CRRT: The Technical Questions
Modality & Dose

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Case

A 24YOM with HTN and OSA presents with acute pancreatitis. Despite aggressive fluid resuscitation and antibiotics for sepsis, he develops oliguric AKI with hyperkalemia. He is intubated on FIO_2 80% and is requiring vasopressin and norepinephrine. He is febrile and weighs 100 kg. He is on antibiotics and IV bicarbonate infusion. His labs are as follows:

Na 138 meq/L, K 6.5 meq/L, Cl 109 meq/L, HCO_3 22 meq/L, BUN 22 mg/dL, Creatinine 3.1 mg/dL (274 µmol/L); ABG: 7.21/pCO_2 40 mmHg/pO_2 108 mmHg on 80% FIO_2; WBC 13,000, Hct 30%, Platelets 104,000; Lactic acid 1.8 mmol/L; INR 1.6; Total Bili 3.2 mg/dL; ALT 694 U/L; AST 640 U/L; and CPK 22,000 U/L. He is 9 liters positive over last 24 hours.

Case

Which CRRT modality do you place him on?

A. CVVH with pre-filter RF
B. CVVH with post-filter RF
C. CVVH with pre- and post-filter RF
D. CVVHD
E. CVVHDF with pre-filter RF
F. CVVHDF with post-filter RF
G. CVVHDF with pre- and post- filter RF
H. Any of the above
I. None of the above
J. I don’t know

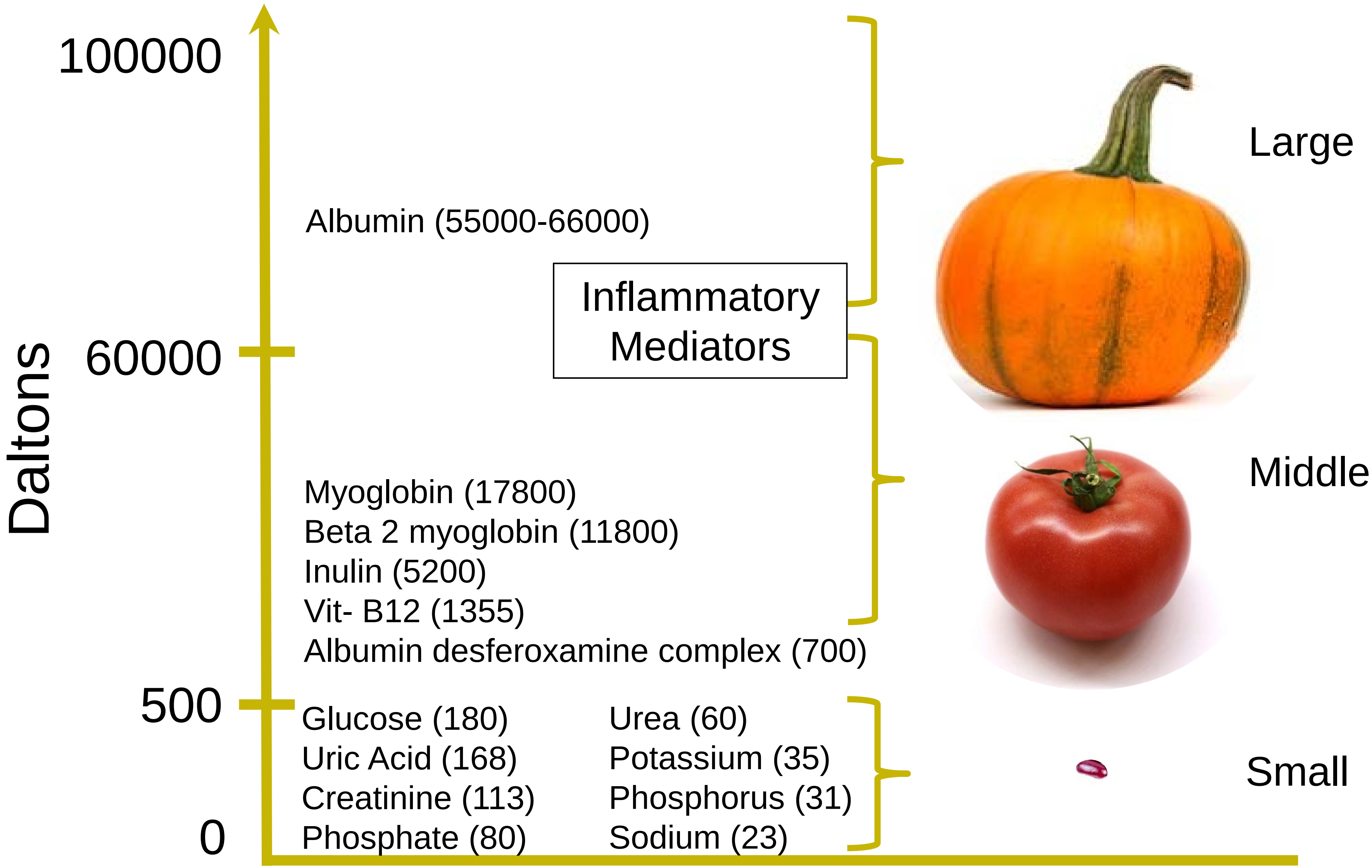
CRRT Treatment Goals

- Volume control
- Metabolic control
- Solute clearance
- Safe anticoagulation with minimal clotting

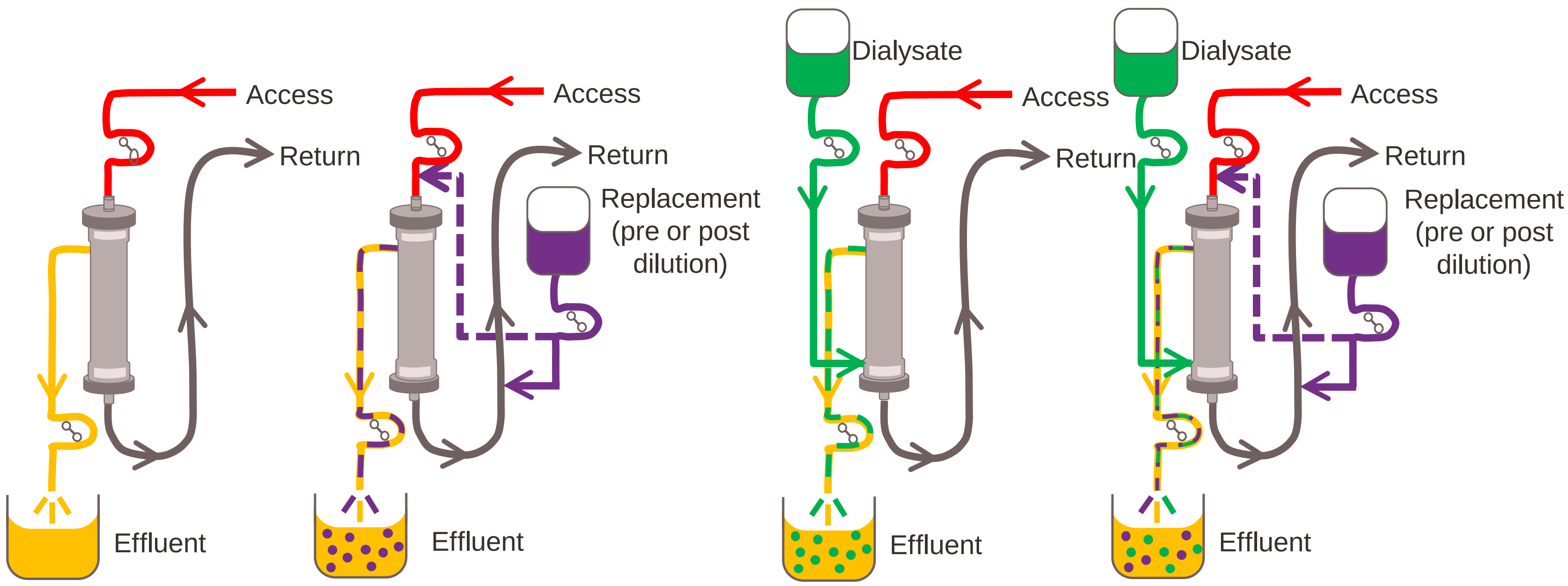
CRRT for AKI
The Technical Questions

- What are the critical elements of the CRRT prescription?
  - CRRT modality
  - Dose
  - Anticoagulation
  - Solutions

