HEMODIAFILTRATION
IS IT IN OUR FUTURE ?

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DISCLAIMER

I have no affiliation to or personal interests in the following companies and/or products:

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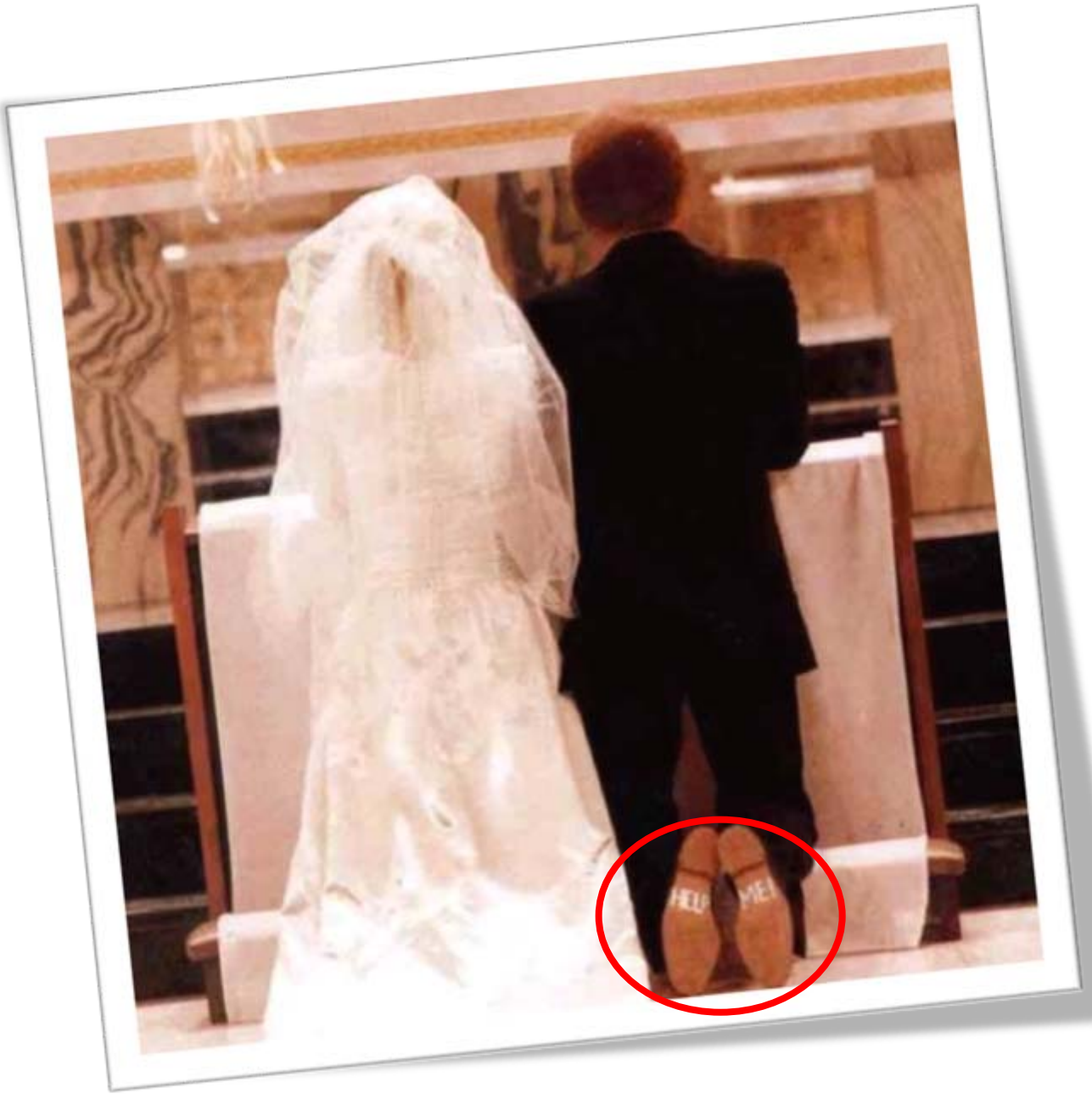
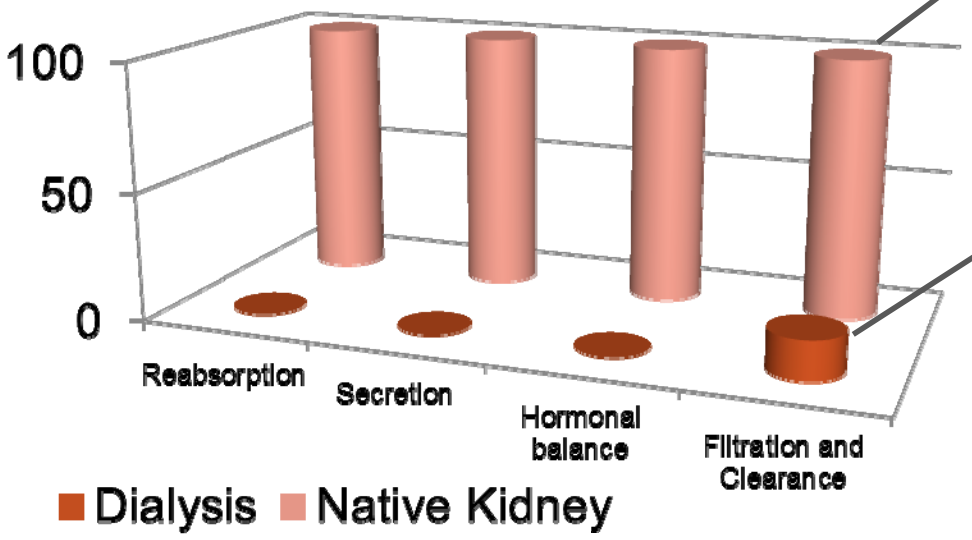
Starbucks



RATIONALE & BACKGROUND

“Dialysis is a life boat”

WHY DO OUR PATIENTS DIE IF WE ARE REPLACING THE ORGAN THAT FAILED?



24 hrs/day = 10,000 min / week
at GFR 120 ml/min → 1200 L / week

3x/week x 4hrs = 720 min / week
at max clearance 200ml/min
→ 200 L / week

Indeed, the true miracle is that these very primitive devices are able to provide several decades of survival times for patients."

Claude Jacobs

Improving the outcome of dialysis – opinion vs scientific evidence. NDT 2000

OUR MOST UNHEALTHY OBSESSION

$$Vt = Qf \times t\left[\left[1-\left[\frac{G-Ct(K+Kr-Qf)}{G-C0(K+Kr-Qf)}\right]^{\frac{Qf}{K+Kr-Qf}}\right]^{-1}-1\right] \quad (1)$$

$$G = \frac{(Kr+\alpha)\left[C0-Ct\left(\frac{Vt+\alpha\theta}{Vt}\right)^{-\frac{Kr+\alpha}{\alpha}}\right]}{1-\left(\frac{Vt+\alpha\theta}{Vt}\right)^{-\frac{Kr+\alpha}{\alpha}}} \quad (2)$$

spKt/V = -ln (R - 0.03) + [(4 - 3.5R) x (UF ÷ W)]

URR = 100 x (1- postdialysis urea/predialysis urea)

KDOQI Targets:

spKt/V >1.2
URR >65%

WHAT NEEDS TO BE CLEARED?

