BC KIDNEY DAYS

Hosted by BC Transplant and the BC Renal Agency

2015

Hemodiafiltration in BC
Current Status and Obstacles

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OUTLINE

What

Why

How

Why Not

What Now

No financial disclosures.

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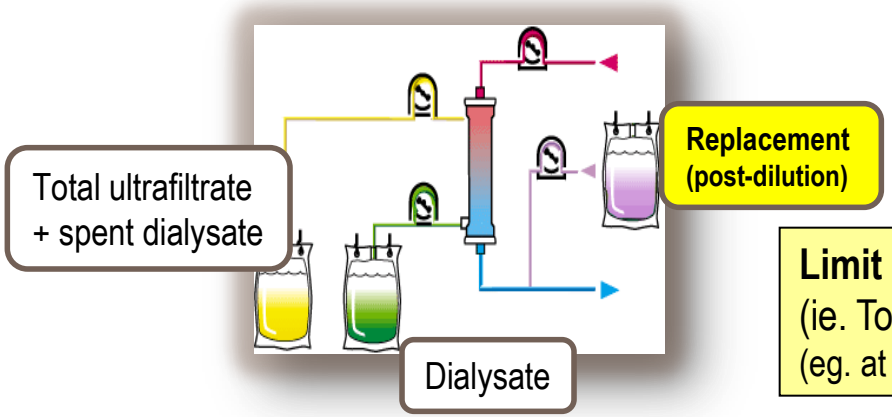
HDF = HD and High volume ULTRAFILTRATION to achieve convective clearance



Limit Filtration Fraction to <25%
(ie. Total UF rate <25% of blood flow rate)
(eg. at 400ml/min = 100ml/min = 24L of UF)

ADVANTAGES OF POST-DILUTION
Does not dilute concentration gradients, so does not decrease clearance efficiency
DISADVANTAGES OF POST-DILUTION
Leads to hemoconcentration within filter (risk of filter clotting)
May change heparin requirements

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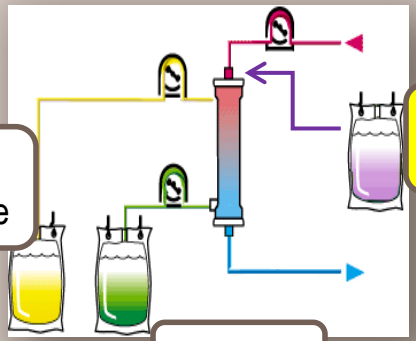
HDF = HD and High volume ULTRAFILTRATION to achieve convective clearance



To compensate, need to use 2x amount of post-dilution replacement fluid

ADVANTAGES
Lower risk of filter clotting
DISADVANTAGES
Dilution of blood pre-filter reduces concentration gradients for clearance
Increases filter TMP

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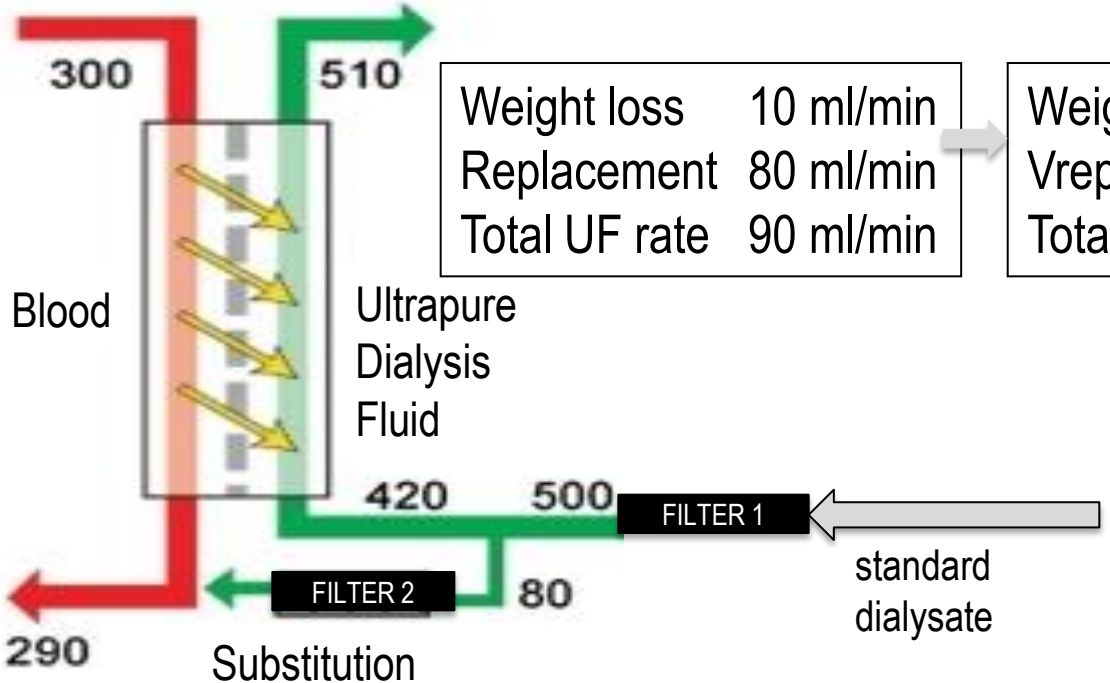
HDF CIRCUIT