Molecular Weights



CRRT Modalities



SCUF

- No solute clearance
- Used for fluid removal

CVVH

- Solute clearance: convection
- Operative fluid: RF

CVVHD

- Solute clearance: diffusion
- Operative fluid: dialysate

CVVHDF

- Solute clearance: diffusion and convection
- Operative fluids: RF and dialysate

Solute Clearance with CRRT

CVVH

CVVHD

CVVHDF

Calculating Solute Clearance

- Generic Clearance =
  - Mass removal rate / Blood concentration
  - Effluent flow rate x Effluent concentration/Blood concentration
  - $K = Q_E \times C_E / C_B$

Calculating Solute Clearance

Effluent Rate (ml/hr) Definition

- CVVH: Total UF Rate (ml/hr) = Pre-Filter Replacement Fluid Rate (ml/hr) + Post-Filter Replacement Fluid Rate (ml/hr) + Fluid Removal Rate (ml/hr)

- CVVHD: Dialysate Rate (ml/hr) + Fluid Removal Rate (ml/hr)

- CVVHDF: Total UF Rate (ml/hr) + Dialysate Rate (ml/hr) = Pre-Filter Replacement Fluid Rate (ml/hr) + Post-Filter Replacement Fluid Rate (ml/hr) + Fluid Removal Rate (ml/hr) + Dialysate Rate (ml/hr)

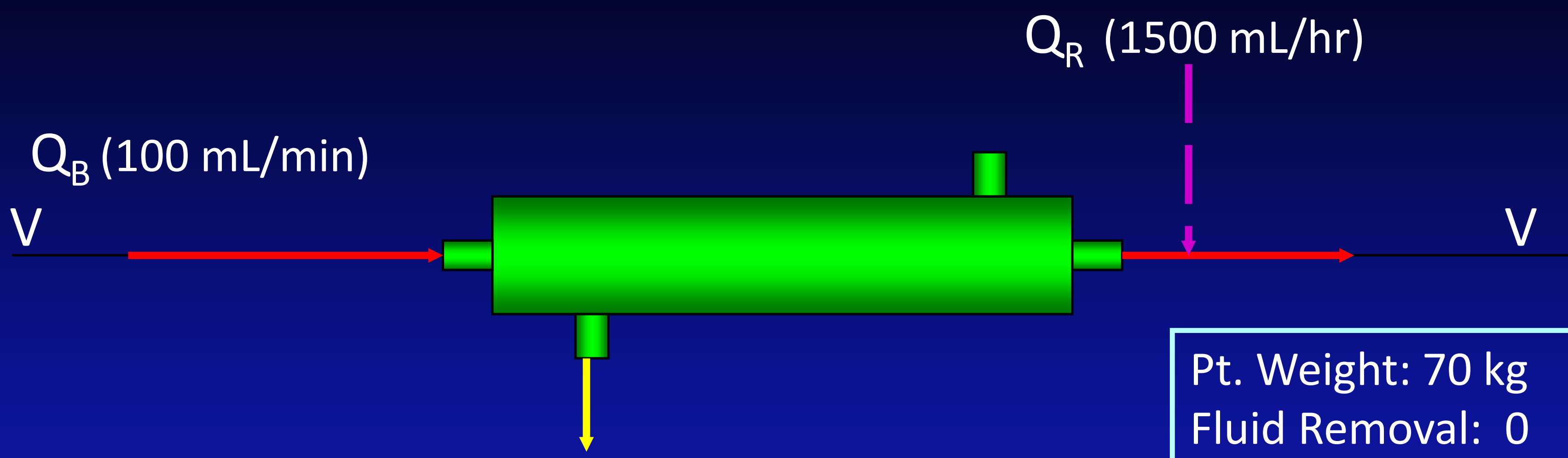
Calculating Solute Clearance

- Using urea as solute
  - $Q_E << Q_B$ (17-50 ml/min vs. 150-200 ml/min)
  - Equilibrium achieved ($C_E = C_B$)
- $C_E/C_B = \sigma$ = Sieving Coefficient
- Sieving coefficients for small MW molecules such as urea = 1
- $K = Q_E \times C_E/C_B = Q_E \times 1$ (for urea) $= Q_E$
- Dose for CRRT is expressed as the effluent rate in ml/hr (Q_E) divided by patient weight = ml/kg/hr

CVVH

- Post-filter (post-dilution) replacement
- Pre-filter (pre-dilution) replacement
- Can be split into pre and post dilution replacement fluid

CVVH Post-Dilution RF



Pt. Weight: 70 kg
Fluid Removal: 0
Hct: 30%
Dose: 1500 / 70 = **21 ml/kg/hr**

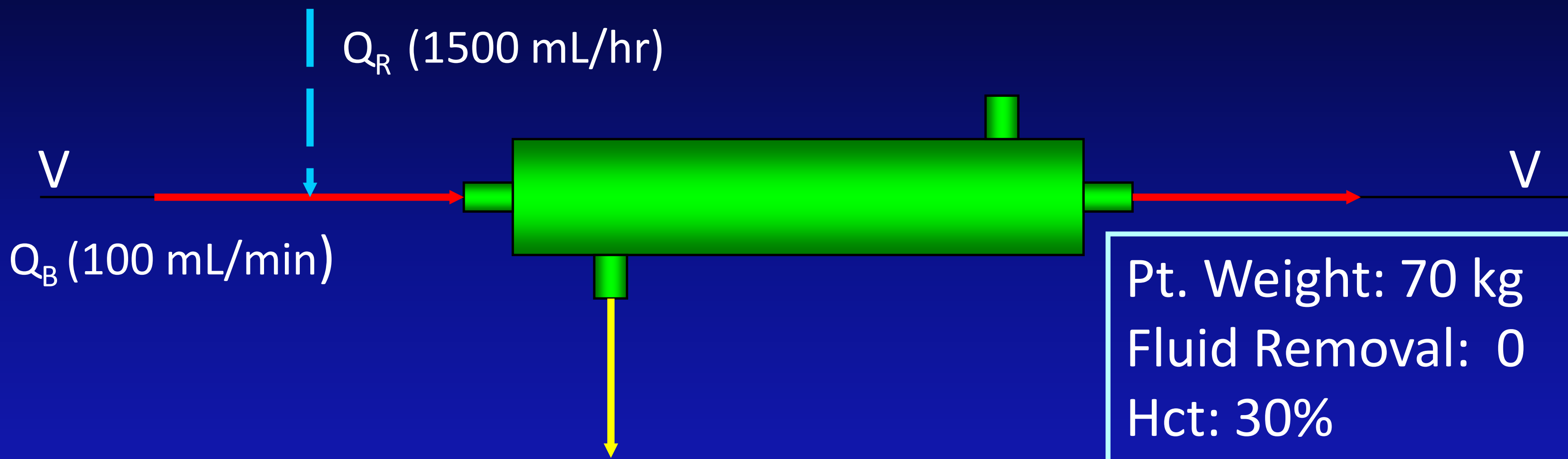
- Filtration Fraction (FF) = $Q_{totalUF}$ / Q_P + $Q_{Pre\text{-}filter\ RF}$
  - $Q_{TotalUF}$ = Total Ultrafiltration Rate*
  - Q_P = Plasma Flow Rate
  - Filtration Fraction (FF) = Total Ultrafiltration Rate / (Plasma Flow Rate + Pre-Filter Replacement Fluid Rate)
- Filter clotting with FF > 20-25%
- FF = 1500 / [6000 x (1-0.30)] = 0.36

*Remember Total UF = Replacement Fluid Rate (Pre and Post) + Fluid Removal Rate

Pre-Dilution Replacement Fluid

- Decreases filtration fraction
- Diminishes solute clearance by diluting blood reaching dialyzer
- Dilution Factor: $$\frac{Q_P}{Q_P + Q_R}$$
- Q_P = blood water flow rate at the blood pump = Q_B X (1-HCT)
- Pre-dilutional CVVH clearance
  - $K = Q_E \times [Q_P / (Q_P + Q_R)]$

