37th Vicenza Course
on
AKI & CRRT
May 28-30, 2019

Barts and The London
School of Medicine and Dentistry

NHS
Barts Health
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CRRT Dose

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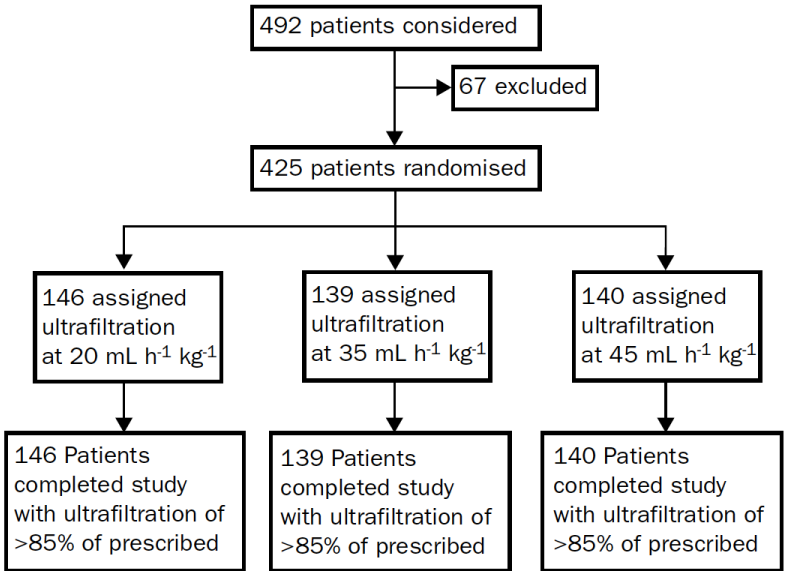
Barts Health NHS
NHS Trust

THE LANCET • Vol 356 • July 1, 2000

ARTICLES

Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial

Claudio Ronco, Rinaldo Bellomo, Peter Homel, Alessandra Brendolan, Maurizio Dan, Pasquale Piccinni, Giuseppe La Greca



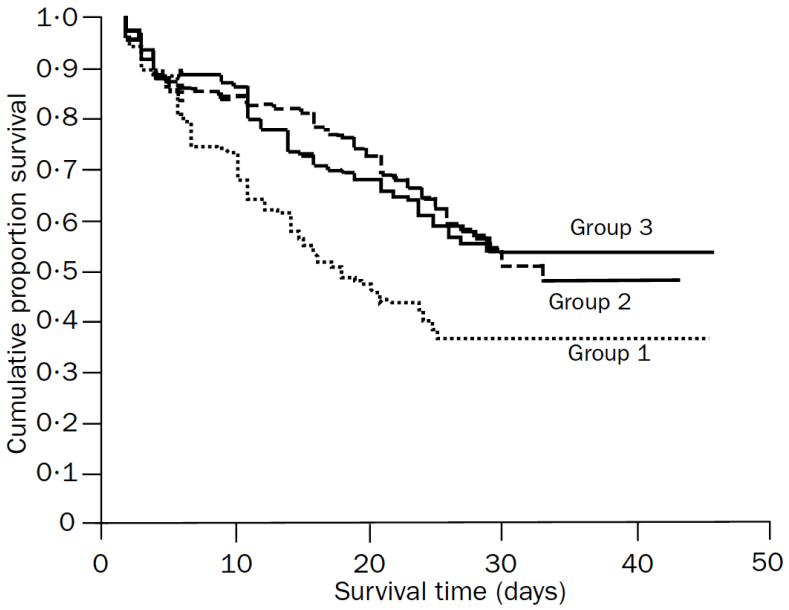


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Table 2: **Results of Cox's proportional hazards regression**

Trial group	No sepsis (%)	Sepsis (%)	p
Group 1	55/126 (44%)	5/20 (25%)	0·90
Group 2	76/122 (62%)	3/17 (18%)	0·001
Group 3	74/125 (59%)	7/15 (47%)	0·256

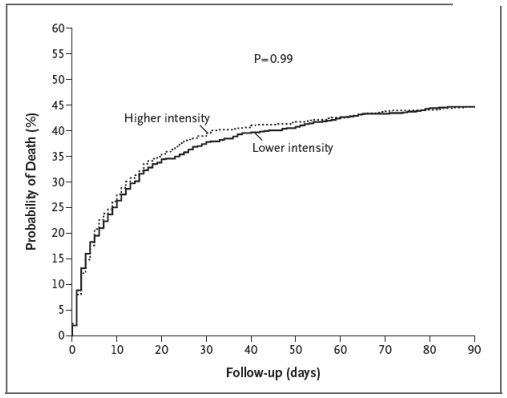
Table 3: **Survival rates stratified by trial group and presence of sepsis**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 22, 2009 VOL. 361 NO. 17