Weight loss	10 ml/min
Replacement	80 ml/min
Total UF rate	90 ml/min

In 4 hour run

Weight loss	2.4L
Vrep	19.2L
Total UF (conv)	21.6L

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WHY

- Challenges with removal of NON-small solutes on HD
- Added convective clearance → Increased middle / large molecule removal
- Hope that this lessens these burdens:
  - Cardiovascular
  - Inflammatory
  - Uremic
- By extension, hope that decreases:
  - Morbidity
  - Mortality

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CURRENT STATE OF AFFAIRS

- There is **no conclusive evidence** that prescribing HDF for any patient will make them live longer

- There are **potential benefits** of HDF therapy
  - These benefits may be confounded by
    - Use of ultra-pure dialysate
    - Avoidance of intradialytic compromise
    - Patient selection bias
  - These benefits are likely “dose” dependent

- Implementation of HDF has logistic challenges

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INTRADIALYTIC STABILITY

- **Major RCT: Italian Convective Study 2010**
  - 146 prevalent HD patients randomized to
    - Ongoing HD
    - HF or HDF
  - 2 year follow-up
  - HDF significantly reduced intradialytic hypotension

- **Systematic review AJKD 2014**
  - 6 trials using HDF
  - Overall risk reduction for IDH 0.49 (0.30 – 0.81)

Hemodynamic stablization presumed due to thermal cooling and mild sodium load

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UREMIA AND INFLAMMATION

- MANY observational studies demonstrate better middle molecule clearance
  - Inflammatory markers
  - Phosphate
  - Protein-bound solutes
- Conflicting results regarding direct clinical outcomes
  - Anemia
  - Phosphate control
  - Clinically assessed inflammation
  - Nutritional status
- No good data on impact on dialysis related symptomatology and QoL

Unclear whether middle molecule clearance translates to direct clinical outcomes

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MORTALITY

- **Observational Data**
  - DOPPS
  - RISCAVID (Italy)
  - EuCLID (Chech R, Hungary, Italy, UK)
  - UK STUDY

Very promising

- **3 Major RCTs**
  - CONTRAST (Netherlands + Montreal)
  - TURKISH-HDF (Turkey)
  - ESHOL (Spain)

Mixed results
Lots of focus on post-hoc analysis

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MAJOR OBSERVATIONAL DATA: MORTALITY

STUDY	PATIENTS	STUDY DESIGN	HDF MODE	F/U	MORTALITY OUTCOMES
DOPPS (2006)	2165 prevalent HD	Retrospective	High (15-25L) vs low (5-15L)	3 Yr	**35% reduction**
EuCLID (2006)	2564 prevalent HD	Retrospective	Online-HDF	3Yr	**35% reduction**
RISCAVID (2008)	757 prevalent HD	Prospective	Bag-HDF (~14L) vs Online-HDF (~23L)	3Yr	**Mortality RR 0.78** (also lower IL-6 levels)
UK STUDY (2009)	858 incident HD	Retrospective	HDF (~15L)	18Yr	**Mortality HR 0.45** (also less IDH and lower inflammatory markers)

Signal that High volume HDF did better

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RCTs: Prevalent HD pts randomized to HD vs HDF

