Metabolism[a]

Characteristic	Nocturnal Hemodialysis[b] (n = 26)	Conventional Hemodialysis[b] (n = 25)
LV mass, mean (SD), g		
Baseline	177.4 (51.1)	181.5 (92.3)
Exit	163.6 (45.2)	183.0 (84.2)
Change	−13.8 (23.0)	1.5 (24.0)
LV mass, mean (SD), g/m^2		
Baseline	92.4 (26.6)	101.8 (50.6)
Exit	85.3 (23.2)	102.8 (46.1)
Change	−7.1 (12.4)	1.0 (14.1)
Blood pressure, mean (SD), mm Hg		
Systolic		
Baseline	129 (23)	135 (19)
Exit	122 (23)	139 (20)
Change	−7 (29)	4 (17)
Diastolic		
Baseline	75 (14)	77 (16)
Exit	68 (16)	75 (12)
Change	−7 (16)	−2 (12)

Culleton et al. JAMA 2007;298:1291-1299

Vascular effects of NHD

	CHD	NHD 1 month	NHD 2 months
Resting SBP, mmHg	140±5	124±3*	119±3*
Resting DBP, mmHg	82±3	75±3*	71±3*
CO, L/min	4.9±0.4	5.3±0.4	5.5±0.5
Stroke Vol, mL	63±5	64±5	68±6
HR, beats/min	78±3	75±3	80±1
TPR, dyne-s-cm5	1967±235	1647±185*	1499±191*
Change in BP Meds (per pt)	2.5	0.6*	0.2*

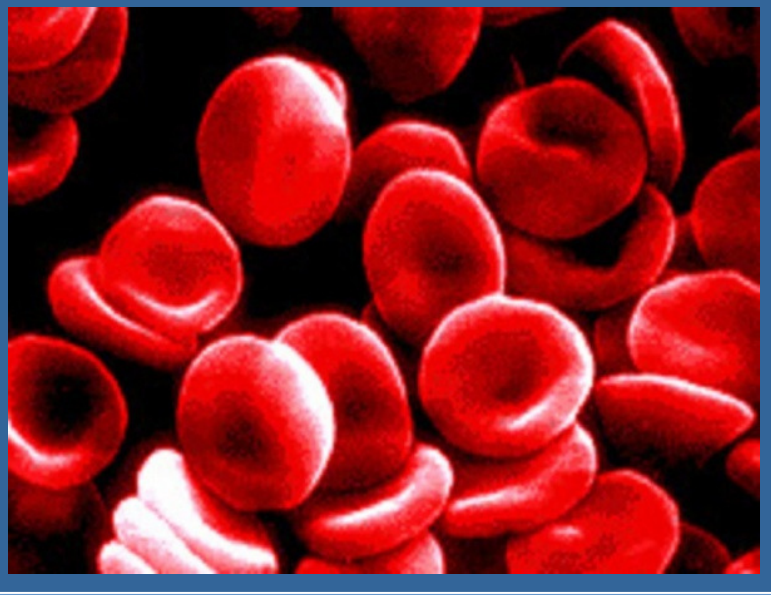
Chan et al Hypertension 2003;42(5):925-31

*p< 0.05

What about Cardio-Protection?

- The question remains for the patient with previous cardiac history- i.e Previous MI?
- Do we keep him on ACE/ARB, BB etc??

Anemia



Impact of NHD on EPO responsiveness

	Initial (CHD)	6 mos	12 mos	p
NHD				
Hb (g/L)	115 ± 2.3	122 ± 2.5	124 ± 2.3*	0.03
EPO dose (u/week)	10,400 ± 1400	8500 ± 1300	7600 ± 1100	0.03
EPO free (%)	19	24	24*	NS
CHD				
Hb (g/L)	110 ± 2.2	115 ± 2.7	115 ± 2.2	NS
EPO dose (u/week)	8300 ± 1100	8100 ± 1300	8600 ± 1000	NS
EPO free (%)	13	13	9.4	NS