CVVH Pre-Dilution RF

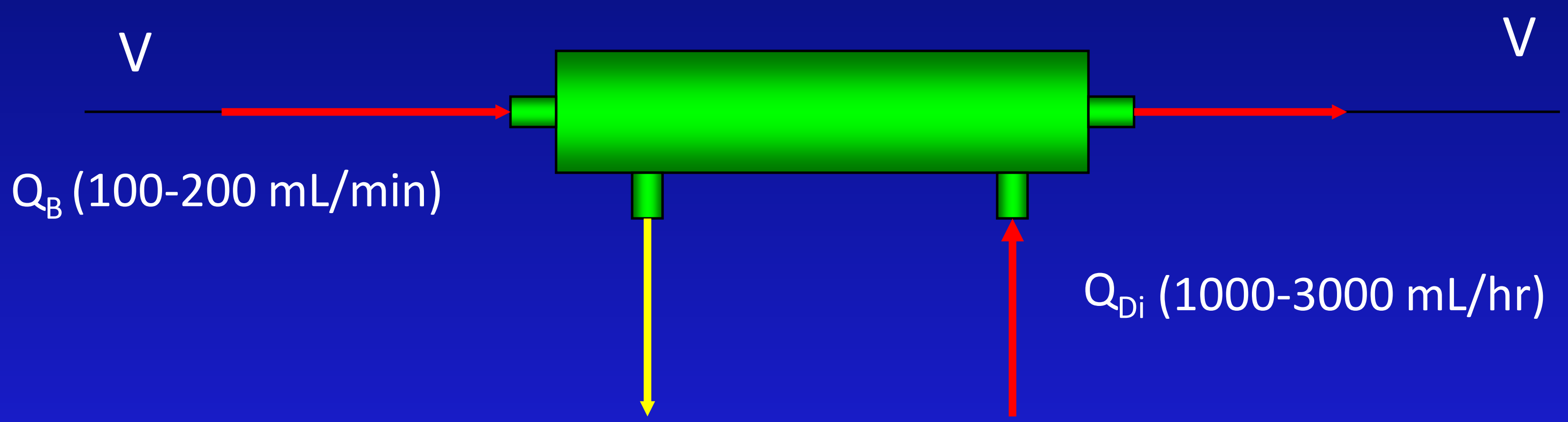


Pt. Weight: 70 kg
Fluid Removal: 0
Hct: 30%

- Dilution factor = $\frac{Q_P}{Q_P + Q_R}$ = 6000 (1 – 0.3) / [(6000 (1-0.3))+ 1500 ml/hr] = 0.74
- K_{urea} = 1.5 L/hr x 0.74 = 1.1 L/hr = **18 mL/min or 16 mL/kg/hr**
- 24% decrease compared to post-dilution
- FF = $Q_{TotalUF}/(Q_P + Q_{Pre\text{-}RF})$ = 1500 / [(6000(1 – 0.3)) + 1500]= 0.26

CVVHD

Solute removal via diffusion dialysis



Effluent Rate (Q_E) = Dialysate Rate + Fluid Removal Rate*

*Fluid Removal Rate can also be called Net UF Rate

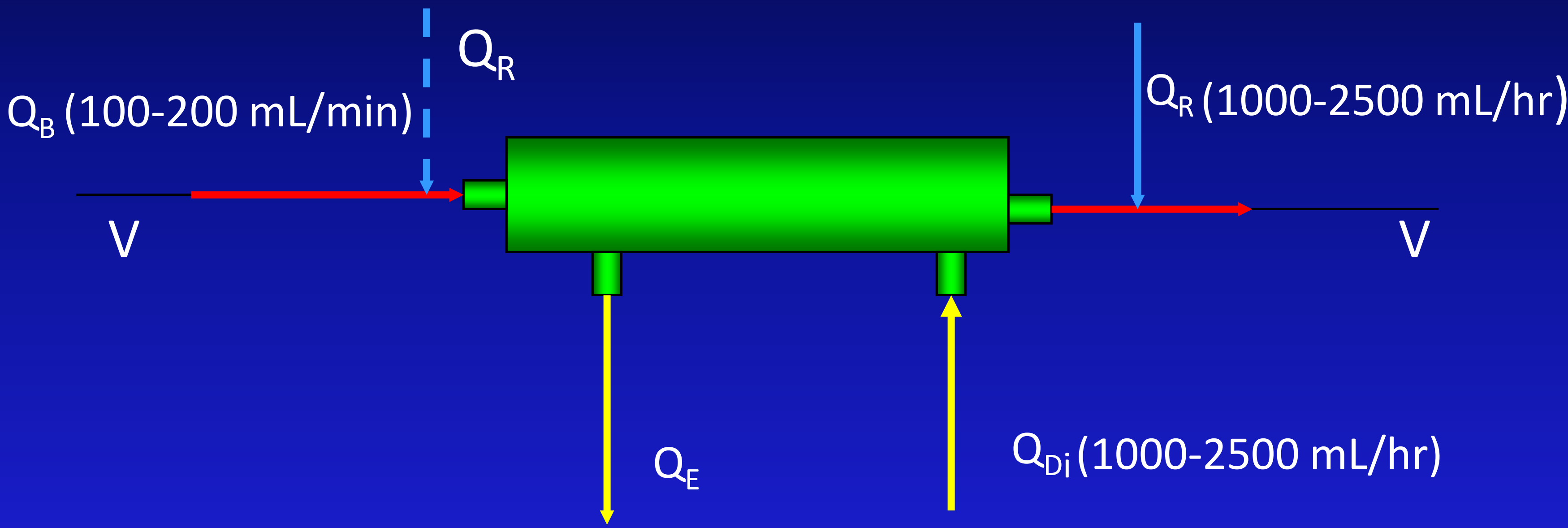
K = Effluent flow rate (Q_E) x C_E/C_B

Example Solute Calculation

- $K = Q_E \times C_E / C_B$
- CVVHD parameters
  - Pt. Wt. 70 kg
  - Dialysate Rate = 1500 mL/hr
  - Fluid Removal (or Net UF) = 0 mL/hr
  - BUN blood conc. = 60 mg/dL
  - BUN dialysate conc. = 60 mg/dL
- What is urea clearance?
  - K =1500 mL/hr X 1 = 1500 mL/hr = **25 mL/min** or **21 ml/kg/hr**