STUDY	PTS	F/U	HDF V_{rep} TARGET	HDF V_{rep} ACHIEVED	OUTCOMES
CONTRAST	714	3 Yr	20L	• Only 1/3 reached 20L • Range 13-23L	• **No difference mortality** • R… …f V_{rep}
TURKISH HDF	7…				…ence IDH, hosp rates • Post-hoc: mortality benefit if V_{rep} >17.4L

ESHOL	9…				• **30% reduction in mortality**
					• Post-hoc analysis:
					  • 40% RR if V_{rep} >22L
					  • 45% RR if V_{rep} >25L

Caveats:
- 40 pts in HDF terminated early due to vascular access
- Used UDP in HDF, but not HD group

Noteworthy:
- Both used UPD
- Qb higher 387 ml/min
- Longer duration (236min)

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RCT: ESHOL

PRIMARY OUTCOME: MORTALITY

	Hemodialysis Group (*n*=450) (867.3 patient-years at risk)		OL-HDF Group (*n*=456) (863.1 patient-years at risk)		HR (95% CI)	*P*[a]
	Events	Events/100 Patient-Years	Events	Events/100 Patient-Years		
Death from any cause	122	14.1	85	9.8	0.70 (0.53–0.92)	0.01
Cardiovascular cause	55	6.3	37	4.3	0.67 (0.44–1.02)	0.06
Heart failure	10	1.2	7	0.8	0.69 (0.26–1.82)	0.46
Ischemic heart disease	15	1.7	14	1.6	0.93 (0.45–1.94)	0.86
Mesenteric thrombosis	6	0.7	5	0.6	0.84 (0.26–2.77)	0.78
Stroke	18	2.1	7	0.8	0.39 (0.16–0.93)	0.03
Dysrhythmia	5	0.6	3	0.3	0.59 (0.14–2.47)	0.46
Peripheral arteriopathy	1	0.0	1	0.0	0.97 (0.06–15.48)	0.98
Infection	22	2.5	10	1.2	0.45 (0.21–0.96)	0.03
Tumor	6	0.7	10	1.2	1.67 (0.61–4.59)	0.32
Sudden death	14	1.6	14	1.6	0.99 (0.47–2.08)	0.98
Cachexia	8	0.9	4	0.5	0.51 (0.15–1.70)	0.27
Death from other causes	17	2.0	10	1.2	0.59 (0.27–1.28)	0.18

Mortality benefit largely driven by infection and stroke

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RCT: ESHOL

OTHER OUTCOMES: HOSPITALIZATIONS AND INTRA-DIALYSIS SYMPTOMS

	Hemodialysis Group (*n*=450) (867.3 Patient-Years at Risk)		OL-HDF Group (*n*=456) (863.1 Patient-Years at Risk)		Rate Ratio (95% CI)	*P*[a]
	No. of Events	No. of Events/100 Patient-Years	No. of Events	No. of Events/ 100 Patient-Years		
All-cause hospitalizations	412	47.5	317	36.7	0.78 (0.67–0.90)	0.001
Infections	73	8.4	72	8.3		
Vascular access	98	11.3	56	6.5		
Heart failure	28	3.2	15	1.7		
Ischemic heart disease	25	2.9	16	1.9		
Respiratory disease	26	3.0	28	3.2		
Gastrointestinal bleeding	10	1.2	4	0.5		
Other reasons	152	17.5	126	14.6		
Symptomatic hypotension episodes[b]	8133	937.7	5862	679.2	0.72 (0.68–0.77)	<0.001
Dysrythmia[b]	444	51.2	477	55.3	1.08 (0.86–1.35)	0.50
Thoracic pain[b]	327	37.7	318	36.8	0.98 (0.75–1.28)	0.87

1. Most hospitalization in HD group due to vascular access issues
2. Intradialytic benefits seem believable and supported by other studies

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RCT: ESHOL

TABLE 1: BASELINE DEMOGRAPHICS

	All (*n*=906)	Hemodialysis (*n*=450)	OL-HDF (*n*=456)
Age (yr)	65.4±14.4	66.3±14.3	64.5±14.4
Male sex	606 (66.9)	289 (64.2)	317 (69.5)
Diabetes	226 (24.9)	122 (27.1)	104 (22.8)
Charlson comorbidity index	7.0 (5.0–8.0)	7.0 (5.0–8.0)	6.0 (5.0–8.0)
Time on dialysis (mo)	28.0 (12.0–59.0)	27.0 (12.0–58.0)	28.5 (12.0–60.0)
Vascular access			
Fistula	779 (86.0)	372 (82.7)	407 (89.3)
Graft	34 (3.8)	19 (4.2)	15 (3.3)
Catheter	93 (10.3)	59 (13.1)	34 (7.5)

HD group disadvantaged from the get-go !