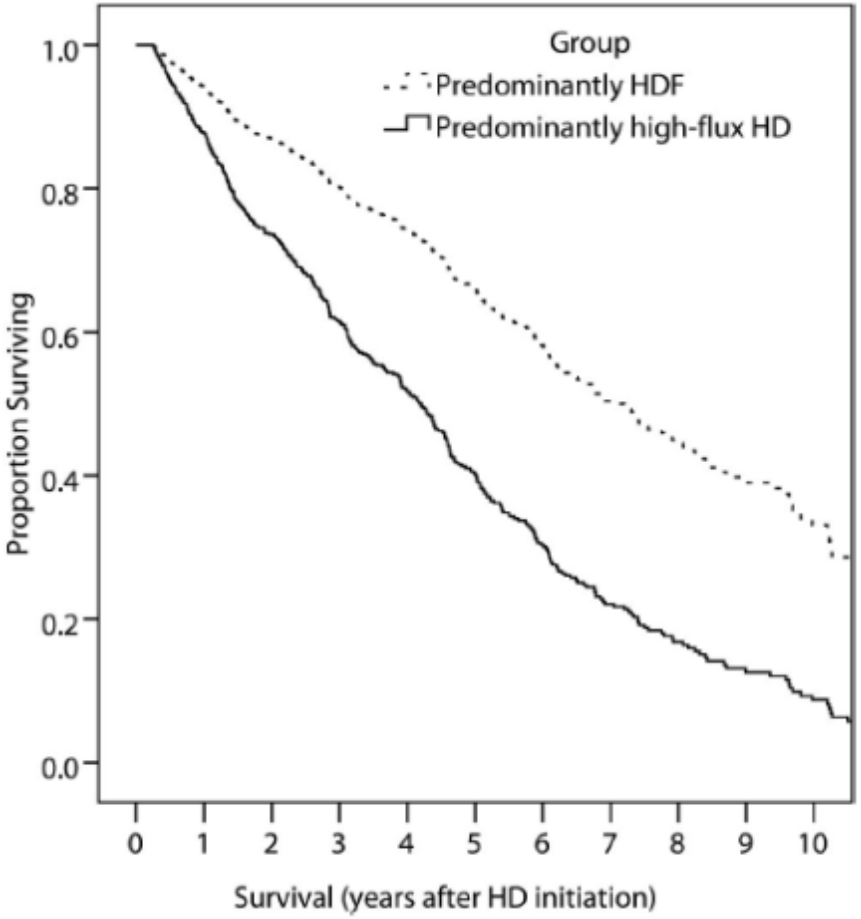
- **Small Solutes**
  - Examples:
    - Urea
    - Creatinine
    - Electrolytes
    - Phosphate (*)
- **Middle and Larger Molecules**
  - Examples
    - Beta-2-microglobulin
    - Inflammatory markers
- **Protein-bound Solutes**
  - Examples
    - P-cresol

SMALL SOLUTE CLEARANCE

- **HEMO** Study
  - No difference in mortality between targetting spKt/V 1.45 (URR 75%) vs standard dose Kt/V 1.25 (URR 65%)
  - But trend towards lower CV mortality in high flux group

- **MPO** Study
  - Comparison of low vs high flux HD in incident pts
  - No overall difference in mortality
  - But significantly lower mortality in diabetics and hypoalbuminemic patients

MIDDLE MOLECULE CLEARANCE



Vilar et al. Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis. CJASN 2009.

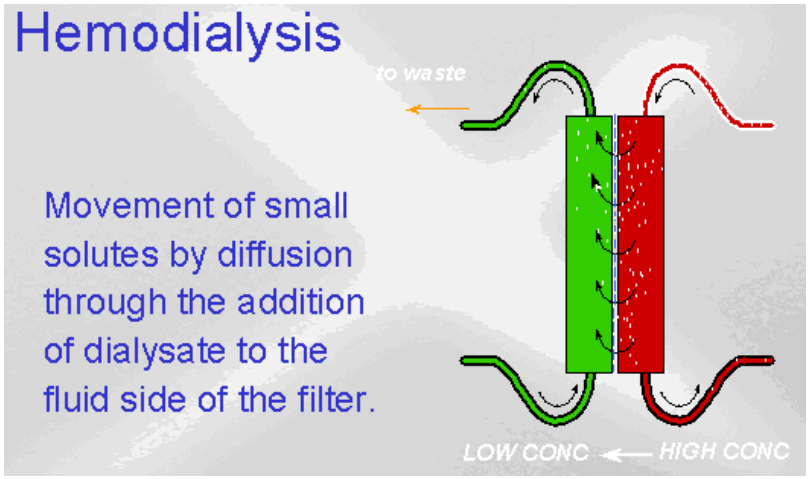
SOME OF THE OBSERVED BENEFITS OF HEMODIAFILTRATION

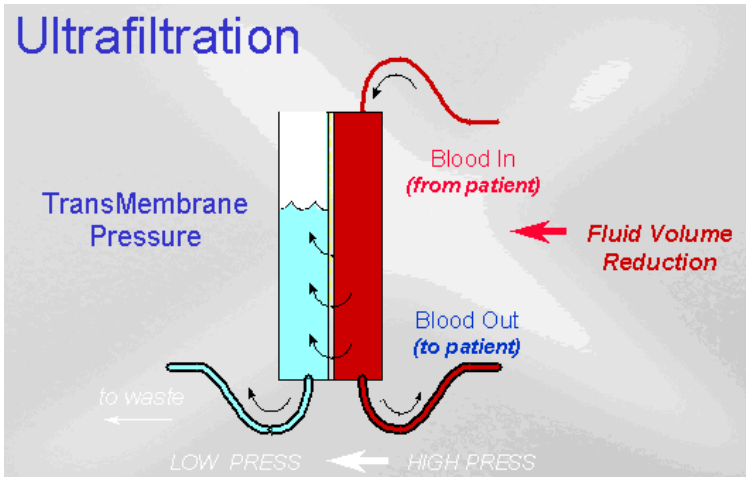
- Decreased mortality
- Better hemodynamic stability during dialysis
- Better phosphate clearance
- Better beta-2-microglobulin clearance
- Decreased inflammatory markers
- Increased EPO responsiveness
- Clearance of light chains

THE CURRENT THINKING

- A minimum amount of small solute clearance is necessary to sustain survival on dialysis
- Above this threshold, however, no study to date has shown that increasing small solute clearance correlates with better survival
- Is it possible that the larger (?undefined) middle molecules play a bigger role than we can appreciate or measure?
- If so, should we shift our focus on getting rid of them?

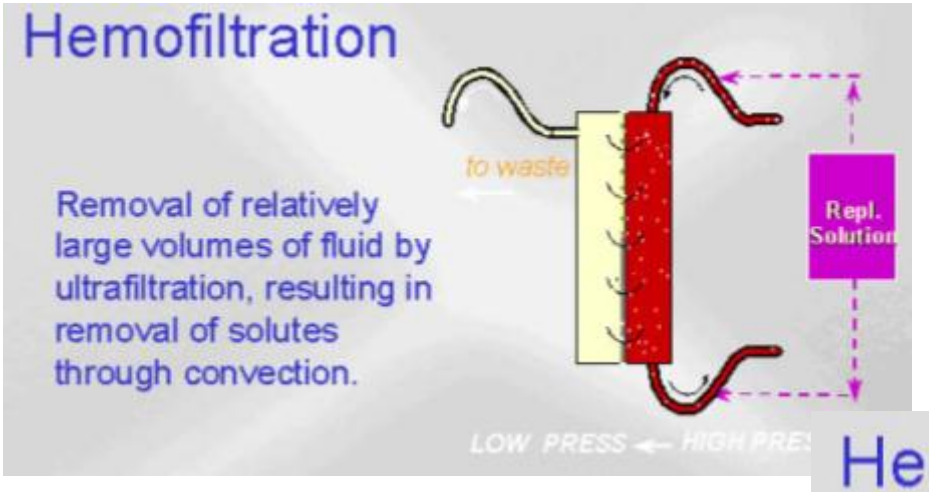
RECALL: WHAT IS HEMODIALYSIS?