Schwartz et al, Clin Nephro 2005;63:202-208

Inflammation and NHD

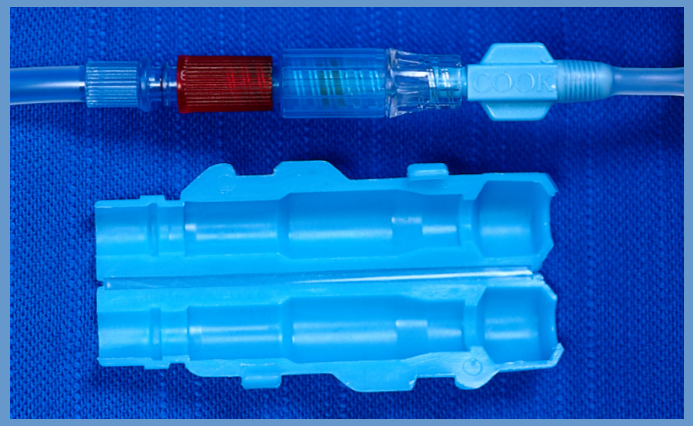
Variables	CHD (n=14)	NHD (n = 14)
Hb (g/L)	120 ± 4	124 ± 4
Ferritin (ng/ml)	482 ± 73	413 ± 123
EPO dose (u/wk)	11, 643 ± 1258	6877 ± 1482 ($p<.05$)
hsCRP (mg/L)	8.4 ± 1.8	4.6 ± 1.3
IL – 6 (pg/ml)	6.5 ± 0.8	3.9 ± 0.7 ($p<.05$)

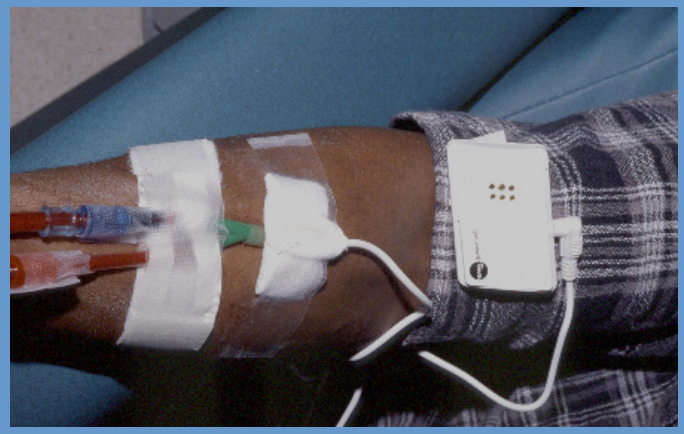
Yuen et al ASAIO J 2005;51:236-241

Vascular Access

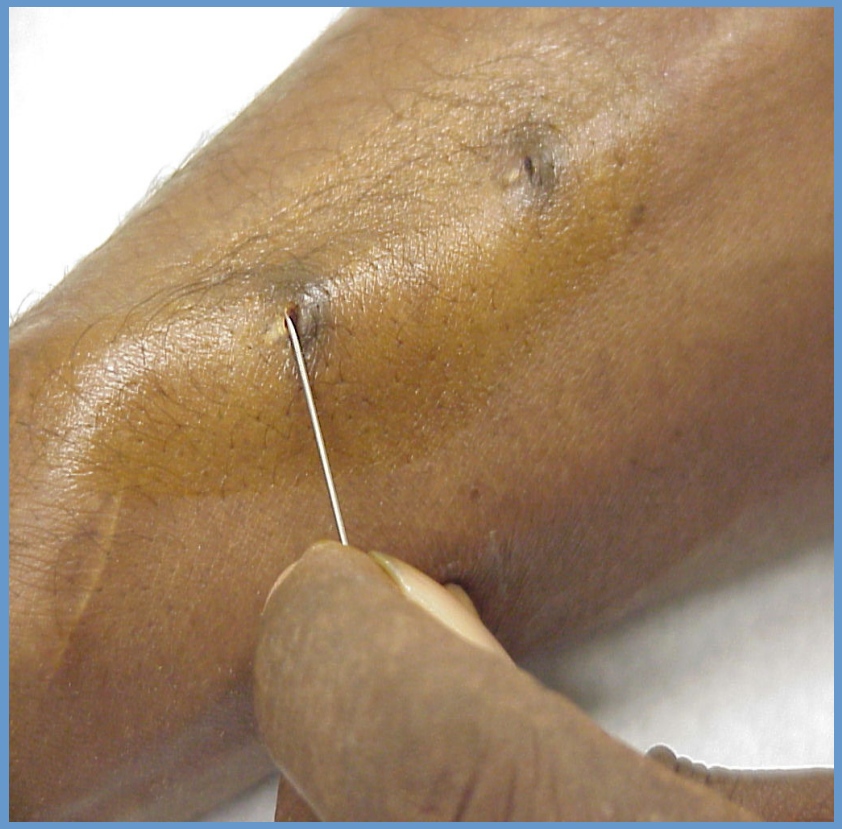
Vascular access

- Central Venous Catheter –
  - Approximately 40% of patients
- AV fistulas / grafts
  - Approximately 60%
  - Buttonhole technique
  - Dual or single needle system
  - Requires
    - InterLink® system
    - Locking boxes
    - ‘Enuresis alarm’ to detect blood leaks
  - ‘Live’ remote monitoring optional
- Heparin – as usual
- EMLA® has been helpful