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*

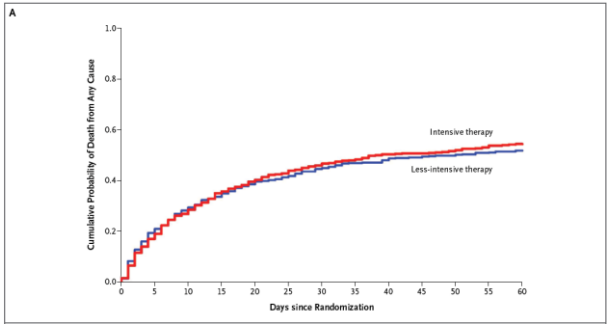


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 3, 2008 VOL. 359 NO. 1

Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury

The VA/NIH Acute Renal Failure Trial Network*



Dose – I Don’t Care

KDIGO Dose

VOLUME 2 | ISSUE 1 | MARCH 2012
http://www.kidney-international.org

KDIGO Clinical Practice Guideline for Acute Kidney Injury

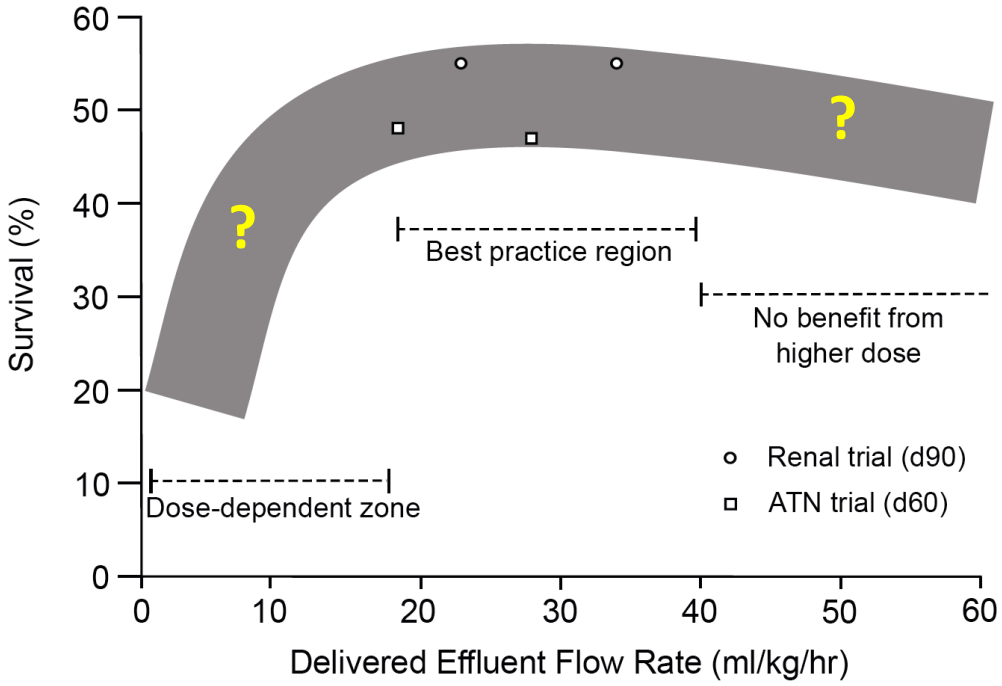
5.8.1: The dose of RRT to be delivered should be prescribed before starting each session of RRT. (*Not Graded*) We recommend frequent assessment of the actual delivered dose in order to adjust the prescription. (*1B*)

5.8.2: Provide RRT to achieve the goals of electrolyte, acid-base, solute, and fluid balance that will meet the patient's needs. (*Not Graded*)

5.8.3: We recommend delivering a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI. (*1A*)

5.8.4: We recommend delivering an effluent volume of 20–25 ml/kg/h for CRRT in AKI *(1A)*. This will usually require a higher prescription of effluent volume. (*Not Graded*)