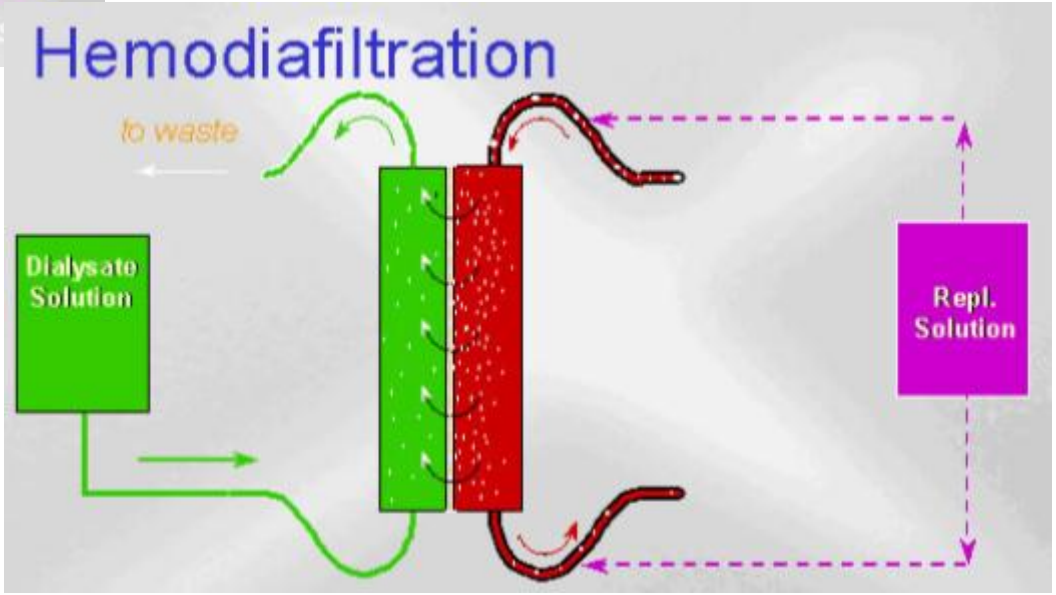




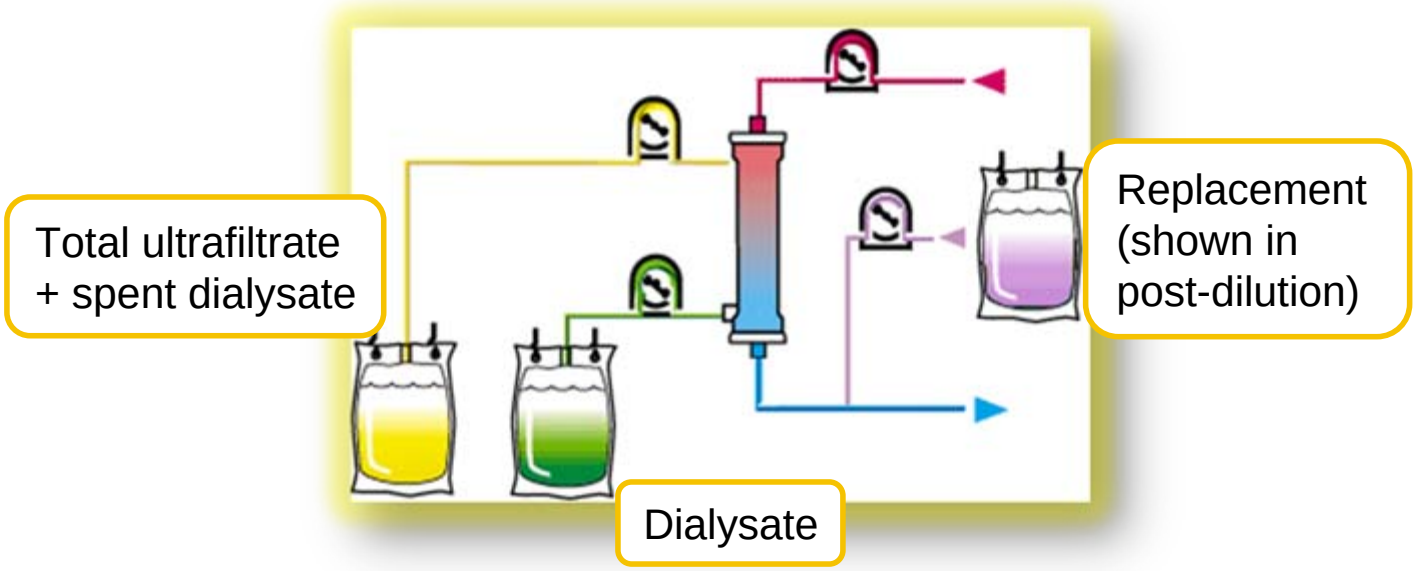
VARIABLE	DEPENDS ON
Concentration gradient	$[X]_{serum}$ and $[X]_{dialysate}$
Blood Flow Rate	Vascular access, hemodynamics
Dialysate Flow Rate	Availability of dialysate
Dialysis Time	Handidart
Efficiency (small solute)	Dialyzer surface area
Flux (middle molecule)	Dialyzer pore size, UF rate

WHAT IS HEMODIAFILTRATION?





COMPONENTS OF CONVECTIVE CLEARANCE



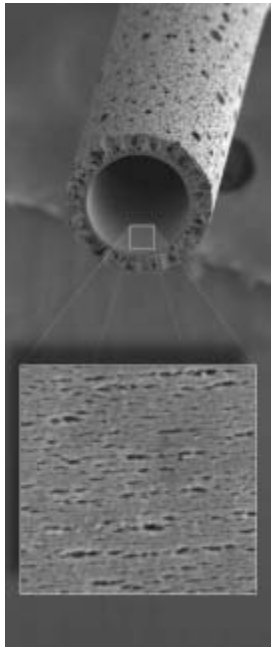
VARIABLE	AFFECTS	DEPENDS ON
Ultrafiltration	Water and solvent removal	TMP, hydrolic permeability
Sieving Coefficient	Degree of solvent drag with water	Size of molecule and size of pores
Replacement Fluid	Clearance Hemodynamic preservation	Amount Pre or post-dilution

THE CRUX OF HDF – MEMBRANE EVOLUTION

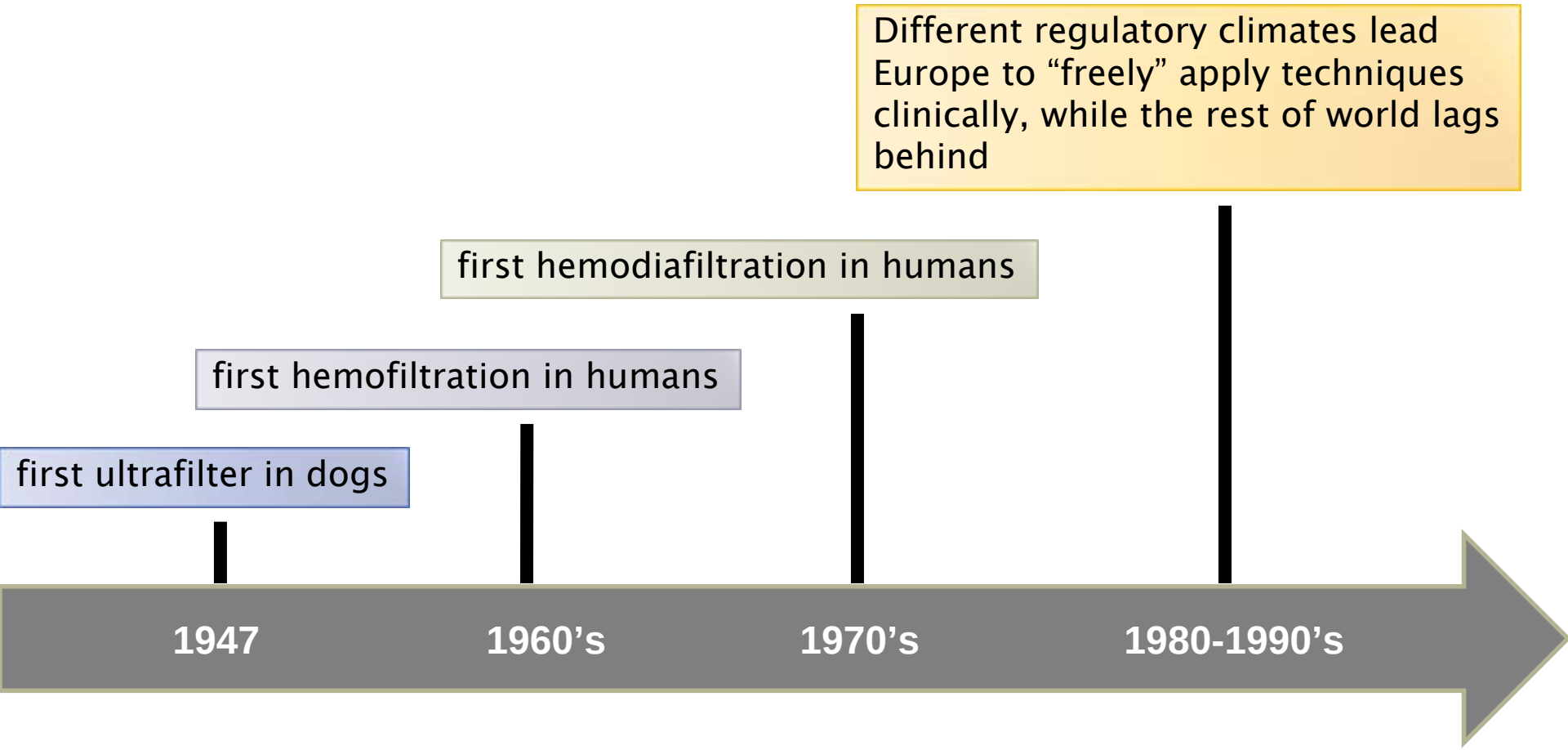
- Early cellulose membranes were thin & hydrophilic, with small pore sizes
- Good small solute clearance
- Insufficient flux for water and sieving coefficients