Buttonhole Technique



Vascular Access - CVC

Table 3 | CVC complications before and after conversion to NHD

Event rate/1000 CVCD	CHD	NHD	$P_{CHD:NHD}$
Infection			
Catheter-related bacteremia			
(i) True	1.08	1.88	0.33
(ii) Suspected	0.22	0.21	0.98
(iii) Exit/tunnel site (true)	0.43	0.21	0.6
(iv) Total	1.73	2.29	0.55
r-TPA administration	4.32	4.38	0.97
CVC-related hospitalization	0	0.42	0.26
Adverse terminal events			
(i) Owing to infection	0.65	1.67	0.16
(ii) Owing to poor flow	4.32	0.42	<0.0001
(iii) Owing to catheter malposition/ cracked hardware	0.65	0.83	0.76
(iv) Unknown	0.22	0	0.49
(v) Total	5.84	2.92	0.03

CHD, coronary heart disease; CVC, central venous catheter; NHD, nocturnal hemodialysis; r-TPA, recombinant tissue plasminogen activator.

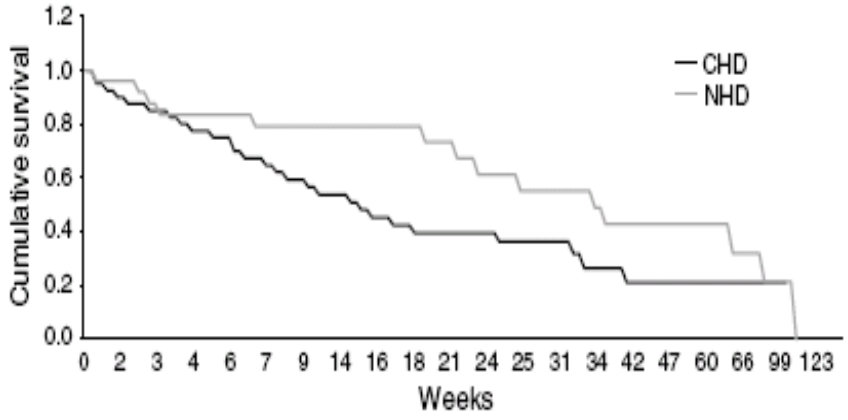


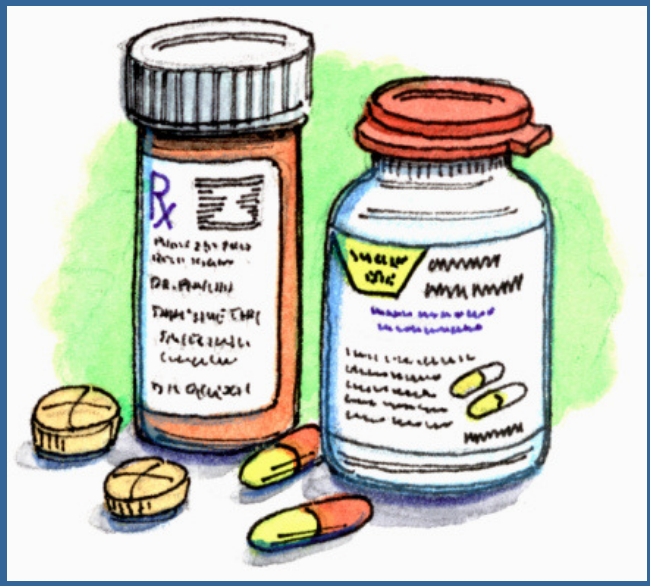
Figure 1 | Catheter survival in CHD and NHD. Time (weeks from catheter insertion). Cumulative patency is shown comparing catheters used for CHD (solid black line) vs those used during NHD (faint gray line). Cumulative survival was superior in NHD catheters as compared to CHD catheters ($P = 0.03$).