CRRT: Dose-response



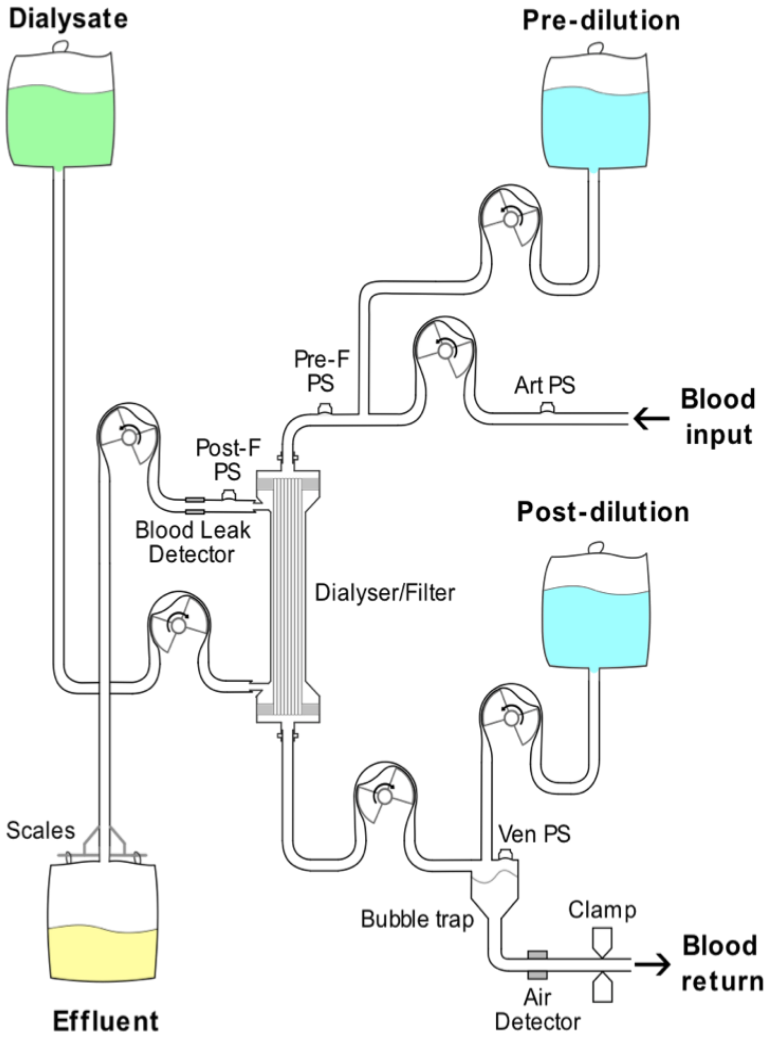
	VA/NIH ATN study	RENAL study
Achieved dose of CRRT (high dose)	27.1 mL/kg per hour[b]	33.4 mL/kg per hour
Achieved dose of CRRT (low dose)	17.5 mL/kg per hour[b]	22 mL/kg per hour

Prowle *et al*. *Critical Care* 2011, **15**:207
http://ccforum.com/content/15/2/207

Dose of RRT - Questions

- Are all doses the same?
- How low can you go?
- Can too much be bad for you?
- Does one size fit all?

Generic CRRT Circuit

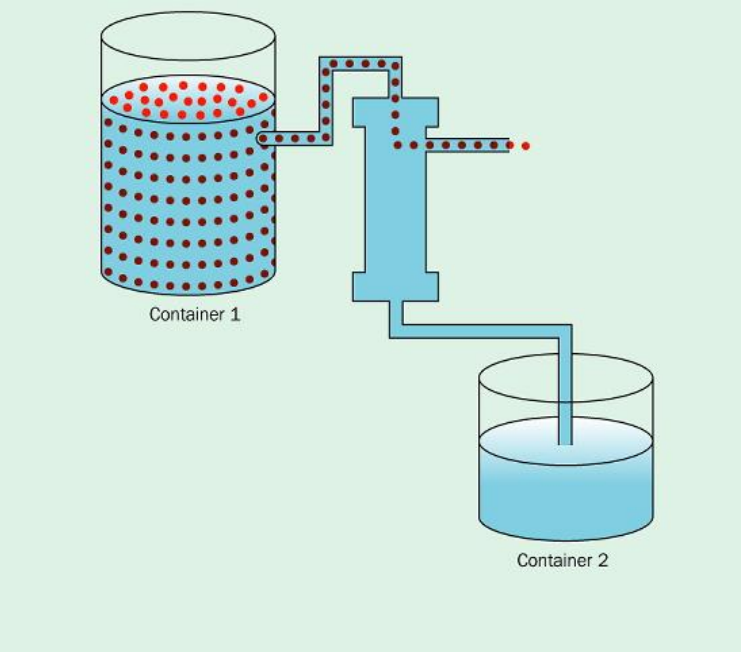


Variables

- Dialyser permeability
- Blood flow rate Q_B
- Dialysis flow rate Q_D
- Ultrafiltration rate Q_F
- Time on RRT