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CURRENT STATE OF AFFAIRS

- Well-established belief that HDF **should** be better for patients
- Current **attempts to prove** this are now focused on HDF "dosing"
  - Recent study suggests fixed dosing, or dosing per TBW or BSA, not body weight
  - Expert opinion recommends **Vrep >20-24L** (post-dilution)
- No basis for patient selection criteria
- No RCT in incident dialysis patients
- No good data on dialysis-related QoL

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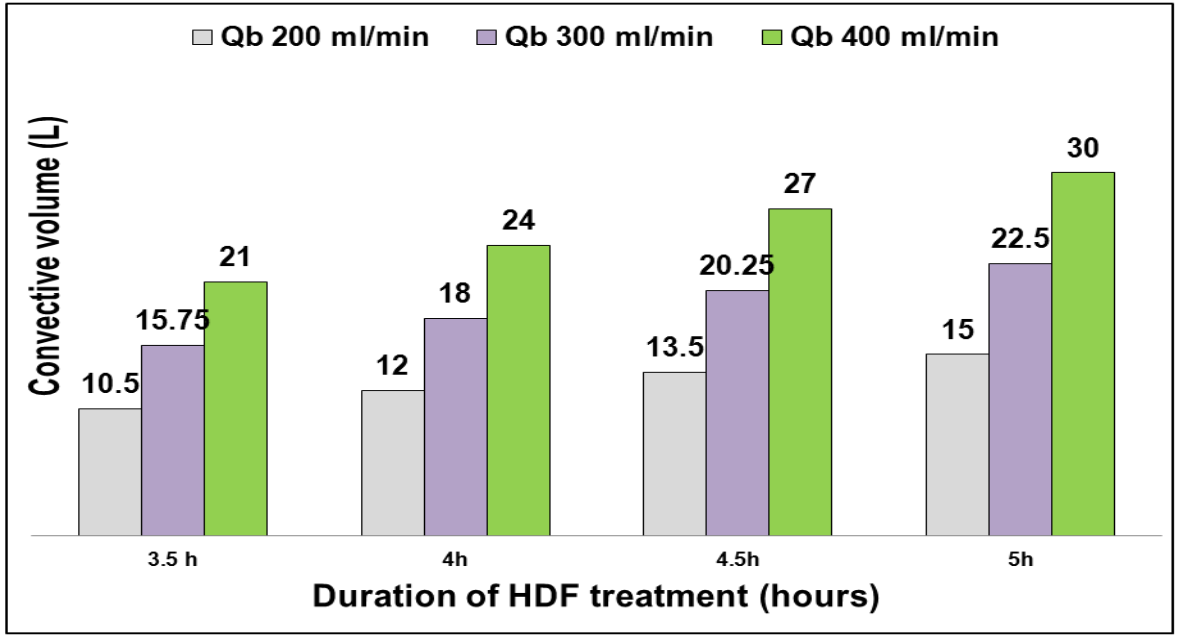
HDF GOAL: Vrep >20-24L, FF <25%

LIMITATIONS: BLOOD FLOW RATE AND DURATION OF THERAPY



Bedside Solutions:

1. Increase Qb
2. Increase duration
3. Increase anticoagulation
4. Accept higher FF

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HDF GOAL: Vrep >20-24L, FF <25%

Qb (ml/min)	400	400	400
Desired Vrep (L)	24	24	24
Target conv UF (ml/min)	100	100	100
Desired weight loss (L)	2	4	6
Target UF for weight loss (ml/min)	8.3	16.7	25
Total UF (conv + weight loss) (ml/min)	108.3	116.7	125
Effective Filtration fraction (%)	27	29	31
Adjusted conv UF (ml/min) to limit FF <25%	91.7	83.3	75
Adjusted Vrep (L)	22	20	18

Bedside Solutions:
1.Consider weight loss UF as part of total UF and lower conv UF (and therefore Vrep)