Perl et al, Kidney Int, 70:1348, 2006

Access

- What is the best AV access to be used at the home?
- Data → inconclusive
- Buttonhole → used with care/caution
- Stepwise approach

Dosing of Medications



Drug Dosing in SDHD or NHD

- Very little in the literature with respect to dosing of drugs in daily dialysis
- Dialyzers (pore size, SA) are similar in daily dialysis to IHD
- What is Different?
  - Blood flow rates
  - Dialysate Flow rates
  - Frequency of Dialysis
  - Duration of Dialysis

Solute clearance in dialysis

	Small Solute Clearance	Large Solute Clearance
Increasing frequency	↑	— SDHD
Increasing time	↑	↑
Time and Frequency	↑ ↑	↑ NHD

Use of Antibiotics

- One PCK study in Slow Daily Home Hemodialysis
- Gentamicin: 0.6mg/kg immediately upon completion of hemodialysis session
- 17 blood samples drawn in 8 pts
- Blood flow rate: 200ml/min and dialysate flow rates at 300ml/min
- F50 dialysis filter used

Manley et al. KI 2003;63: 1072-1078

Gentamicin in Slow Daily Dialysis

Table 2. Gentamicin volume of distribution, elimination rate constants, and corresponding half-lives on and off hemodialysis

Patient	K_{HD} h^{-1}	$t_{1/2}$ HD h	K_{ID} h^{-1}	$t_{1/2}$ ID h	Vd L/kg
A	0.15	4.6	0.03	26.8	0.24
B	0.23	3.0	0.03	23.6	0.25
C	0.16	4.5	0.05	15.1	0.25
D	0.20	3.5	0.06	12.3	0.29
E	0.14	4.9	0.03	22.9	0.24
F	0.26	2.6	0.03	21.6	0.36
G	0.19	3.8	0.03	21.4	0.32
H	0.23	3.0	0.04	19.8	0.31
Mean	0.19	3.7	0.04	20.4	0.28
SD	0.04	0.8	0.01	4.7	0.05

Abbreviations are: k_{el}, serum elimination rate; $t_{1/2}$, half-life; Vd, volume of distribution; HD, intradialytic; ID, interdialytic.

Manley et al. KI 2003;63: 1072-1078

70.5% + 19.3% of administered dose was removed by dialysis

Gentamicin in Slow Daily Dialysis

Table 4. Model predicted gentamicin serum concentrations in a 70 kg individual undergoing typical slow daily home hemodialysis

	Gentamicin 2 mg/kg	Gentamicin 2.5 mg/kg
	Serum concentration $\mu g/mL$	
After infusion	6.0	7.5
Prior to hemodialysis	3.0	3.7
After hemodialysis	0.7	0.8
Prior to next dose	0.7	0.8

Few limitations:

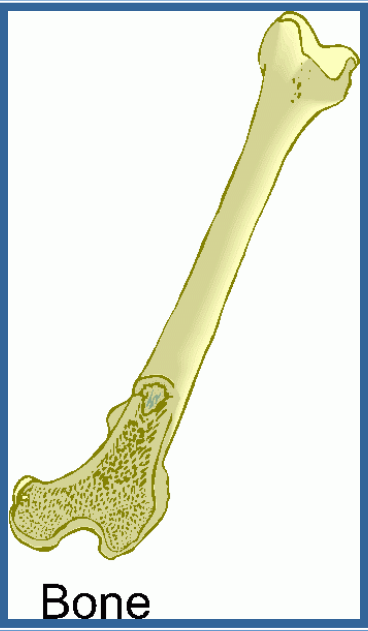
- Single dose study: ie. not at steady state
- SA of dialyzer was smaller

Manley et al. KI 2003;63: 1072-1078

What do we do?

- Gentamicin/Tobramycin 1-1.5mg/kg dose at the end of every 2nd HD session or every HD but have never really used longer than 2-3 doses
- Vancomycin 1g at the end of every 2nd HD session or every HD - will do levels.
- Ancef 1-2g at the end of every HD session