CVVHDF

Diffusion dialysis + Convective hemofiltration



Effluent Rate (Q_E) = Dialysate Rate + Total UF Rate

$Q_{TotalUF} = Q_R + Q_{Fluid\ Removal}$

K = Effluent flow rate (Q_E) x C_E/C_B

Example Solute Calculation

- CVVHDF parameters

  Pt Wt. 70 kg

  Blood Flow Rate = 100 mL/min; hct = 30%

  Pre-filter Replacement Fluid Rate = 1500 mL/hr

  Dialysate Rate = 1500 mL/hr; Fluid Removal Rate = 0 mL/hr

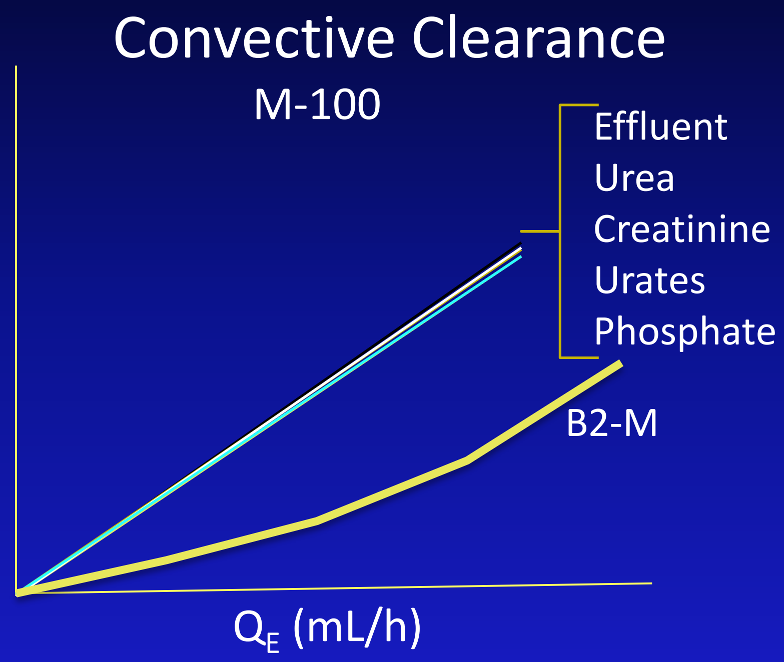
- $K = Q_E \times [Q_P / (Q_P + Q_R)]$

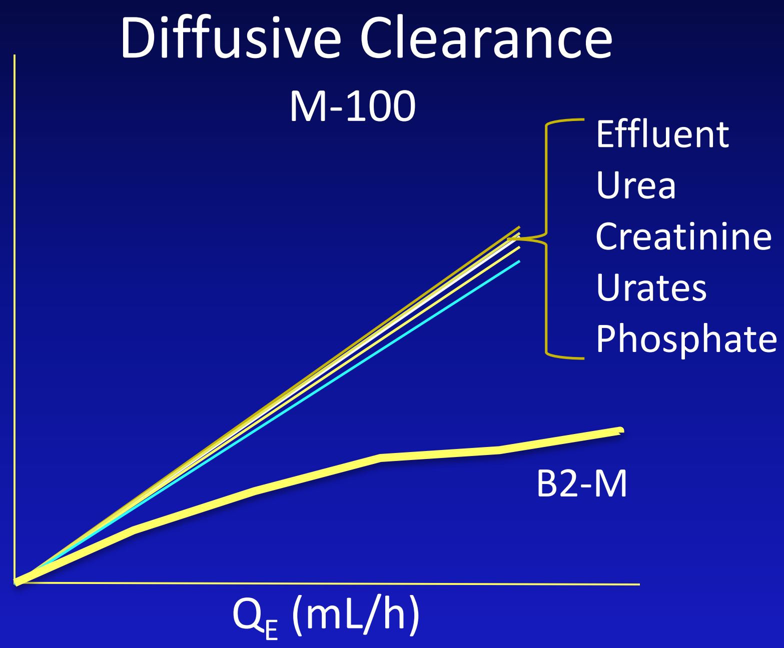
  K = 3000 X [6000 (1-0.3)]/[6000 (1-0.3)+1500] = 2211 ml/hr =

  37 ml/min or **32 mL/kg/hr**

- $FF = Q_{TotalUF} / (Q_P + Q_{Pre\text{-}filter\ RF})$ = 1500 / [(6000(1-0.30)) + 1500] = 0.26

Convection vs. Diffusion





- Clearance is proportional to effluent rate for small molecular weight particles
- Increasing effluent rate increases solute clearance
- CVVH clearance = CVVHD clearance for same effluent rates for small molecular weight particles

Brunet et al. Am J Kidney Dis 1999;34:486-492

Which CRRT Modality?

- Depends on CRRT device
- Depends on need for convective vs. diffusive therapy
- Depends on technical aspects of delivering dose (pre- vs. post dilution RF, filtration fraction, anticoagulation, etc.)

CRRT Machines

NxStage

Prismaflex

CRRT Machines

NxStage

- Has 3 pumps
  - Blood
  - Effluent
  - Dialysate or replacement fluid (pre- or post- replacement fluid)
- Can be used for SCUF, CVVH and CVVHD modalities.
- Cannot perform CVVHDF

Prismaflex

- Has 5 pumps
  - Blood
  - Effluent
  - Dialysate
  - Pre blood
  - Pre and/or Post Replacement fluid
- Can be used for SCUF, CVVH, CVVHD and CVVHDF modalities

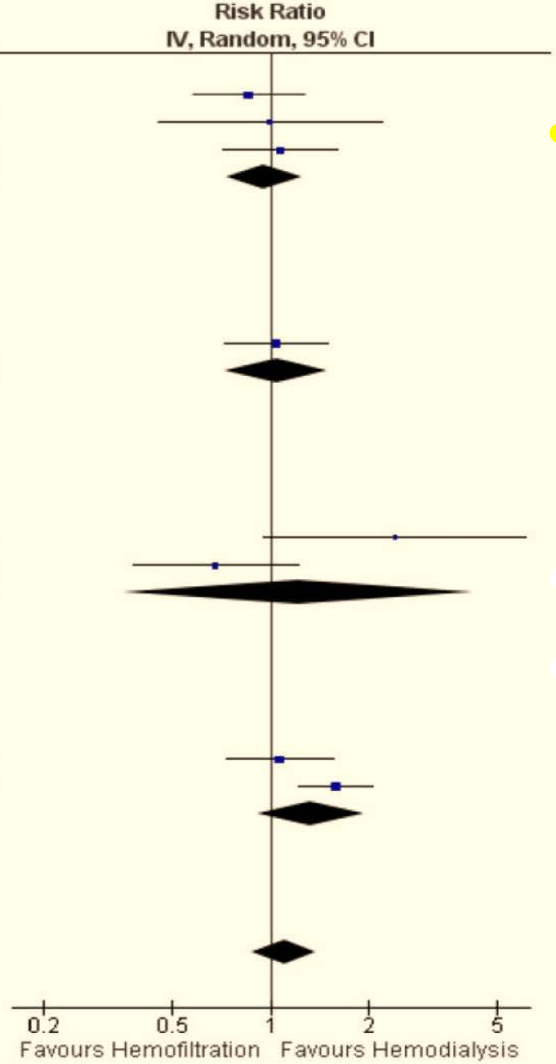
Replacement Fluid Consideration for Prismaflex

DEAERATION CHAMBER

Manages air in the return line, the deaeration chamber provides a unique conveyance path that works like a vortex to propel all air out of the blood. Post-filter replacement solution is added into the deaeration chamber on top of the blood. Using a minimum of 200 to 500 ml/hr of post filter replacement will prevent air/blood interface. This is recommended to minimize clotting and foaming into deaeration chamber.

Are convective therapies better than diffusive therapies?

Study or Subgroup	Hemofiltration Events	Hemofiltration Total	Hemodialysis Events	Hemodialysis Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Similar Dose Filtration vs Dialysis						
Daud 2006 [25]	7	9	10	11	14.7%	0.86 [0.58, 1.27]
Morgera 2004 [24]	6	12	6	12	6.1%	1.00 [0.45, 2.23]
OMAKI 2012 [30]	22	39	20	38	14.3%	1.07 [0.71, 1.61]
Subtotal (95% CI)		**60**		**61**	**35.1%**	**0.96 [0.73, 1.25]**
Total events	35		36			
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.76)						
1.1.2 Similar Dose Filtration vs Dialysis-Filtration						
Chang 2009 [27]	26	47	26	49	15.7%	1.04 [0.72, 1.51]
Subtotal (95% CI)		**47**		**49**	**15.7%**	**1.04 [0.72, 1.51]**
Total events	26		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.82)						
1.1.3 Similar Dose (Intermittent) Dialysis-Filtration vs Dialysis						
Pettila 2001 [23]	12	21	4	17	4.8%	2.43 [0.95, 6.18]
Ratanarat 2012 [29]	10	27	18	33	9.6%	0.68 [0.38, 1.22]
Subtotal (95% CI)		**48**		**50**	**14.4%**	**1.22 [0.35, 4.22]**
Total events	22		22			
Heterogeneity: Tau² = 0.65; Chi² = 5.15, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 0.31 (P = 0.76)						
1.1.4 Filtration vs Higher-Dose Dailysis-Filtration						
Davenport 1993 [21]	7	8	9	11	15.2%	1.07 [0.73, 1.57]
Saudan 2006 [26]	67	102	43	104	19.6%	1.59 [1.21, 2.08]
Subtotal (95% CI)		**110**		**115**	**34.8%**	**1.34 [0.91, 1.96]**
Total events	74		52			
Heterogeneity: Tau² = 0.05; Chi² = 2.76, df = 1 (P = 0.10); I² = 64%						
Test for overall effect: Z = 1.47 (P = 0.14)						
Total (95% CI)		**265**		**275**	**100.0%**	**1.10 [0.88, 1.38]**
Total events	157		136			
Heterogeneity: Tau² = 0.05; Chi² = 13.96, df = 7 (P = 0.05); I² = 50%						
Test for overall effect: Z = 0.87 (P = 0.38)						
Test for subgroup differences: Chi² = 1.97, df = 3 (P = 0.58), I² = 0%						



- HF Compared to HD for AKI: Systematic Review and Meta-analysis
- 19 RCTs
- 16 used CRRT

Friedrich JO, Wald R, Bagshaw SM, Burns KE, Adhikari NK. Crit Care.2012 Aug 6; 16(4):R146

Dose of Acute RRT

- There are no well-established standard methods for assessing efficacy of RRT in AKI

- Assessment of Dose in AKI limited to:
  - Urea kinetics in for IHD
  - BUN levels
  - Effluent volume in CRRT

Is There an Optimal Dose of RRT?