Dose of RRT

Based on clearance of marker molecules from bloodstream



$$K = \frac{Amount\ Excreted}{Blood\ Concentration}$$

Comparison of RRT Regimens

	IHD	SLED	CVVHF	CVVHD
Q_B	200-350	100-300	100-250	100-250
Q_D	500-800	100	0	17-50
Q_F	Var	Var	17-50	Var
Time	4hrs	8-12hrs	20-24hrs	20-24hrs

Small Solute Clearances on Continuous Therapy

Post-dilution CVVHF

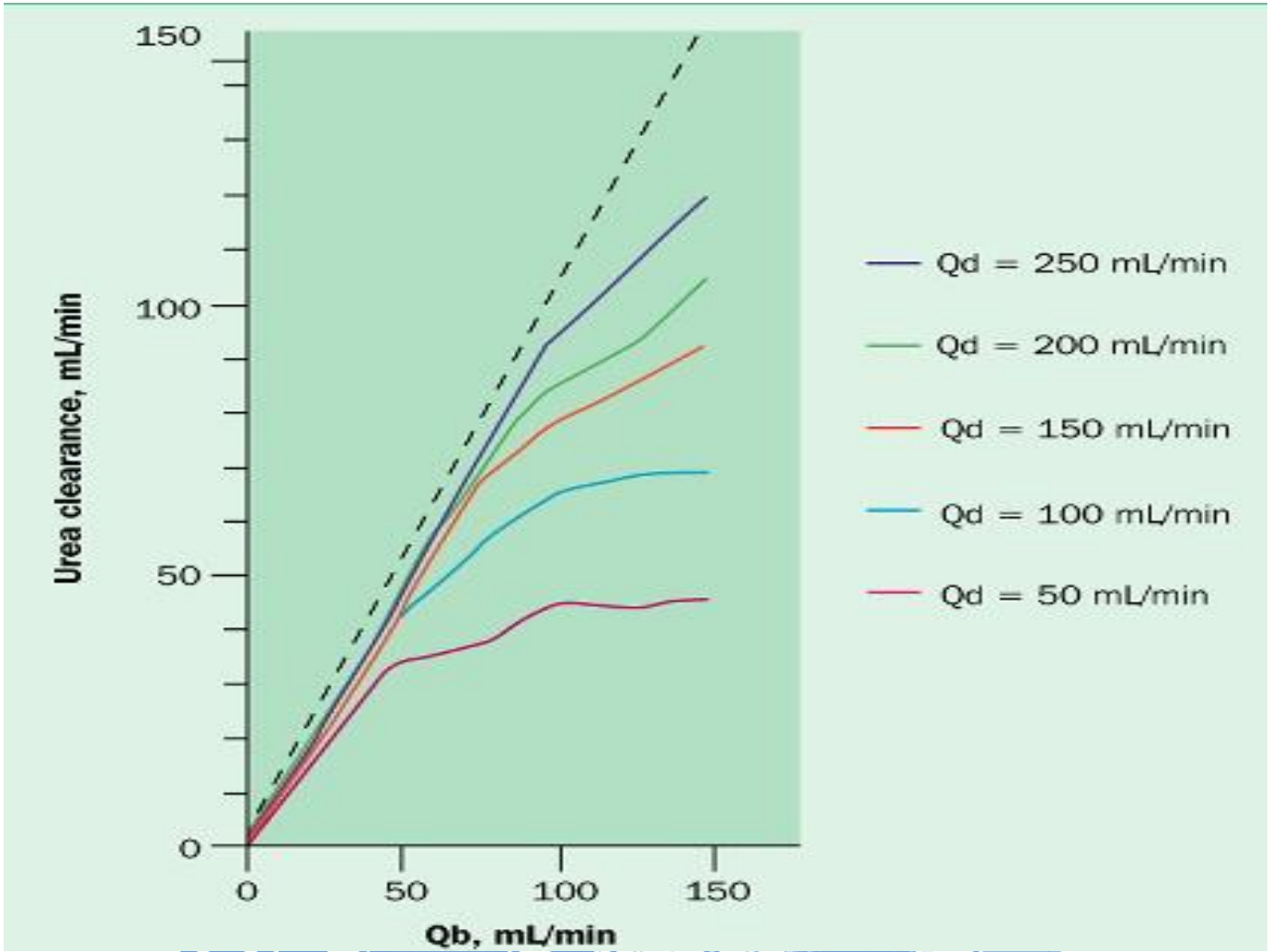
$K_{urea} = Sc.Q_f$

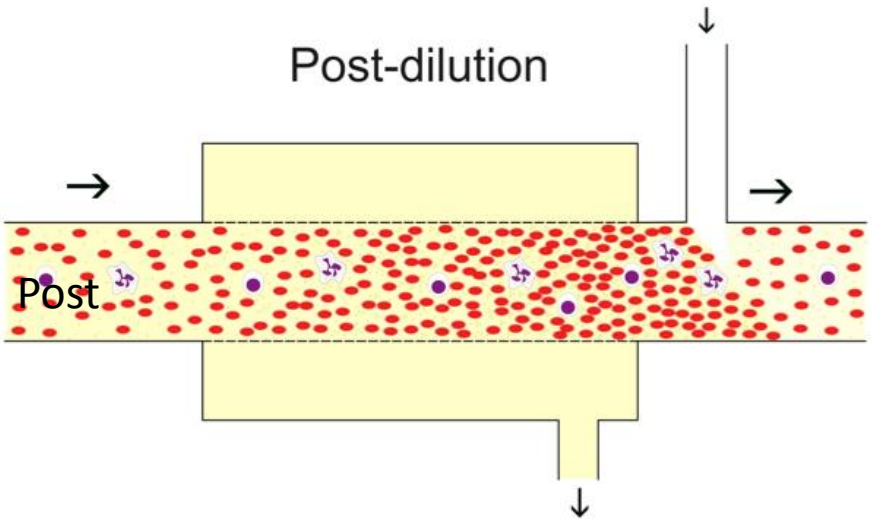
CVVHD with $Q_d << Q_b$

$K_{urea} = Sc.Q_d$

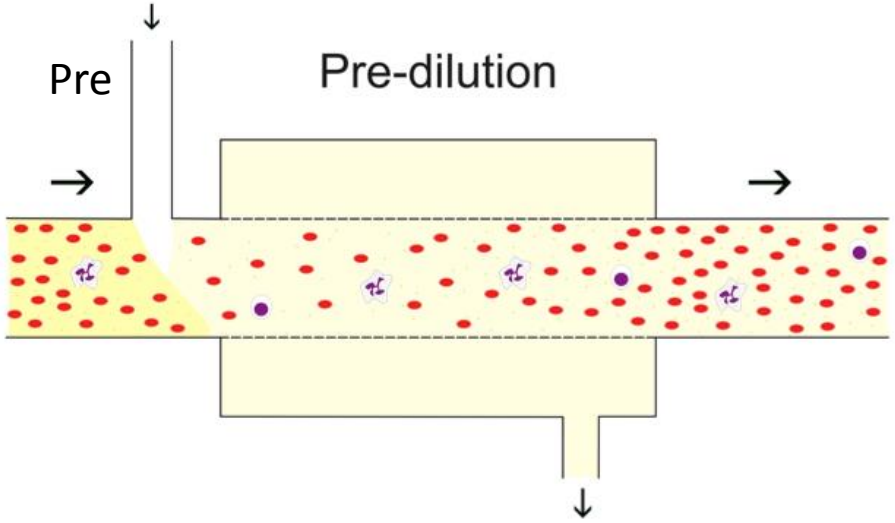
Dose is assessed in CRRT by effluent flow rate ($Q_f + Q_d$) with adjustment for pre-dilution if necessary.