Bone Metabolism



Control of Serum Phosphate

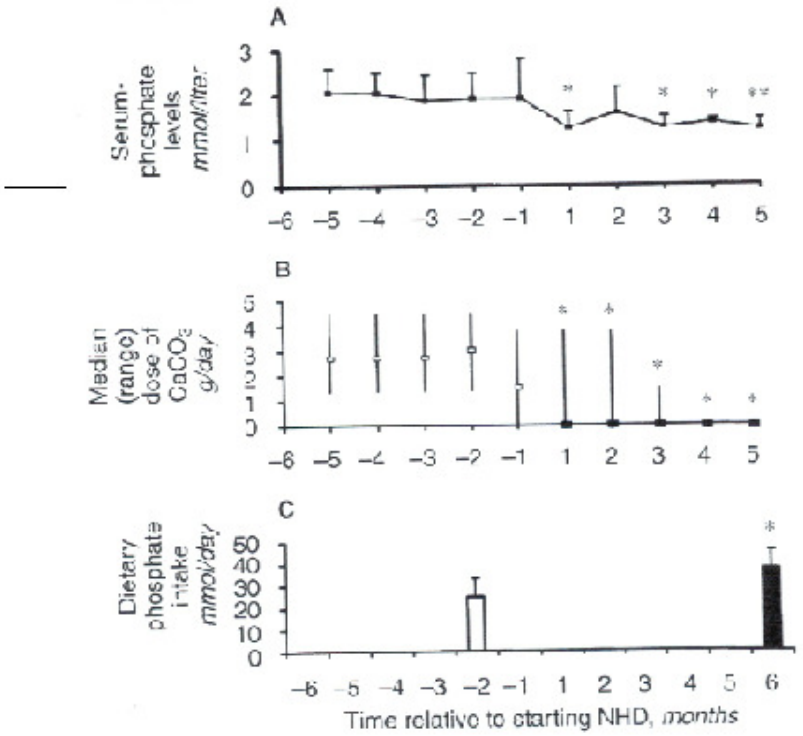


Fig. 3. Serum phosphate, dose of calcium carbonate and dietary phosphate intake during conventional hemodialysis (CHD; □) versus nocturnal hemodialysis (NHD; ■). (*A*) Serum phosphate levels as measured monthly. (*B*) Daily oral dose of calcium carbonate as phosphate binder. Values are median and range as data distribution not normal. (*C*) Dietary phosphate intake. Values are mean ± SD, $N = 7$. $^{*}P < 0.05$; $^{**}P < 0.01$ as compared to month −5. (*Note.* To convert mM to mg/dl for PO_4 multiply values by 3.096.)

Mucsi et al. KI 1998;53:1399-1404

How much Fleet ® or P tablets?

- 1.748mmol of Phosphorous in Fleet® enema
- So 90 ml of Fleet® = 157.32mmol of Phosphorous

- If you add 90 ml to 5L bath then really adding 157.32 mmol of Phosphorous to 5L bath = a Phosphorous concentration of 31.46mmol/L

- With a 1:45 dilution (31.36/45) we get a final concentration of 0.70mmol/L of Phosphorous.

How much Fleet ® or P tablets?

- 16 mmol of Phosphorous in one Phosphate Novartis® Tablet
- So 10 tabs = 160 mmol of Phosphorous

- If you add 10 tabs to 5L bath then really adding 160 mmol of Phosphorous to 5L bath = a Phosphorous concentration of 32 mmol/L

- With a 1:45 dilution (32/45) we get a final concentration of 0.71mmol/L of Phosphorous.