- 2008 VA/NIH Acute Renal Failure Trial (ATN) Network
- Large US multicenter RCT
- Primary endpoint: Death from any cause at day 60
- Objective: To determine the optimal intensity of RRT in critically ill patients with AKI

- 2009 RENAL Replacement Therapy Study Investigators
- Large Australian and New Zealand multicenter RCT
- Primary endpoint: Death within 90 days after randomization
- Objective: To determine the optimal intensity of RRT in critically ill patients with AKI

Bellomo R, *et al*. New Engl J Med 2009;361:1627-1638
Palevsky PM, *et al*. New Engl J Med 2008; 359:7-20

ATN Trial

Modality	Intensive management strategy	Less-intensive management strategy
Hemodynamically stable patients: IHD*	6x/week	3x/week
Hemodynamically unstable patients: CVVHDF	35 mL/kg/hr	20 mL/kg/hr
Hemodynamically unstable patients: SLED*	6x/week	3x/week

*target Kt/V: 1.2-1.4/treatment

Palevsky PM, *et al*. New Engl J Med 2008; 359:7-20

RENAL Trial

1508 patients
35 sites
3 years

Randomization

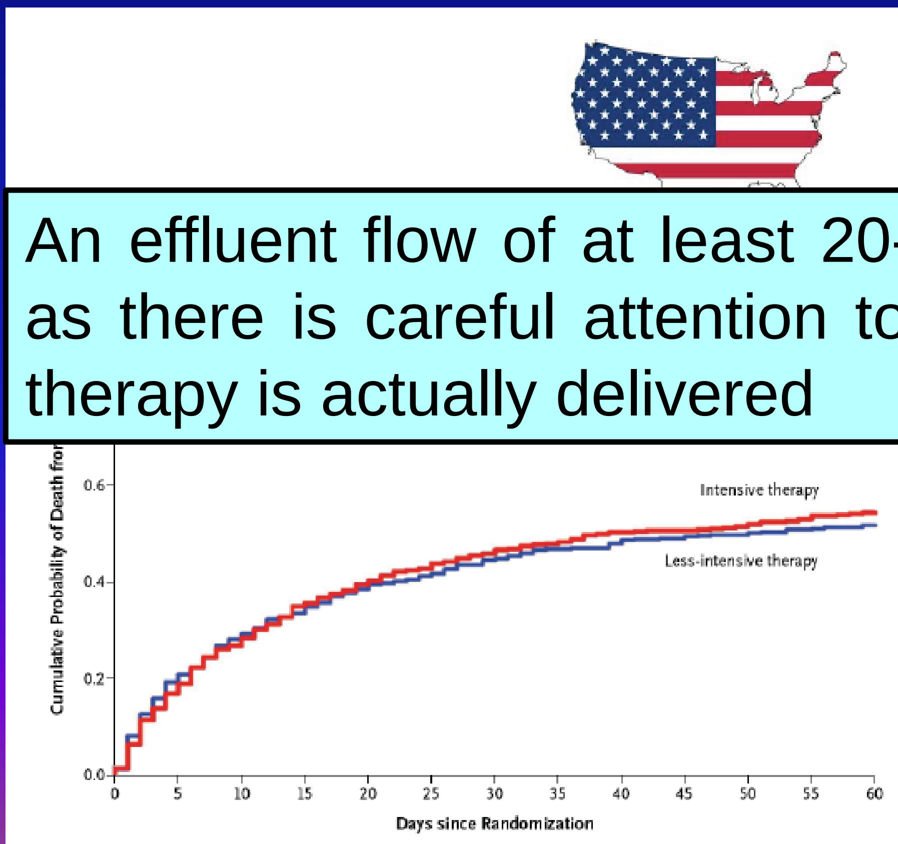
- Intensive CRRT (post-dilution CVVHDF 40 mL/kg/hr effluent)
- 747 patients

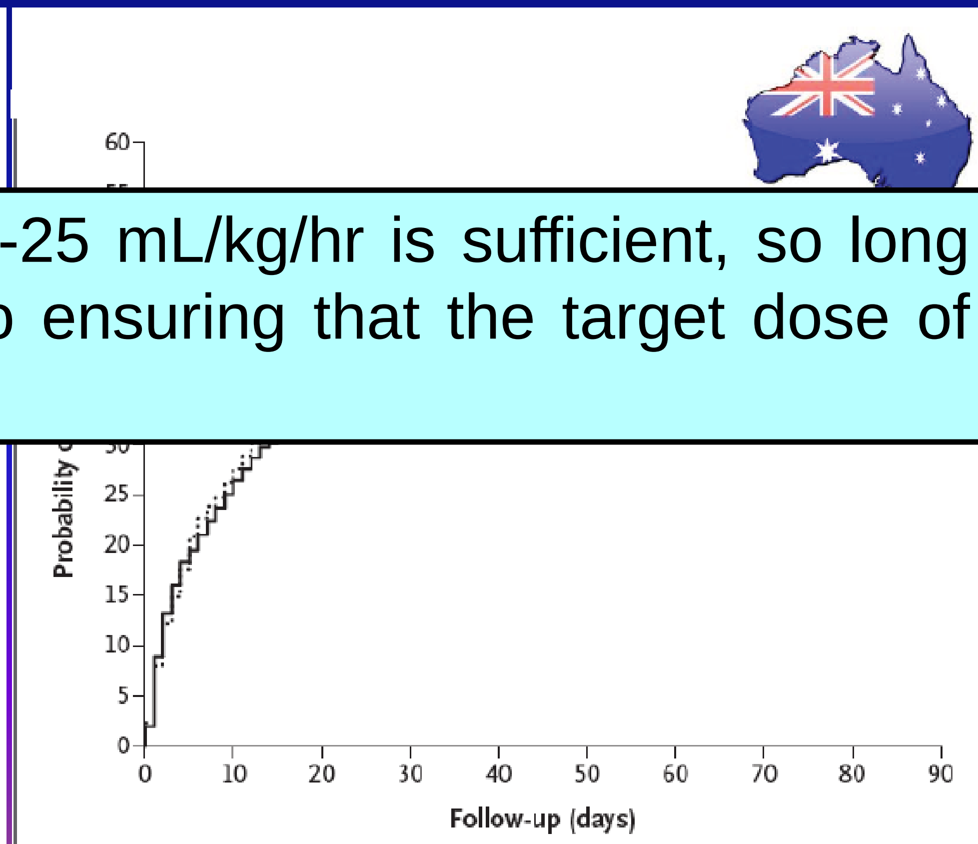
- Conventional CRRT (post-dilution CVVHDF 25 mL/kg/hr effluent)
- 761 patients

Bellomo R, *et al*. New Engl J Med 2009;361:1627-168

		
Mortality at day 60 (%)	52.5	NR
Mortality at day 90 (%)	NR	44.7
Survivors dependant on RRT at day 28 (%)	45.2	13.3
Survivors dependant on RRT at day 60 (%)	24.6	NR
Survivors dependant on RRT at day 90 (%)	NR	5.6