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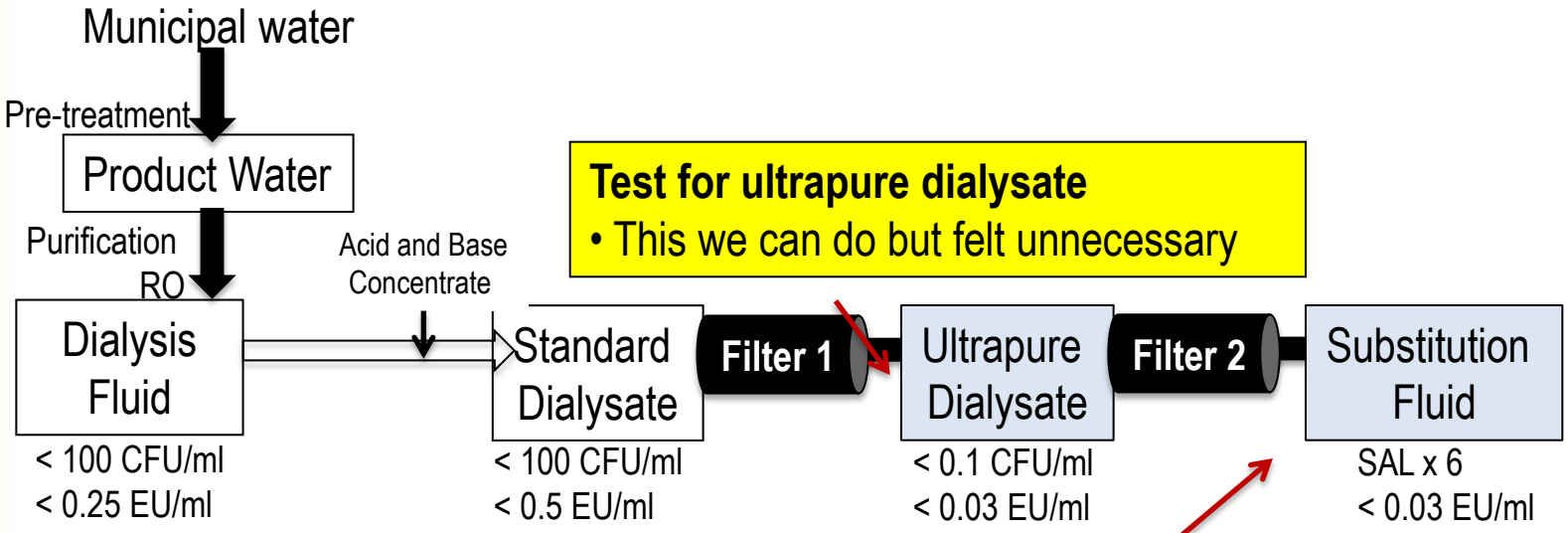
WATER REQUIREMENTS FOR HDF



Test for ultrapure dialysate
- This we can do but felt unnecessary

Test for substitution fluid
- SAL 6 – sterility assurance level 6 means: "1 in 1,000,000 chance of contamination"
- No test is this sensitive
- Testing of substitution fluid therefore futile

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WHY NOT

"COST" OF NEW THERAPY

POTENTIAL ADDITIONAL COST	POTENTIAL COST SAVINGS	UNKNOWNS
Medications •heparin	Medications •EPO, phosphate binders, BP meds	Quality of Life
Water •Additional testing (if we do it) •Additional dialysate use (depends on Rx)	Hospitalization rates	Quantity of Life
Impact on system •Machine disinfection time •scheduling	Impact on system •duration / frequency of runs	
Disposables •Tubing •Filters	Disposables •on-lime priming vs NS bags	

- Cost Utility Analysis Studies from CONTRAST cohort suggest favourable cost-utility ratio (adjusted to QALY)
- Direct cost comparison to HD likely a wash (depending on disposable costs for machine

WHAT NOW

CURRENT STATE

•Very good likelihood that increased convective clearance could have short-term and long-term clinical benefits

•Hoping for mortality reduction may be an unrealistic expectation, especially in prevalent dialysis patients

•Lack of robust RCT evidence for mortality should not deter reasonable clinical application

FUTURE DIRECTIONS

•HDF implementation can be exciting and informative, IF we establish:

1. Patient selection criteria
2. Target HDF prescription
3. Logistics of water testing
4. Prospective data collection (Cost, Dialysis related symptoms, QoL)

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DISCUSSION