Coronary Calcification Progression

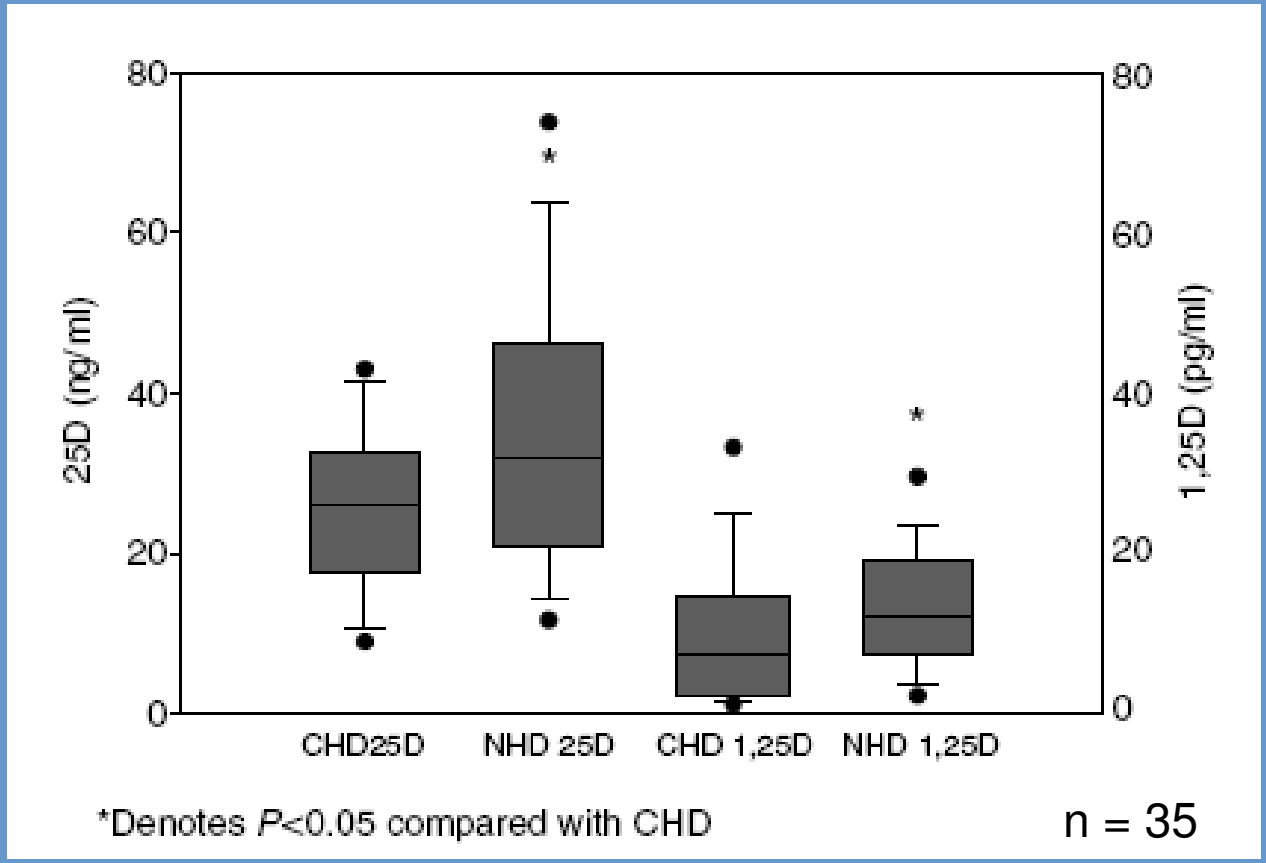
Table 1. Changes in CACS before and after conversion to NHD ($n=38$)

Variables	All Patients	Baseline CACS ≤10	Baseline CACS >10
Mean baseline CACS (range)	691 ± 295 (0–8217)	0.7 ± 0.5 (0–10)	1874 ± 697 (112–8217)
Mean follow-up CACS (range)	765 ± 316 (0 to 8356)	6 ± 4 (0–71)	2066 ± 739 (179–8356)
ΔCACS per year	64 ± 38	5 ± 3	164 ± 98
1 year standardized CACS[a]	755 ± 315	6 ± 3	2038 ± 740
Percentage change in CACS over 1 year	9%	762%	9%

Results are expressed as mean ± SEM, median (range).
[a]1 year standardized CACS refers to the change in CACS adjusted for a 1 year interval assuming a linear rate of CACS change (see Methods section).

Yuen et al. NDT 2006;21:1407-1412

Vitamin D levels before and after conversion to NHD



Nessim et al. KI 2007;71:1172-1176

Quality of Life

QoL & Illness Intrusiveness in PD vs NHD

Table 1. Baseline patient characteristics[a]

Variable	NHD	PD	*P*
Age (yr; mean ± SD)	49 ± 12	61 ± 13	<0.01
Male (%)	67	55	0.28
Race (%)			0.16
white	73	52	
black	6	16	
Asian	9	28	
other	12	4	
Highest education level (%)			0.051
elementary school	0	14	
high school	28	30	
college/undergraduate	53	43	
postgraduate	19	13	
Previous kidney transplant (%)	31	14	0.08
Living alone (%)	25	18	0.41
Charlson Index (mean ± SD)	1.14 ± 0.25	1.82 ± 0.33	0.14
Years of renal replacement (yr; mean ± SD)	10.8 ± 1.7	7.6 ± 1.0	0.10

[a]NHD, nocturnal home hemodialysis; PD, peritoneal dialysis.