Outcomes





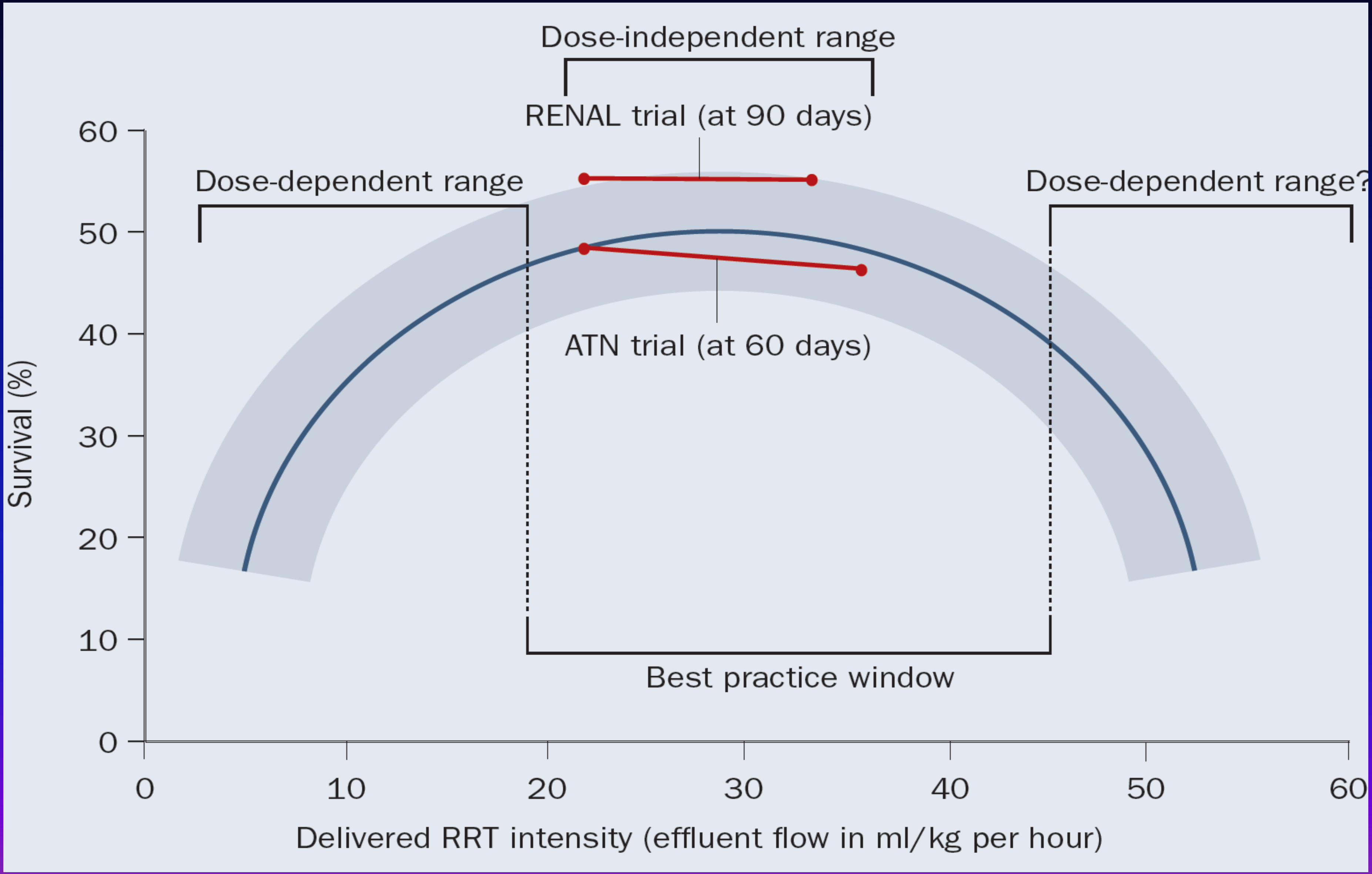
An effluent flow of at least 20-25 mL/kg/hr is sufficient, so long as there is careful attention to ensuring that the target dose of therapy is actually delivered

Prescribed vs Actual Delivered Dose

	Standard dose (20 mg/kg/h)	High dose (35 mg/kg/h)	P
Prescribed clearance (K_P)	17.62 ± 0.96	28.10 ± 1.44	<0.0001
Estimated clearance (K_E)	15.79 ± 2.47	25.10 ± 3.16	<0.0001
Urea clearance (K_U)	15.55 ± 3.07	23.31 ± 5.30	<0.0001
Creatinine clearance (K_C)	15.67 ± 3.88	21.62 ± 5.5	<0.0001

CVVHDF Clearance Comparisons

Delivered RRT Dose and Survival



Kellum JA and Ronco C Nature Reviews Nephrology; 2010

Dosing of RRT in AKI

- Intermittent hemodialysis

  No need to provide treatments more than 3x/week so long as a target Kt/V_{urea} of 1.2-1.4 per treatment is achieved

- Continuous renal replacement therapy

  An effluent flow of at least 20 mL/kg/hr is sufficient, so long as there is careful attention to ensuring that the target dose of therapy is actually delivered

- Delivered dose is less than prescribed dose

  Clearances should be measured in routine care and used to optimize dose

What about high volume hemofiltration (HVHF) for sepsis?

HVHF for Septic AKI: Meta-analysis

Objective:

- To evaluate the effects of HVHF compared with SVHF for septic AKI

Methods:

- Publications between1966 and 2013
- RCTs that compared HVHF (effluent rate >50 ml/kg/hr) vs. SVHF in the treatment of sepsis and septic shock

Clark E, et al. Crit Care 2014

What about high volume hemofiltration (HVHF) for sepsis?

Primary outcome: 28-day mortality

Secondary outcomes:

- Recovery of kidney function
- Lengths of ICU and hospital stay
- Vasopressor dose reduction

Clark E, et al. Crit Care 2014

HVHF for Septic AKI

Study	Location	Setting	Jadad scale	Primary endpoint	Follow-up
Boussekey 2008	France	Single-center ICU	3	75% decrease in vasopressor dose after 24 hrs	28 days
Sanchez (2010)	Spain	Single-center ICU	1	All cause mortality at 28 days	---
Zhang (2012)	China	Single-center ICU	2	All cause mortality at 28 days	90 days
Joannes-Boyau (2013)	France, Belgium, the Netherlands	18 ICUS	3	All cause mortality at 28 days	90 days

Clark E, *et al*. Crit Care 2014;27:42-49

HVHF for Septic AKI

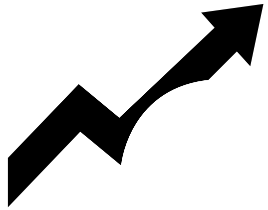
Details of high-volume and standard-volume hemofiltration (CVVH) for included studies

Study	Prescribed effluent rate (mL/kg/hr) HVHF	Prescribed effluent rate (mL/kg/hr) control HVHF	Delivered effluent rate (mL/kg/hr) HVHF	Delivered effluent rate (mL/kg/hr) control HVHF	Days in ICU prior to enrollment HVHF	Days in ICU prior to enrollment control HVHF	Duration of HF (days) HVHF	Duration of HF (days) control HVHF
Boussekey 2008	65	35	62	32	Not stated	Not stated	7	6
Sanchez (2010)	55	35	---	---	---	---	5.7	6.4
Zhang (2012)	85	50	87.54	49.99	5.4	6.2	9.38	8.88
Joannes-Boyau (2013)	70	35	65.6	33.2	2.4	1.9	6	7