- Modified cellulose membranes were thick & hydrophobic
- Good flux for water & sieving coefficients
- Too thick for efficient small solute clearance

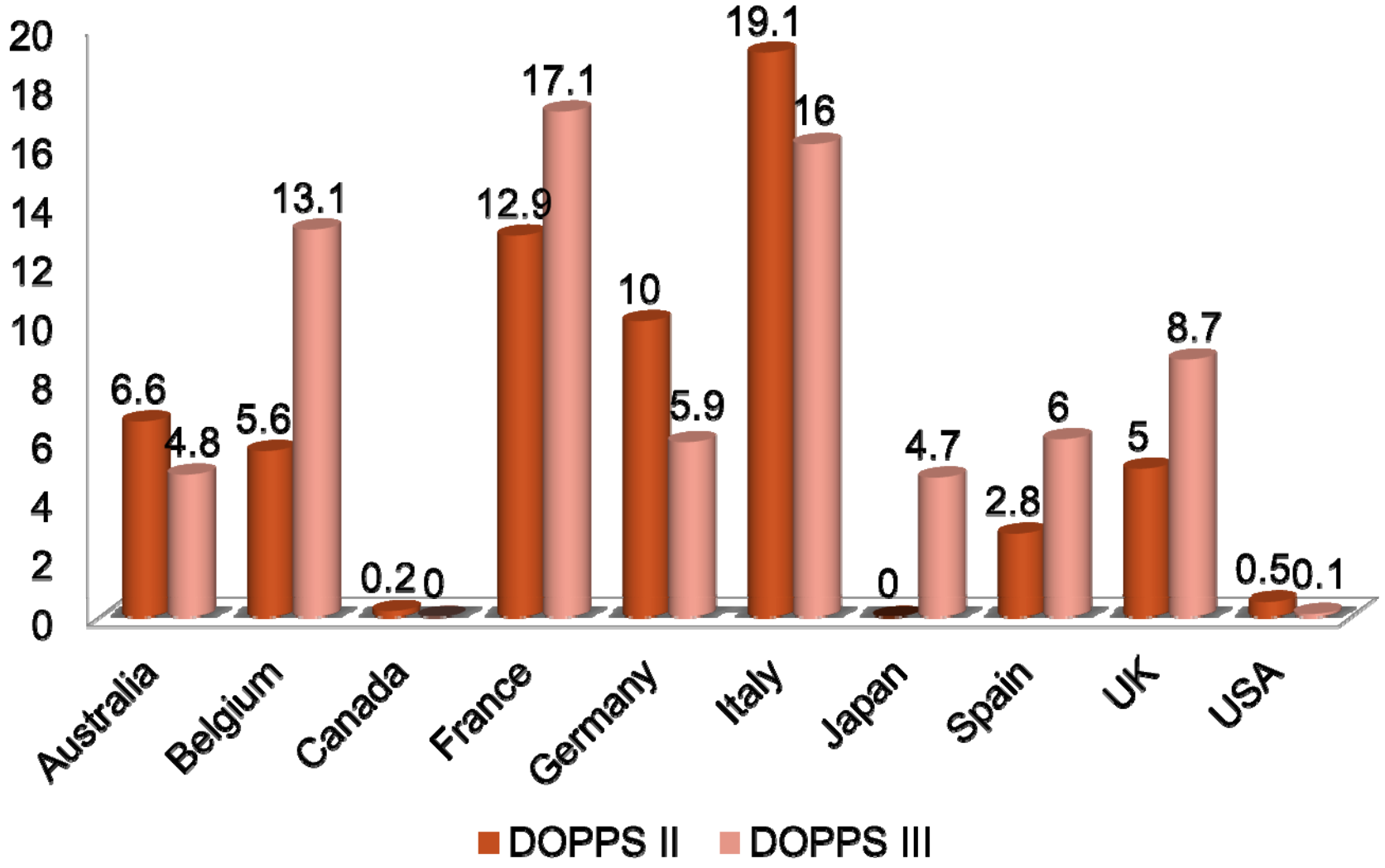
- New generation of synthetic fibers with combined hydrophilic/ hydrophobic structure and reduced thickness
- Allows for filtration and dialysis