Urea clearance on Dialysis





$$K_{urea} = Sc.Q_F$$

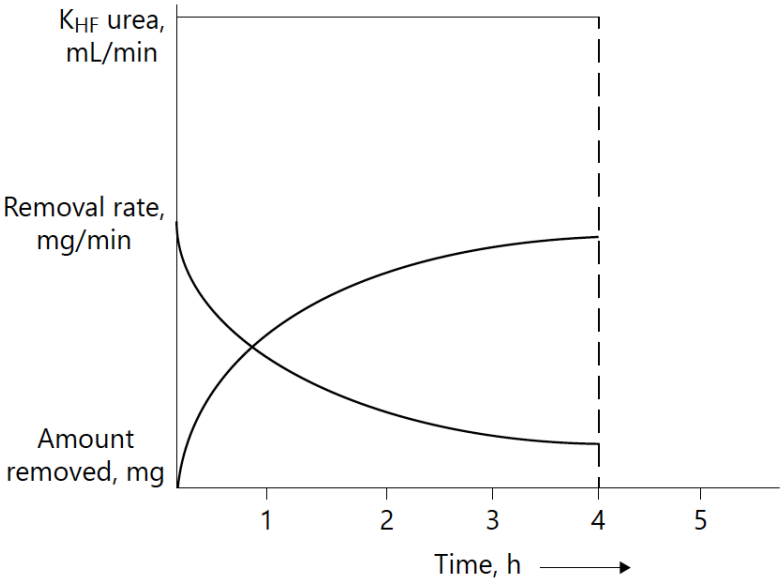


$$K_{urea} = \frac{Sc.Q_F}{1 + Q_R / Q_P}$$

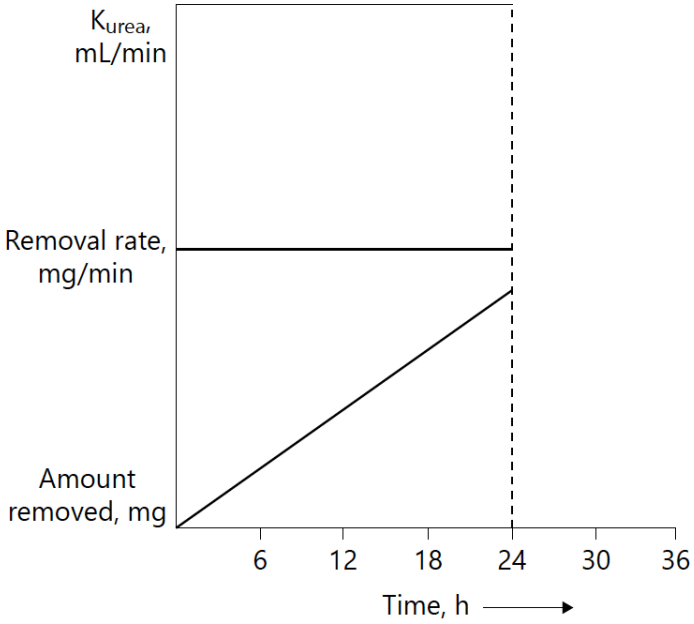
Blood Purif 2017;44:140–155

Clearance vs Solute removal

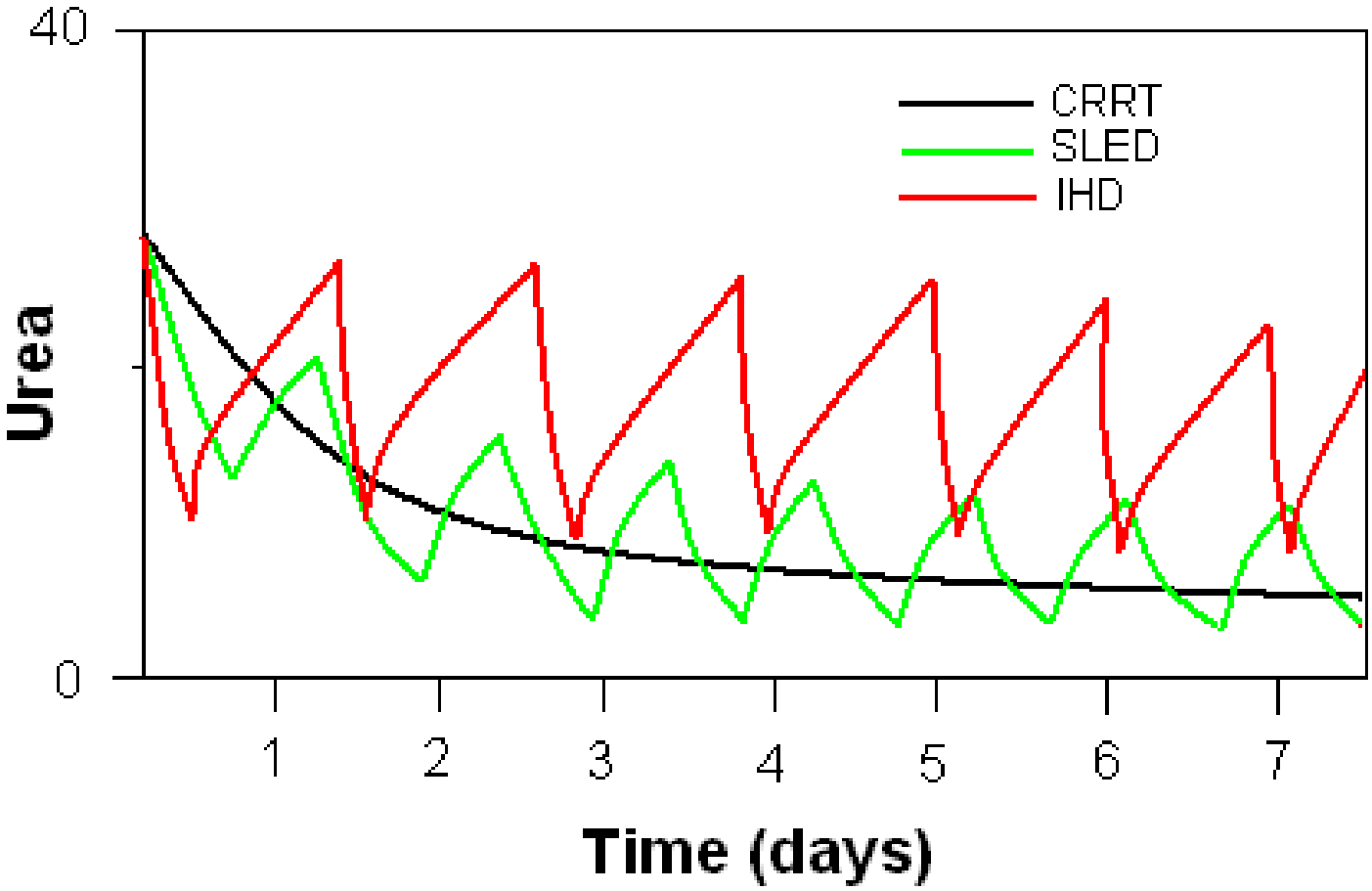
Non-Steady State = IHD



CRRT with *Steady State*



Urea kinetics on RRT



Comparators of dialysis dose for intermittent modalities

- Kt/V per treatment
- Standardised Kt/V
- EKR = G/TAC