Clark E, *et al*. Crit Care 2014;27:42-49

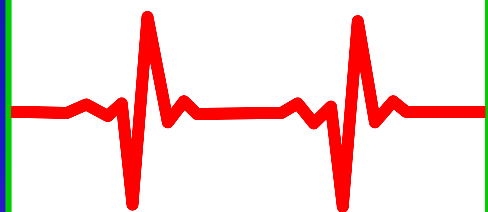
HVHF for Septic AKI

Results



No difference in renal recovery

No reduction in vasopressor requirements



No mortality reduction with HVHF

Clark E, *et al*. Crit Care 2014;27:42-49

Early HVHF vs Standard Care for Post-Cardiac Surgery Shock: HEROICS Study

ICU admission postcardiac surgery

3-24 h

Severe shock requiring high-dose catecholamines

Randomization

Early HVHF 80 mL/kg/h for 48 h

After 48 hrs, stop HVHF, then start CVVHDF until:
- urine output >1500 mL/J and
- epinephrine (E) <0.1 μg/kg/min and
- E + (NE/2) <0.1 μg/kg/min

CVVHDF settings
- reinfusion + dialysate <35 mL/kg/h
- (maximum 3500 mL/h)
- 50% reinfusion/50% dialysate
- Reinfusion 100% pre-filter

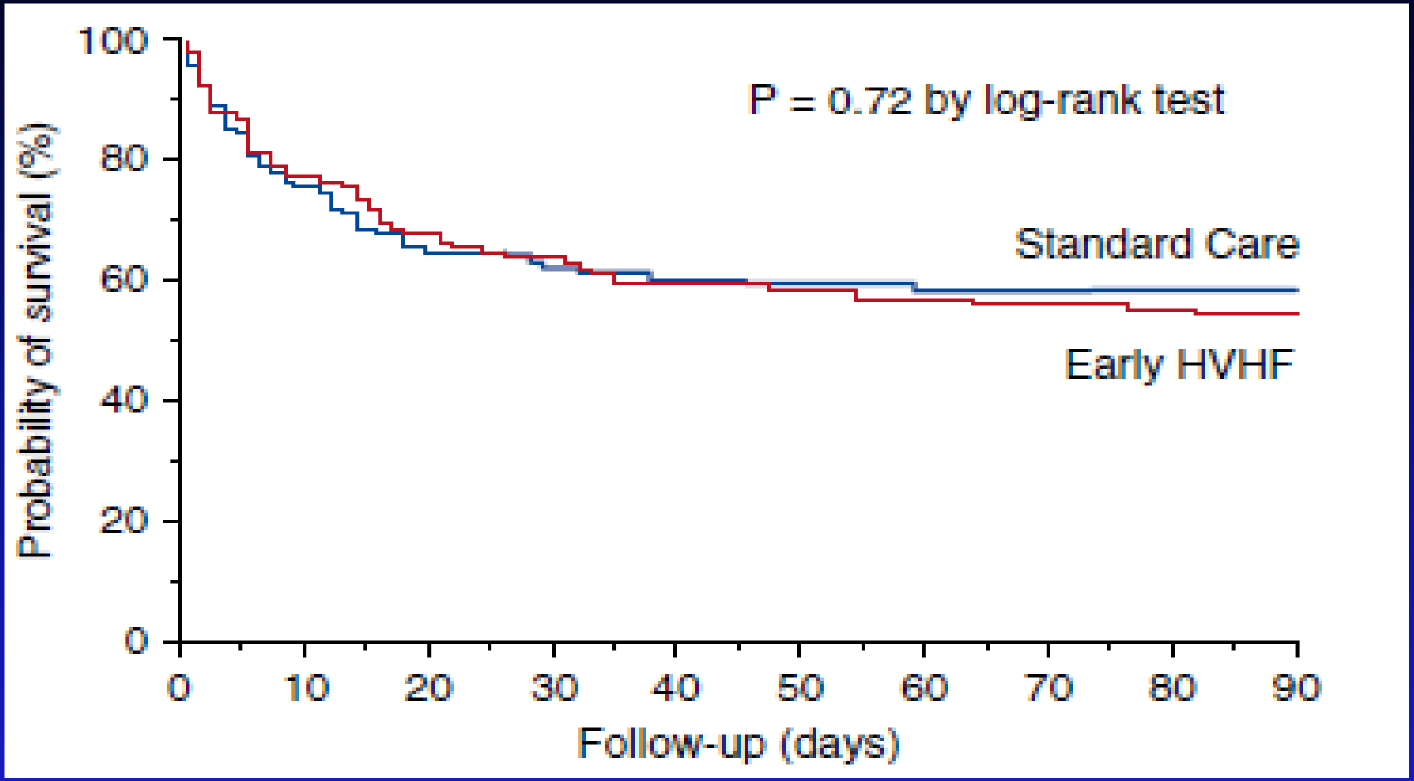
Standard care

Initiate CVVHDF only if:
- creatinine >4 mg/dL
- preoperative creatinine x 3 or
- urine output <0.3 mL/kg/h /24 h or
- urea >36 mmol/L or
- life-threatening hyperkalemia

CVVHDF settings
- reinfusion + dialysate <35 mL/kg/h (maximum 3500 mL/h)
- 50% reinfusion/50% dialysate
- reinfusion 100% pre-filter

Combes A, *et al*. Am J Crit Care Med 2015;27:1179-1190

Results



- Early HVHF did not lower Day-30 mortality and did not impact other important patient-centered outcomes compared with delayed CVVHDF initiation for patients with persistent, severe AKI
- HVHF patients experienced faster correction of metabolic acidosis and tended to be more rapidly weaned off catecholamines but had more frequent hypophosphatemia, metabolic alkalosis, and thrombocytopenia

High-Dose vs. Conventional-Dose CVVHDF and Patient and Kidney Survival and Cytokine Removal in Sepsis-AKI: A RCT

- SETTING & PARTICIPANTS:
  - Septic patients with AKI receiving CVVHDF for AKI
- INTERVENTION:
  - Conventional (40mL/kg/h) and high (80mL/kg/h) doses of CVVHDF
- OUTCOMES:
  - Patient and kidney survival at 28 and 90 days, circulating cytokine levels
- RESULTS:
  - 212 patients randomized
  - No differences in 28-day mortality (HR, 1.02; 95% CI, 0.73-1.43; P=0.9) or 28-day kidney survival (HR, 0.96; 95% CI, 0.48-1.93; P=0.9) between groups
  - High-dose CVVHDF, but not the conventional dose, significantly reduced interleukin 6 (IL-6), IL-8, IL-1b, and IL-10 levels

HICORES Investigators. Am J Kidney Dis. 2016

Case

A 24YOM with HTN and OSA presents with acute pancreatitis. Despite aggressive fluid resuscitation and antibiotics for sepsis, he develops oliguric AKI with hyperkalemia. He is intubated on FIO_2 80% and is requiring vasopressin and norepinephrine. He is febrile and weighs 100 kg. He is on antibiotics and IV bicarbonate infusion. His labs are as follows:

Na 138 meq/L, K 6.5 meq/L, Cl 109 meq/L, HCO_3 22 meq/L, BUN 22 mg/dL, Creatinine 3.1 mg/dL; ABG: 7.21/pCO_2 40 mmHg/pO_2 108 mmHg on 80% FIO_2; WBC 13,000, Hct 30%, Platelets 104,000; Lactic acid 1.8 mmol/L; INR 1.6; Total Bili 3.2 mg/dL; ALT 694 U/L; AST 640 U/L; and CPK 22,000 U/L. He is 9 liters positive over last 24 hours.

Case

Which CRRT modality do you place him on?