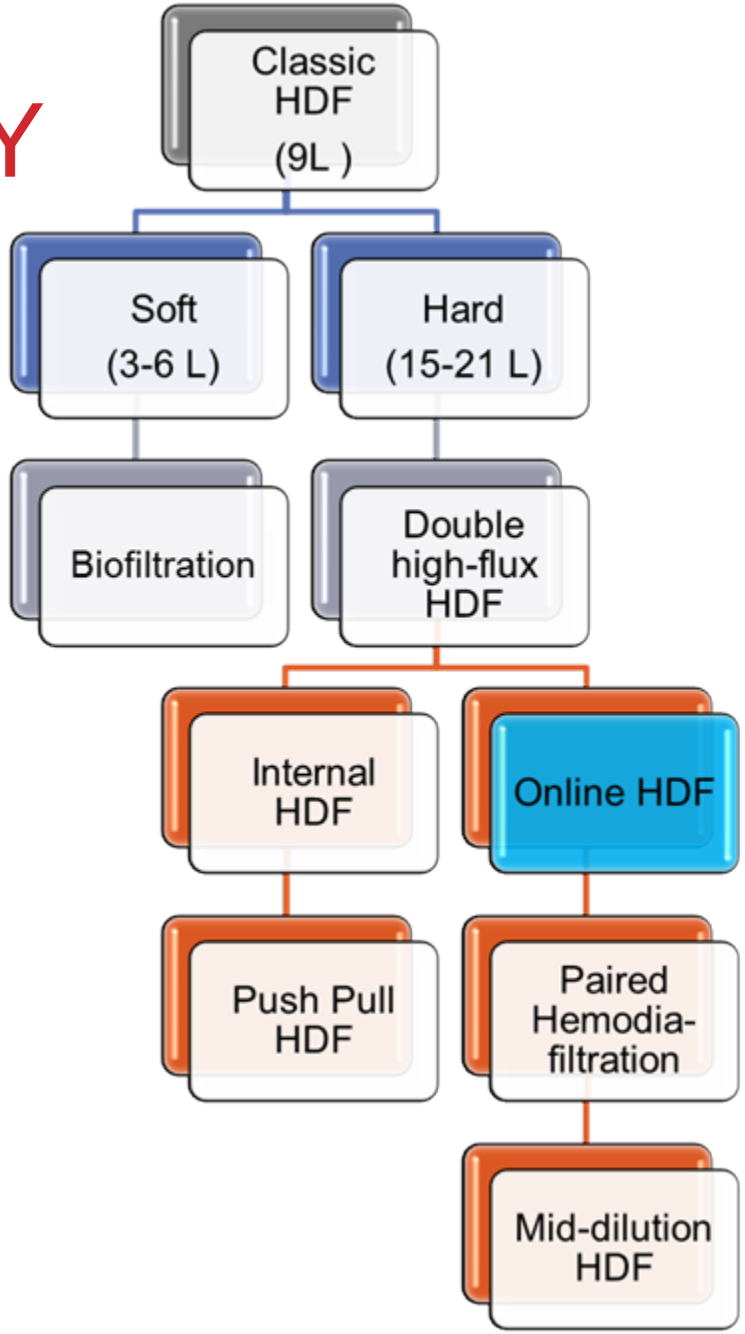
HISTORY OF HDF



PREVALENCE OF HDF

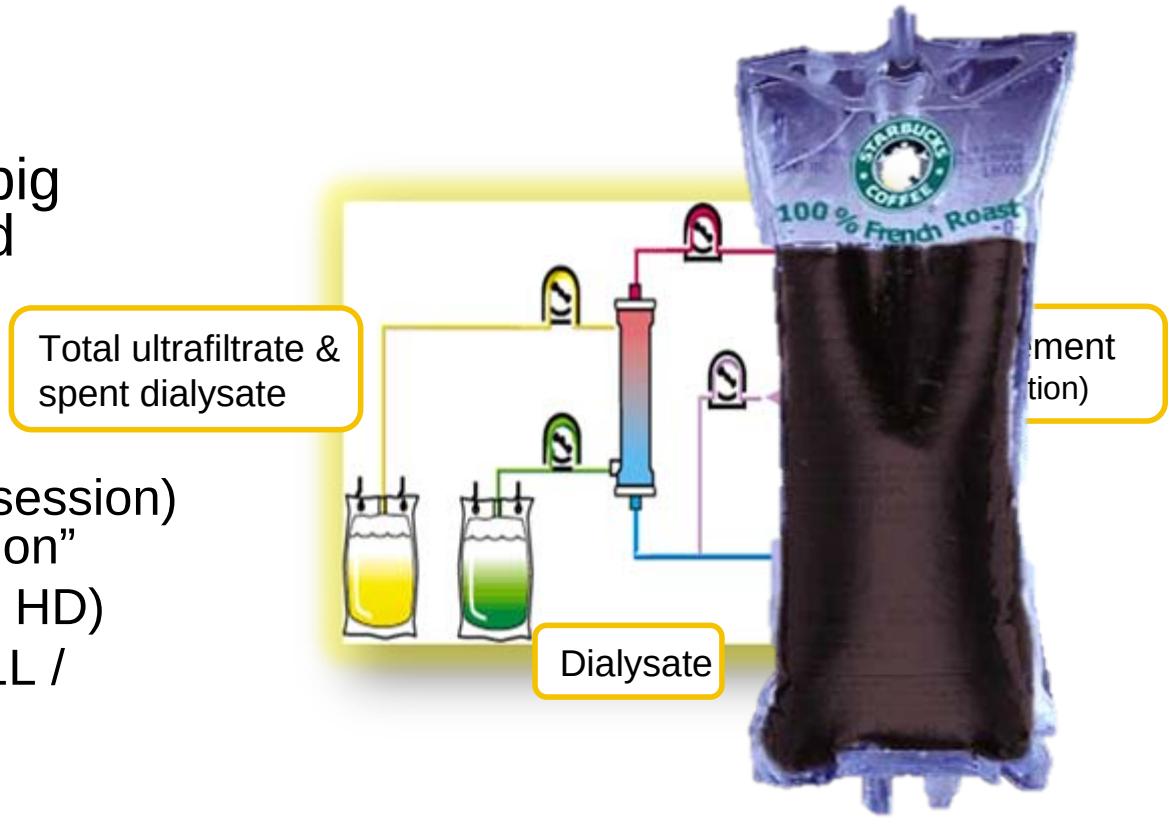


TERMINOLOGY



CLASSIC HDF – AKA “BAG” HDF

- First used in 1970s
- Reinfusate supplied in big bags (like in CRRT) and reinfused post-dilution
- Typically ~9L / session
  - If lower volumes (3-6L / session) – “soft” HDF or “biofiltration” (likely similar to high flux HD)
  - If higher volumes (15-21L / session) – “hard” HDF
- Limited by
  - Number of available bags (cost)
  - Nursing labour!



ONLINE HDF

- Introduced in 1980s
- High volumes of replacement fluid made “ONLINE”
  - dialysate from dialysate inlet processed through a number of filtration steps to make it safe enough for infusion into patient (ie. ultrapure dialysate)
- Eliminates cost and labour
- Limiting factors
  - Water Quality
  - Equipment approval
  - Safety Data and Analysis

WATER REQUIREMENTS

What every office needs

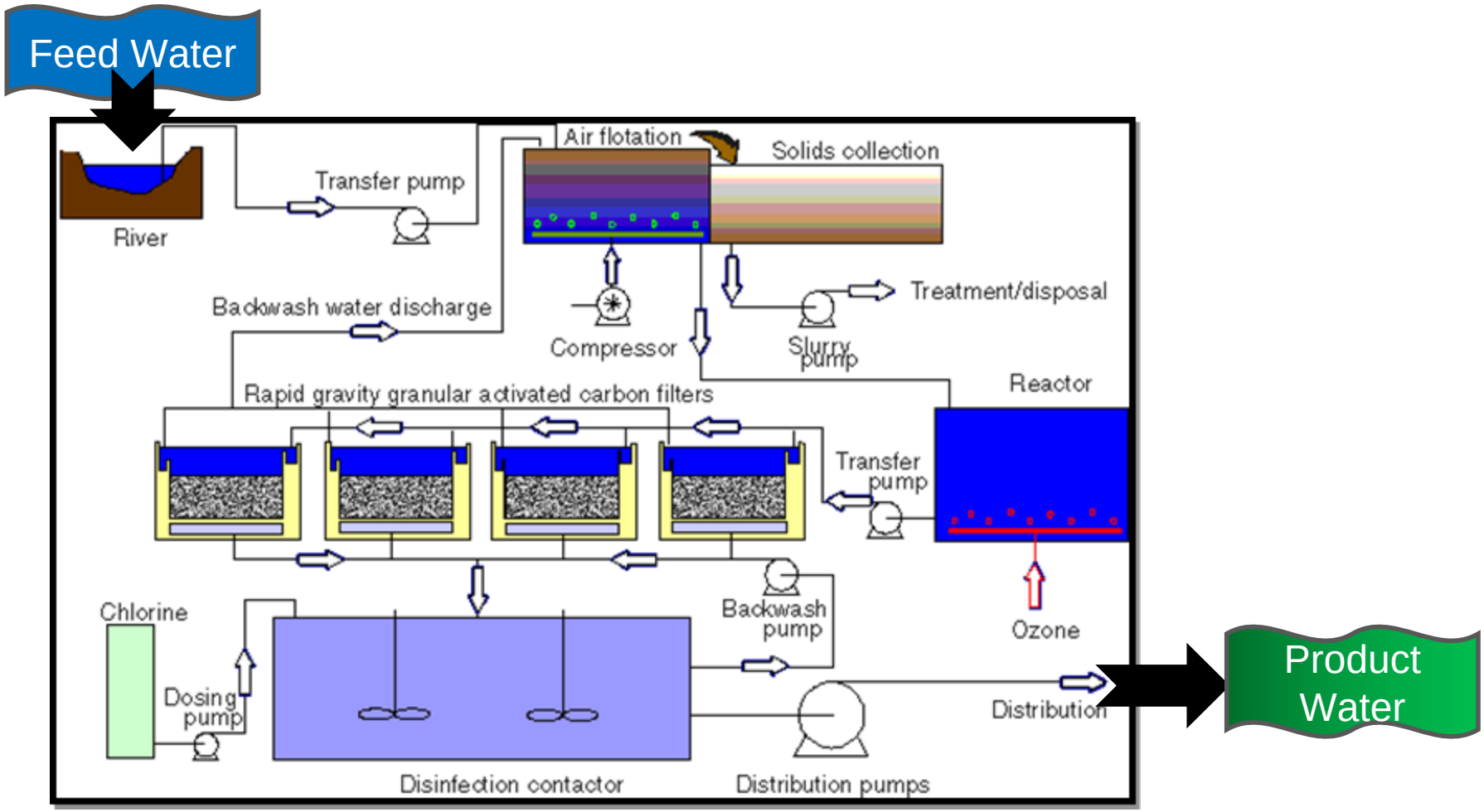
REQUIRED WATER STANDARDS

- Criteria for Dialysate
  - European standards: <100 CFU/ml and <0.25 EU/ml

- For use as replacement fluid, must meed criteria for Ultrapure Dialysate (ie safe for infusion into patient)
  - European standards: <0.1 CFU/ml and <0.03 EU/ml