Fong et al. CJASN 2007;2:1195-1200

QoL & Illness Intrusiveness in PD vs NHD

Table 2. Comparisons of biochemical indices between NHD and PD patients

Variable	NHD	PD	*P*
Plasma creatinine (μ mol/L)	503 ± 34	800 ± 43	<0.001
Hemoglobin concentration (g/L)	124 ± 2	117 ± 2	0.026
Plasma urea (mmol/L)	11.7 ± 1.0	18.4 ± 0.8	<0.001
Plasma calcium (mmol/L)	2.41 ± 0.03	2.27 ± 0.30	0.002
Plasma phosphate (mmol/L)	1.11 ± 0.06	1.63 ± 0.07	<0.001
Plasma albumin (g/L)	39 ± 2	37 ± 2	<0.001

Fong et al. CJASN 2007;2:1195-1200

QoL & Illness Intrusiveness in PD vs NHD

Table 3. Comparisons of KDQOL values between NHD and PD patients

Variable	NHD	PD	*P*
Symptom problem list	76.3 ± 2.5	71.9 ± 2.6	0.22
Effect of kidney disease	61.5 ± 3.7	60.7 ± 2.7	0.85
Burden of kidney disease	37.0 ± 4.4	47.0 ± 3.8	0.092
Work status	48.6 ± 7.6	36.0 ± 5.4	0.17
Cognitive function	75.6 ± 4.8	81.4 ± 2.2	0.27
Quality of social interaction	73.5 ± 3.0	75.8 ± 2.3	0.55
Sexual function	81.7 ± 5.4	61.8 ± 9.0	0.07
Sleep	52.8 ± 3.9	54.1 ± 2.7	0.79
Social support	65.7 ± 5.3	79.2 ± 2.8	0.027
Dialysis staff encouragement	89.2 ± 2.6	85.7 ± 2.8	0.37
Patient satisfaction	75.5 ± 4.3	79.2 ± 2.7	0.46

Fong et al. CJASN 2007;2:1195-1200

QoL & Illness Intrusiveness in PD vs NHD

Table 4. Comparisons of illness intrusiveness score between NHD and PD patients

Variable	NHD	PD	*P*
Physical well-being and diet	3.81 ± 0.3	3.98 ± 0.20	0.65
Work and finance	3.77 ± 0.35	3.30 ± 1.64	0.27
Marital, sexual, and family relations	3.32 ± 0.31	2.78 ± 0.22	0.16
Recreation and social relations	3.23 ± 0.28	3.11 ± 0.18	0.72
Other aspects of life	2.46 ± 0.25	2.47 ± 0.20	0.96

Fong et al. CJASN 2007;2:1195-1200

Cost Utility of Home NHD vs Conventional HD

Table 3. Summary of costs[a]

	Mean annual cost				
	Quality of Life study subgroup			Full-study group	
	IHD	HNHD	*P* value[b]	IHD	HNHD
Number	19	24		23	33
Staff	$22,005	$10,938	<0.01	$22,056	$10,932
Direct hemodialysis materials	$ 6,413	$16,669	<0.01	$ 6,575	$16,587
Medications	$11,546	$ 8,150	0.11	$12,029	$ 8,989
Overhead and support	$12,365	$ 4,181	<0.01	$12,393	$ 4,178
Physician fees	$ 6,650	$ 6,650	1.00	$ 6,650	$ 6,650
Admissions and procedures	$ 5,271	$ 818	0.09	$ 6,997	$ 1,173
Depreciation	$ 871	$ 6,139	<0.01	$ 871	$ 6,139
Lab tests and imaging	$ 1,246	$ 1,594	0.04	$ 1,364	$ 1,744
Total	$66,367	$55,139	0.03	$68,935	$56,394

Abbreviations are: IHD, in-center hemodialysis; HNHD, home nocturnal home dialysis.
[a]All costs expressed in year 2000 Canadian dollars
[b]*P* value for comparison of IHD quality of life subgroup to HNHD quality-of-life subgroup

McFarlane et al: KI 2003:1004 – 1011

Pregnancy

Successful Pregnancies on NHD

Table 1. Pregnancy outcomes[a]

	Number of Weeks at Delivery	Mode of Delivery	Baby's Birth Weight (g)	Baby's APGAR Scores at 1 and 5 min
Patient 1	36	C/S	2020	9/9
Patient 2: Pregnancy 1	38	SVD	3000	5/8
Patient 2: Pregnancy 2	37^{4}	SVD	2785	9/9
Patient 3	36^{5}	Induced labor, vacuum extraction	2690	6/9
Patient 4	38^{5}	C/S	2750	8/9
Patient 5	30	SVD	1260	5/7

[a]C/S, cesarean section; SVD, spontaneous vaginal delivery. Superscript numerals indicate days.