Clearances on IHD

Calculated using Urea Kinetic Modelling

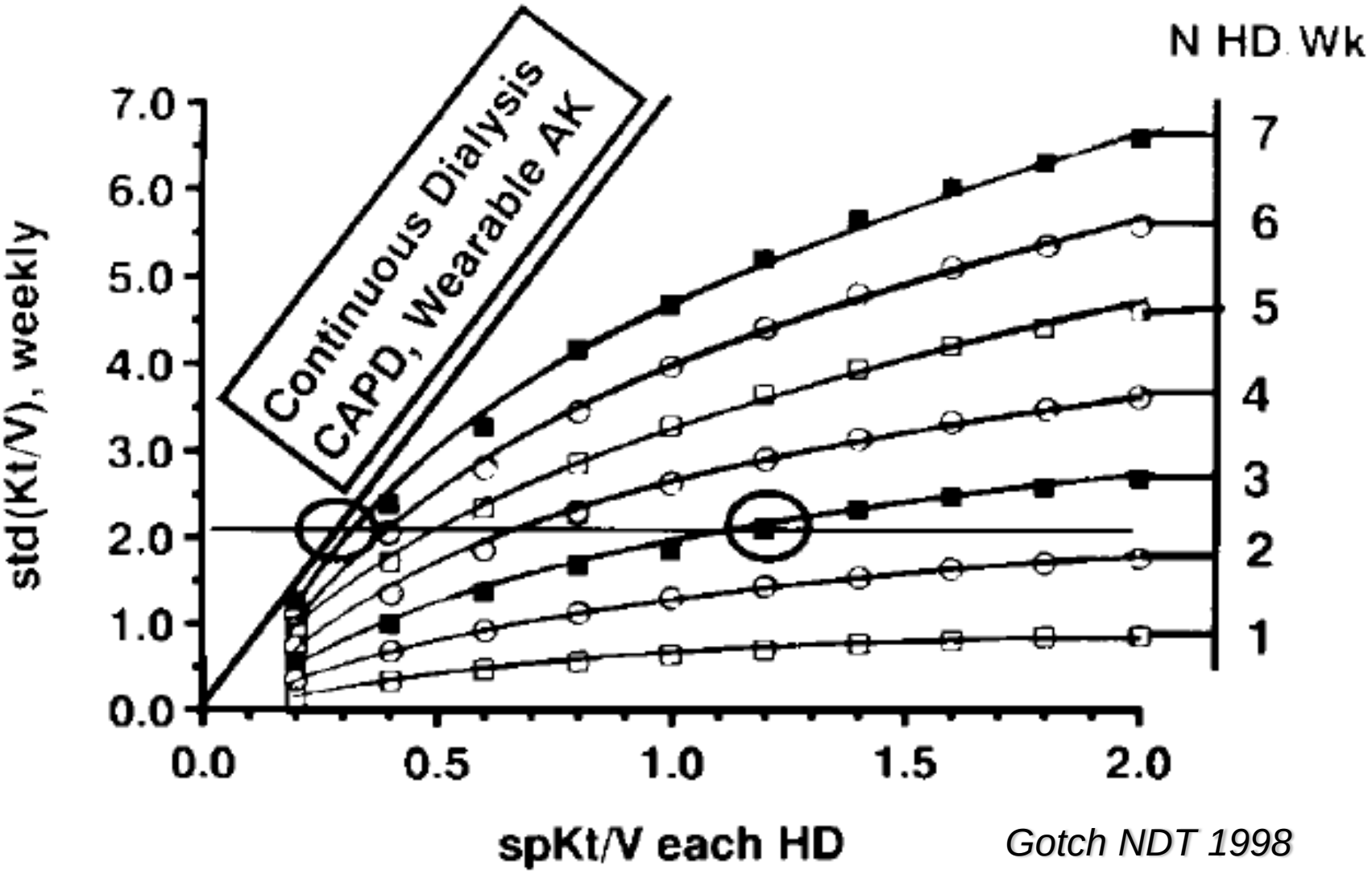
$$Vt = Qf \times t\left[\left[1 - \left[\frac{G - Ct(K + Kr - Qf)}{G - C0(K + Kr - Qf)}\right]^{\frac{Qf}{K + Kr - Qf}}\right]^{-1} - 1\right] \quad (1)$$

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

$$Kt/V = -\ln(UUR - 0.008t) + (4 - 3.5UUR) \times UF/W$$

Comparison of RRT Regimens

	Daily IHD	SLED	CVVHF	CVVHD	Kidney
Q_B	200-350	100-300	100-250	100-250	800-1500