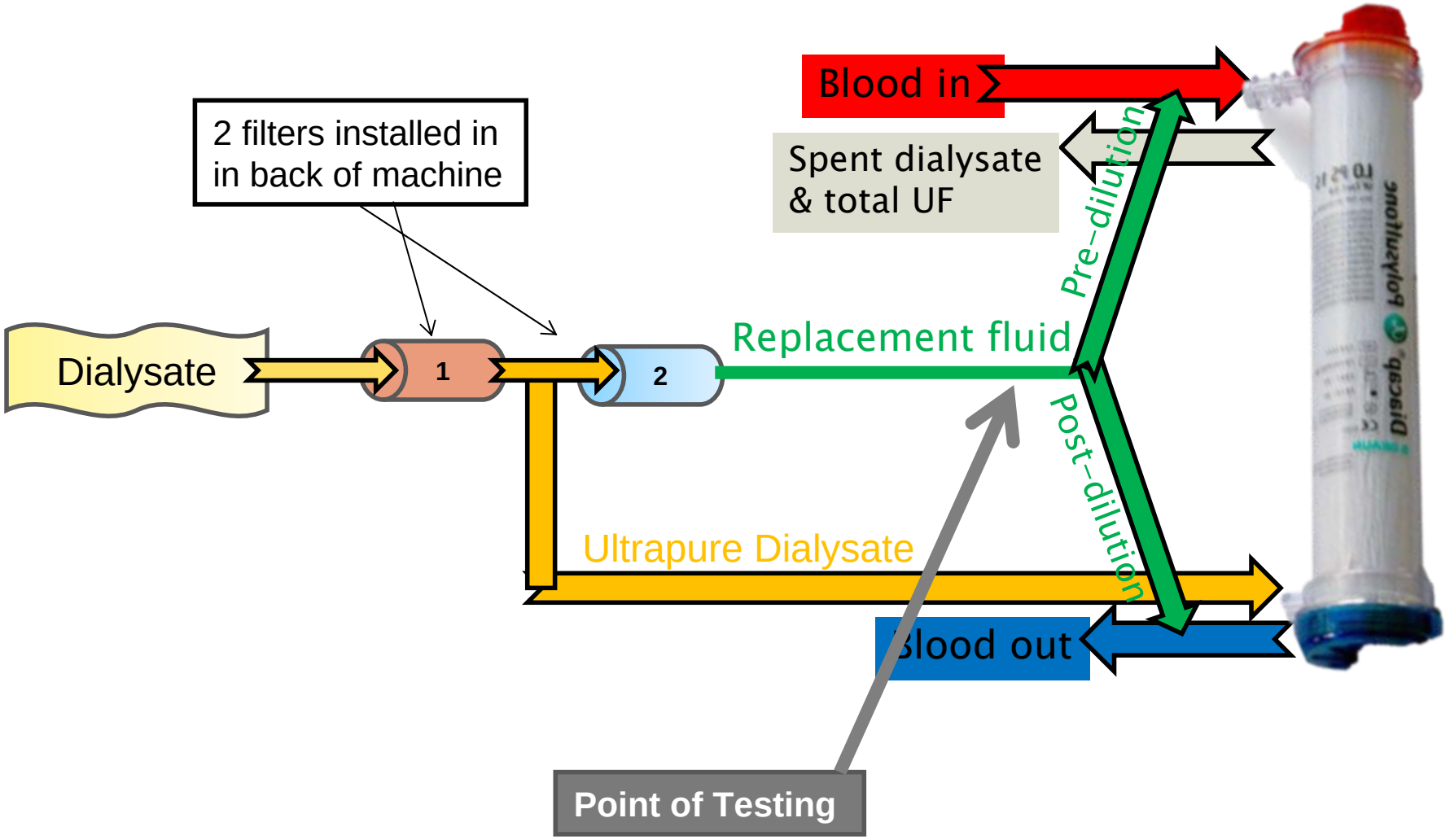
- How can we achieve this?

1. MUNICIPAL WATER TREATMENT



2. REVERSE OSMOSIS

3. ULTRAPURE DIALYSATE CREATION

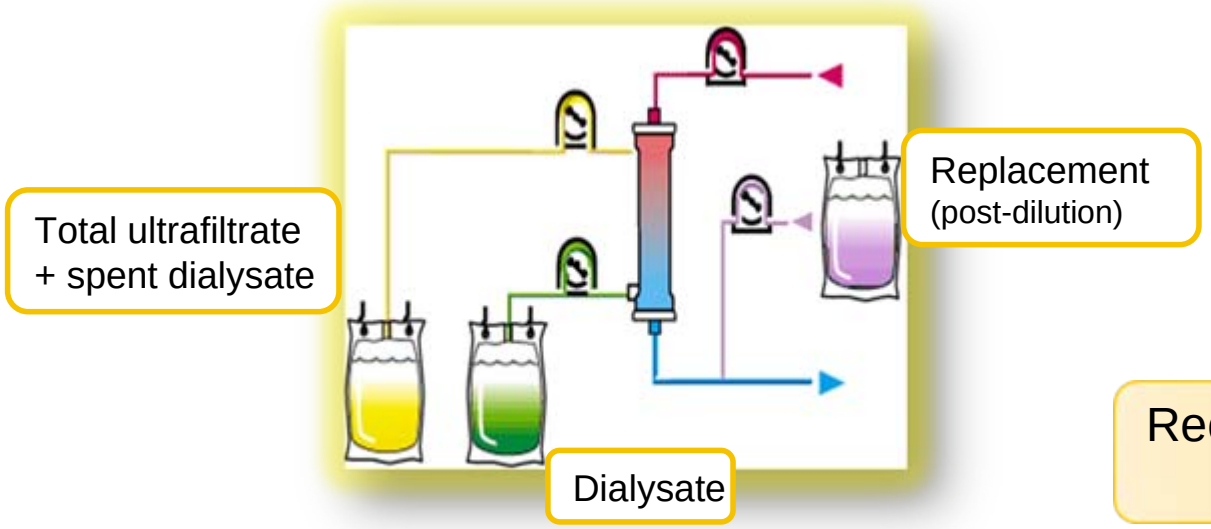


TECHNIQUE AND PRESCRIPTION

DOSE OF HDF – MORE IS MORE

- Degree of solvent drag depends on how much fluid is being removed by filtration and subsequently replaced
- Dose of HDF therefore correlates with UF rate
- Total UF rate = prescribed replacement fluid + desired fluid loss
- What limits UF rate
  - The filter
  - The patient
  - Effect on concentration gradients