Barua et al. CJASN 2008;3:392-396

Vitamins and Pregnancy

- Folate recommended from ~1-2 mg daily
- 1 mg folic acid in Materna
- 1 mg x 2 tabs Replavite daily = 2 mg
- Total folic acid = 3 mg daily

- Some women took additional folic acid

Stover J et al. Adv Chronic Kidney Dis. 2007 Apr;14(2):212-4.
Reddy SS et al. Adv Chronic Kidney Dis. 2007 Apr;14(2):146-55.

Mortality Data

Survival among NHD Patients

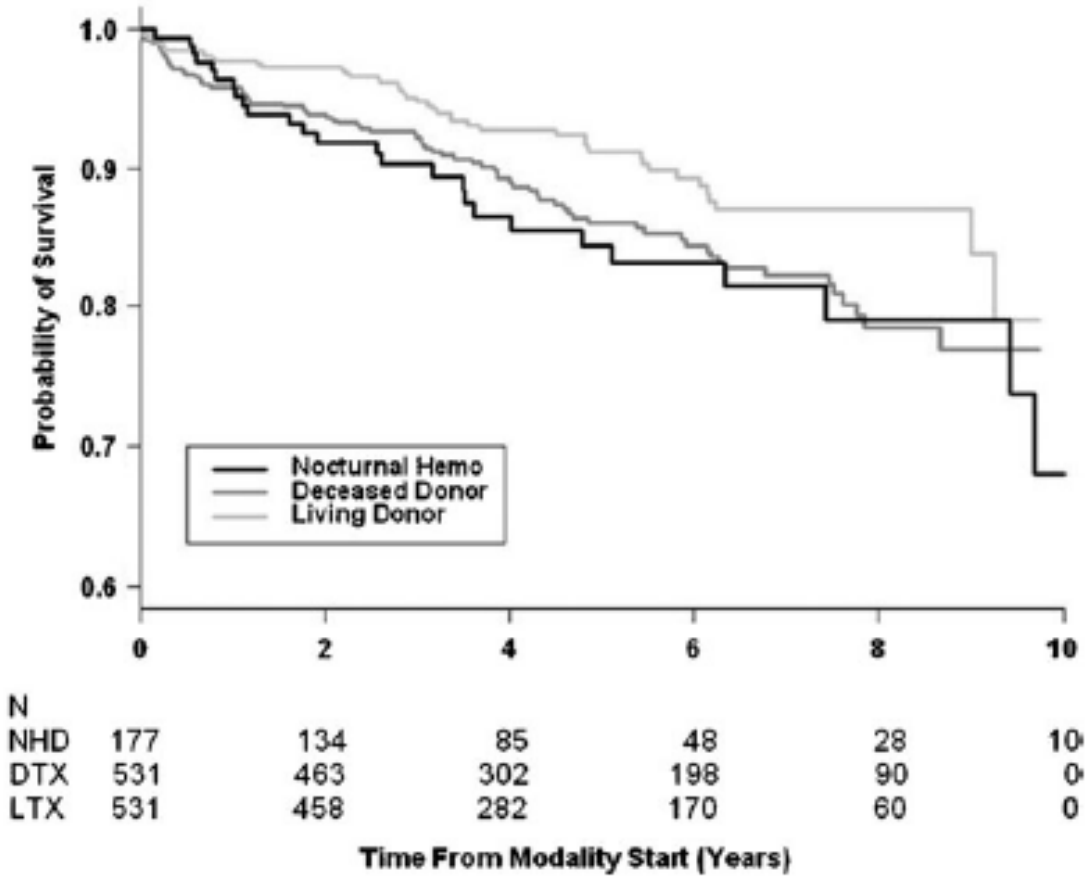


Fig. 1. Time to death in patients treated with nocturnal haemodialysis, deceased and living donor kidney transplantation (log-rank test, $P = 0.03$).

Pauly et al NDT 2009;24:2915-2919

So what is pharmacy's role?

Medication Reconciliation

- Patients are seen during training sessions (6-8 weeks)
- Patients are seen in a multidisclipinary clinic- about q2-3 months
- DRUG COVERAGE
  - EAP (formerly Section 8 program)
  - Compassionate use of medications
- Dosing of Drugs
  - antibiotics

CQI for the NHD Program

- Development of CQI indicators
  - Meet quarterly
- Development of RN dispensing policy- Delegated Controlled Act
  - Antibiotics-cefazolin, tobra, vanco
  - Sodium citrate/heparin
  - Calcium polystyrene
  - Iron

Summary

- NHD Patients have decreased Uremic signs and symptoms
- NHD patients are on very few medications
- Pharmacy's role is unique
- Multidisciplinary care is fundamental