A. CVVH with pre-filter RF
B. CVVH with post-filter RF
C. CVVH with pre- and post-filter RF
D. CVVHD
E. CVVHDF with pre-filter RF
F. CVVHDF with post-filter RF
G. CVVHDF with pre- and post- filter RF
H. Any of the above
I. None of the above
J. I don't know

Patient is placed on the following CRRT Rx:

CRRT Parameters:

- CVVH with NxStage
- BF: 100 ml/min
- Post-filter RF: 1500 ml/hr
- Fluid Removal: 200 ml/hr
- No anticoagulation

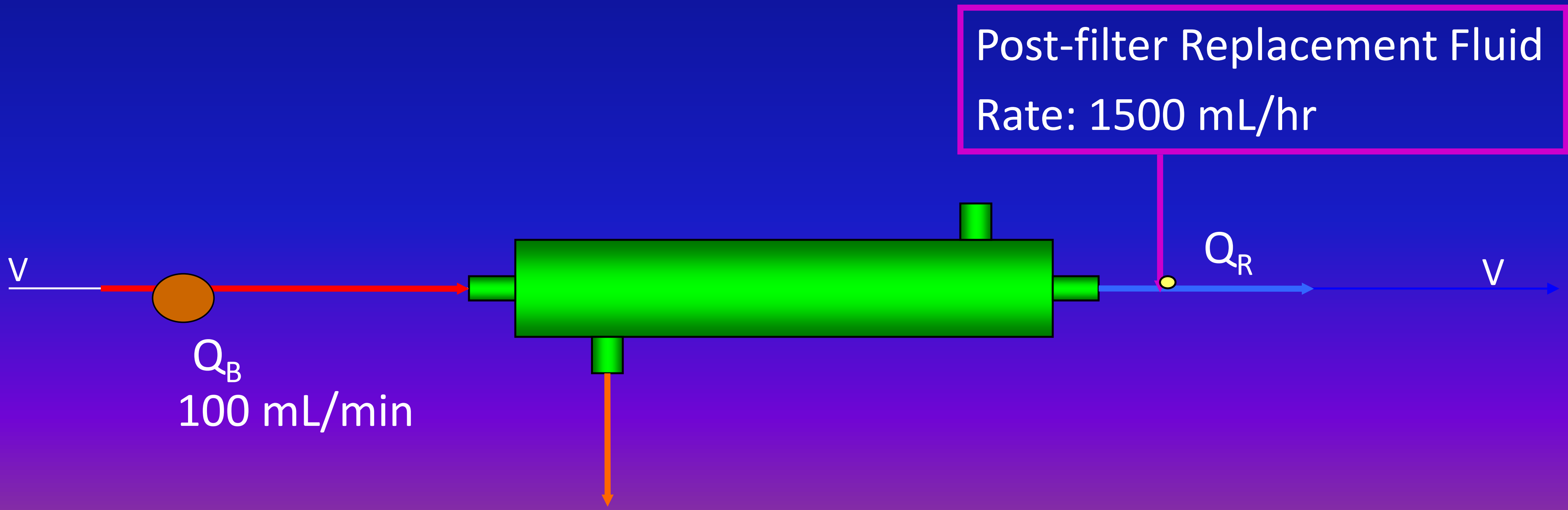
What are your thoughts on prescription?

- CRRT modality?
- Dose?
- Filtration fraction?
- Anticoagulation?

Dose?

- CVVH
- BF: 100 ml/min
- Post-filter RF: 1500 ml/hr
- Fluid Removal: 200 ml/hr
- Patient weight: 100 kg
- Hct: 30%

- Effluent Rate = 1500 ml/hr + 200 ml/hr = 1700 ml/hr
- Dose = 1700 / 100 kg = 17 ml/kg/hr



Filtration Fraction?

- BF: 100 ml/min
- Post-filter RF: 1500 ml/hr
- Fluid Removal: 200 ml/hr
- Patient weight: 100 kg
- Hct: 30%

- $FF = Q_{UF} / (Q_P + Q_{Pre\text{-}filter\ RF})$
- $Q_P = [Q_B \times (1 - Hct)]$
- $FF = (Q_R + Q_{netUF}) / [Q_B (1 - 0.3)]$
- $FF = (1500 + 200)/[(6000 \times 0.7)] = 40\%$
- FF > 25-30%, clotting can occur

Patient is placed on following CRRT prescription:

CRRT Parameters:

- CVVH with Prismaflex
- BF: 200 ml/min
- Pre-filter RF: 2000 ml/hr
- Fluid Removal: 200 ml/hr
- Post-filter RF: 200 ml/hr
- Anticoagulation: ACD-A 2.2% 300 ml/hr delivered through PBP

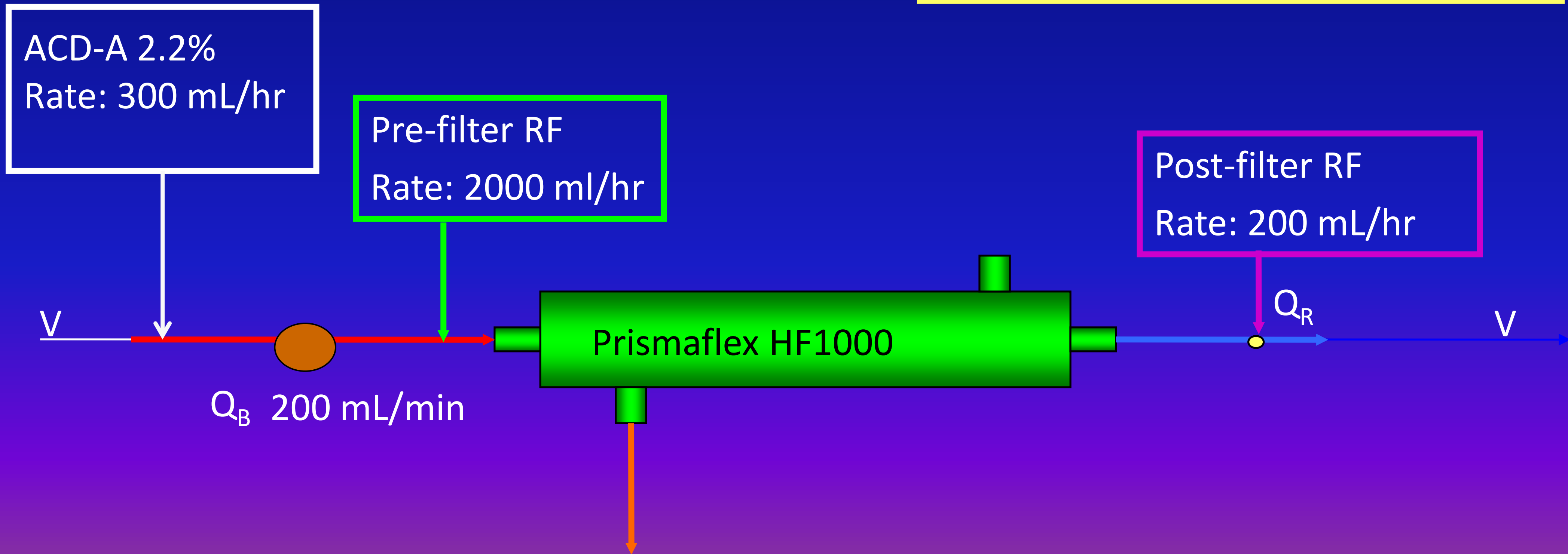
What are your thoughts on prescription?

- CRRT modality?
- Dose (prescribed and delivered)?
- Filtration fraction?
- Anticoagulation?

Dose?

- Effluent Rate = 2000 ml/hr + 200 ml/hr + 200 ml/hr + 300 ml/hr = 2700 ml/hr
- Dose = 2700 / 100 kg = 27 ml/kg/hr
- Dilution factor = (12000 x 0.7)/ [(12000 x 0.7) + 2300] = 0.81
- Dose = 27 ml/kg/hr x 0.81 = 22 ml/kg/hr

- CVVH
- BF: 200 ml/min
- Pre-filter RF: 2000 ml/hr
- Post-filter RF: 200 ml/hr
- Fluid Removal: 200 ml/hr
- Patient weight: 100 kg
- AC: ACD-A 300 ml/hr
- Hct: 30%



Filtration Fraction?

- CVVH
- BF: 200 ml/min
- Pre-dilution: 2000 ml/hr
- Post-filter RF: 200 ml/hr
- Fluid Removal: 200 ml/hr
- Patient weight: 100 kg
- AC: ACD-A 300 ml/hr
- Hct: 30%

- FF = Q_{UF} / (Q_{P} + $Q_{\text{Pre-filter RF}}$)
- FF = ($Q_{\text{Pre-filter}}$ + $Q_{\text{Post-filter}}$ + Q_{NetUF} + Q_{PBP})/ [Q_{B} (1- 0.3) + 2000 + 300]
- FF = (2000 + 200 + 200 + 300)/[(12000 x 0.7) + 2300] = 25%
- FF > 25-30%, clotting can occur