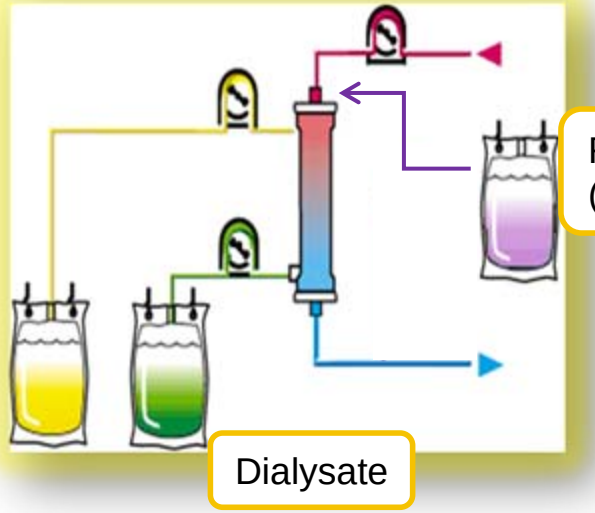
POST-DILUTION REPLACEMENT



Recommendation
> 20L

ADVANTAGES	DISADVANTAGES
Does not dilute concentration gradients, so does not decrease clearance efficiency	Leads to hemoconcentration within filter (high risk of filter clotting)
	Should limit UF rate to <25-30% of Qb (eg. at 400ml/min = 100ml/min = 24L of UF)
	May change heparin requirements

PRE-DILUTION REPLACEMENT

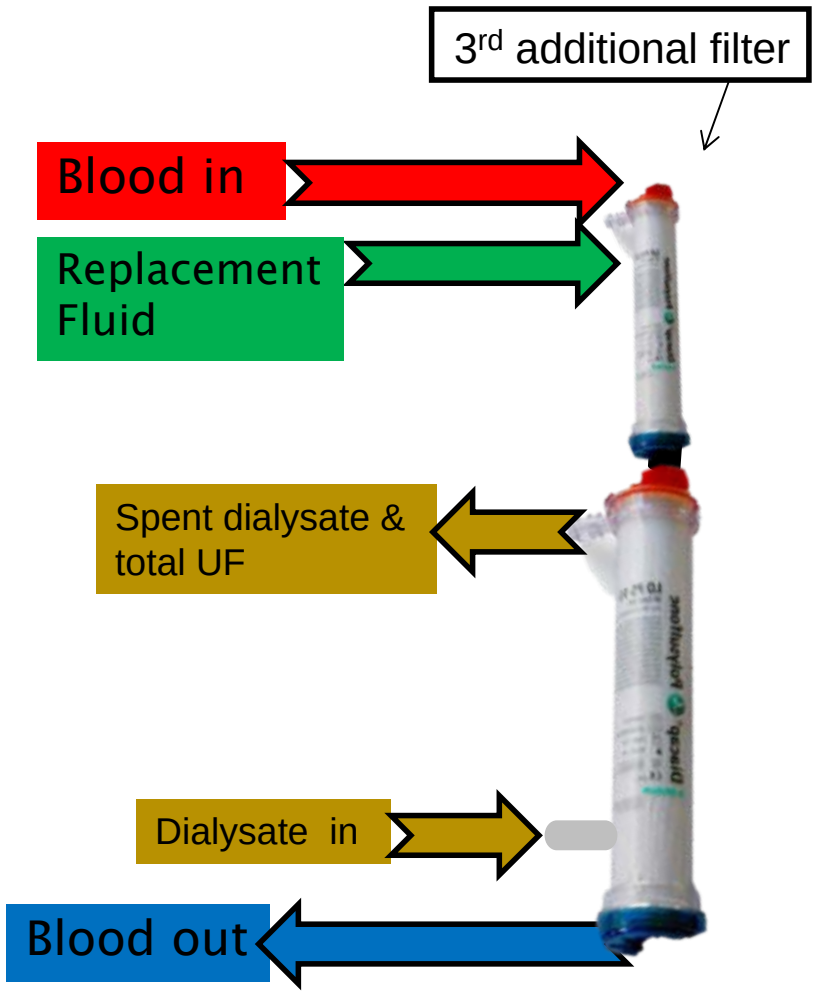


Recommendation
> 40L

ADVANTAGES	DISADVANTAGES
Lower risk of filter clotting	Dilution of blood pre-filter reduces concentrations and thus gradients for clearance
	To compensate, need to use 2x amount of replacement fluid used in post-dilution mode
	Increases filter TMP
	Increased total exposure to replacement fluid

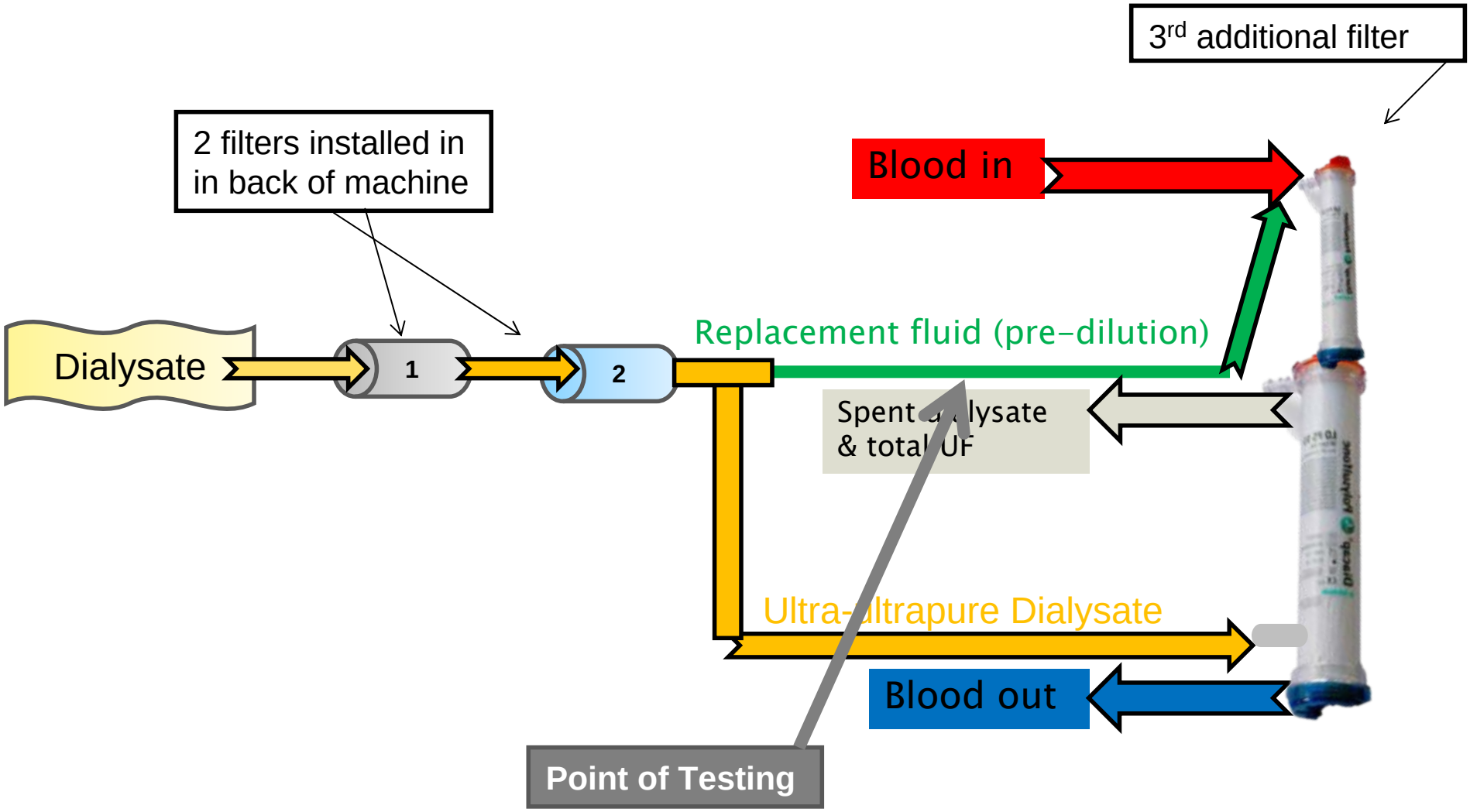
PAIRED HEMODIAFILTRATION

- Dual chamber dialyzer with two dialyzers connected in series
- Top dialyzer acts as an additional filter for reinfusate as it is delivered to patient via backfiltration
- Extra safety measure to “guarantee” ultrapure dialysate



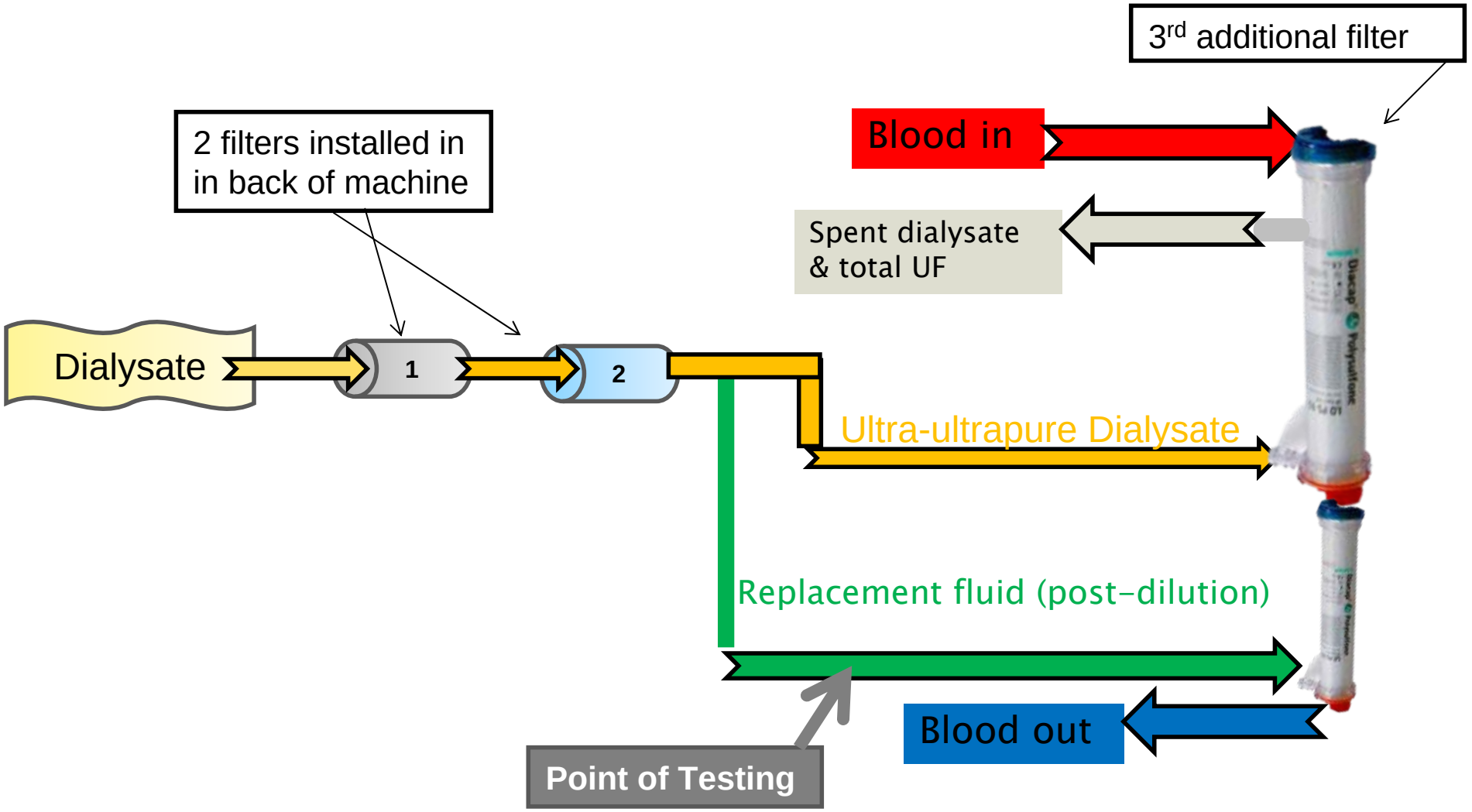
PAIRED HEMODIAFILTRATION

Pre-Dilution Mode



PAIRED HEMODIAFILTRATION (BellCo)

Post-Dilution Mode



PAIRED HDF IN ACTION

Foreclean and Multipure

Pre-dilution Mode

Post-dilution Mode

WHAT DO WE KNOW

AND

WHERE DO WE GO FROM HERE?

OBSERVATIONAL TRIALS

- Decreased mortality
- Better phosphate clearance
- Better beta-2-microglobulin clearance
- Decreased inflammatory markers
- Increased EPO responsiveness
- Better hemodynamic stability during dialysis
- Use in clearance of light chains
- Use in treatment of acute hepatic failure

STUDY	PATIENTS	STUDY DESIGN	HDF MODE	HD MODE	F/U	MAJOR OUTCOMES
DOPPS (2006)	2165 prevalent HD	Retrospective Observational	High (15-25L) vs low (5-15L)	High flux vs Low flux	3 Yr	35% reduction in all cause mortality
EuCLID (2006)	2564 prevalent HD	Retrospective Observational	Online-HDF	HD	3Yr	35% reduction in mortality
RISCAVID (2008)	757 prevalent HD	Prospective observational	Bag-HDF (~14L) vs Online-HDF (~23L)	HD	3Yr	Mortality RR 0.78 for HDF
UK STUDY (2009)	858 incident HD	Retrospective Observational	HDF (~15L)	High flux	18Yr	Mortality HR 0.45 for HDF

THEORIES ON BENEFITS OF HDF

- Enhanced middle molecule clearance
- Improved intradialytic hemodynamic stability
- Enhanced biocompatibility of ultrapure fluid

LIMITATIONS TO CURRENT HDF DATA

- Mostly observational studies, therefore no proven cause and effect, only associations
- Relatively few people on HDF at any time, on various regimens and doses
- Comparisons mostly to low flux HD (rather than high flux HD mostly in Canada)
- No North American data

ONGOING STUDY (COUNTRY)	PATIENTS	STUDY DESIGN	HDF MODE	HD MODE	F/U	PRIMARY OUTCOME	SECONDARY OUTCOMES
CONTRAST Netherlands Norway Canada (1)	Prevalent HD (~700)	Randomized prospective	Post (6L/hr)	Low flux	2 Yr	All cause mortality CV m&m	Phosphate ,LVMI, carotid intima, PWV, inflammatory markers, uremic toxins, QoL, nutrition
ESHOL Spain	Prevalent HD (~750)	Randomized Prospective	?	?	3 Yr	All cause mortality	
TURKISH study	Prevalent HD (~780)	Randomized prospective	Post (15L/run)	High flux	2 Yr	All cause mortality & new CV events	CV mort, hosp rate, intradialytic cxs, QoL, med chnages, EPO req, middle molec,
ITALIAN study	Prevalent HD (146)	Randomized Prospective	Pre	Low flux	2 Yr	HD stability BP control	Total mortality CV m&m
FRENCH study	Prevalent HD > 60y (~600)	Randomized Prospective					
McGill study	Prevalent HD with sleep apnea	Randomized crossover	?	?	3mos	Reduction in AHI	QoL, RLS symptoms, BP, etc
KOREAN study	Prevalent HD	Cross-over non-rand.	?	Low flux	2mos	Flow mediated vasodilation	

REQUIREMENTS FOR HDF

- Water that meets standards for ultrapure dialysate
- HD machines that can do HDF and have Health Canada approval to operate in HDF mode
- Extra supplies for HDF (tubing, filters, etc)
- Nursing and technician training and in-service
- Money

DIRECT COST COMPARISON

SOMEONE'S MOM

$at 5 PER RUN

2000 DIALYSIS PTS IN BC

$1.5 million PER YEAR

UNANSWERED QUESTIONS…

- Is HDF truly better than optimum high flux HD in Canada?
  - How do we define “better”?
- Are there certain patients who are most likely to derive a benefit from this modality?
  - Who are they and how do we identify them?
- Stay tuned for answers…

QUESTIONS / COMMENTS ?