Q_D	500-800	100	0	17-50	
Q_F	Var	Var	17-50	Var	100
Time	4hrs	8-12hrs	20-24hrs	20-24hrs	24hrs
Kt/V	**0.8-1.4**	**1.0-1.7**	**0.8-1.5**	**0.8-1.5**	**3.4**
EKR(Cr)	**20**	**32**	**34**	**34**	**100**



Gotch NDT 1998

Determinants of dialysis dose

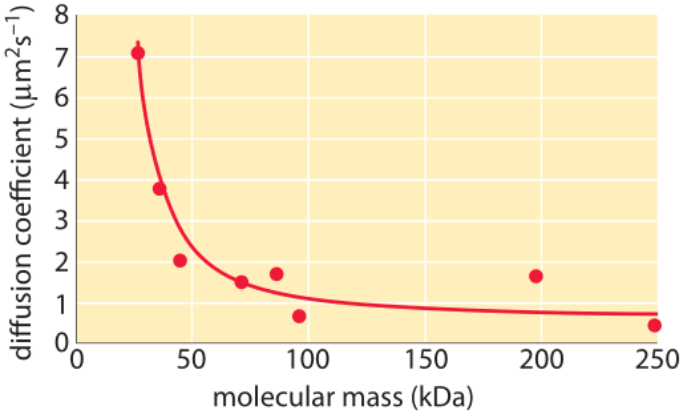
- Ultrafiltration
- Dialyser
  - Bigger molecules
  - If Qb and Qd high
- Dialysis flow rates
  - If Qb low
- Blood flow rates
  - If Qd high
- Time
  - All the time

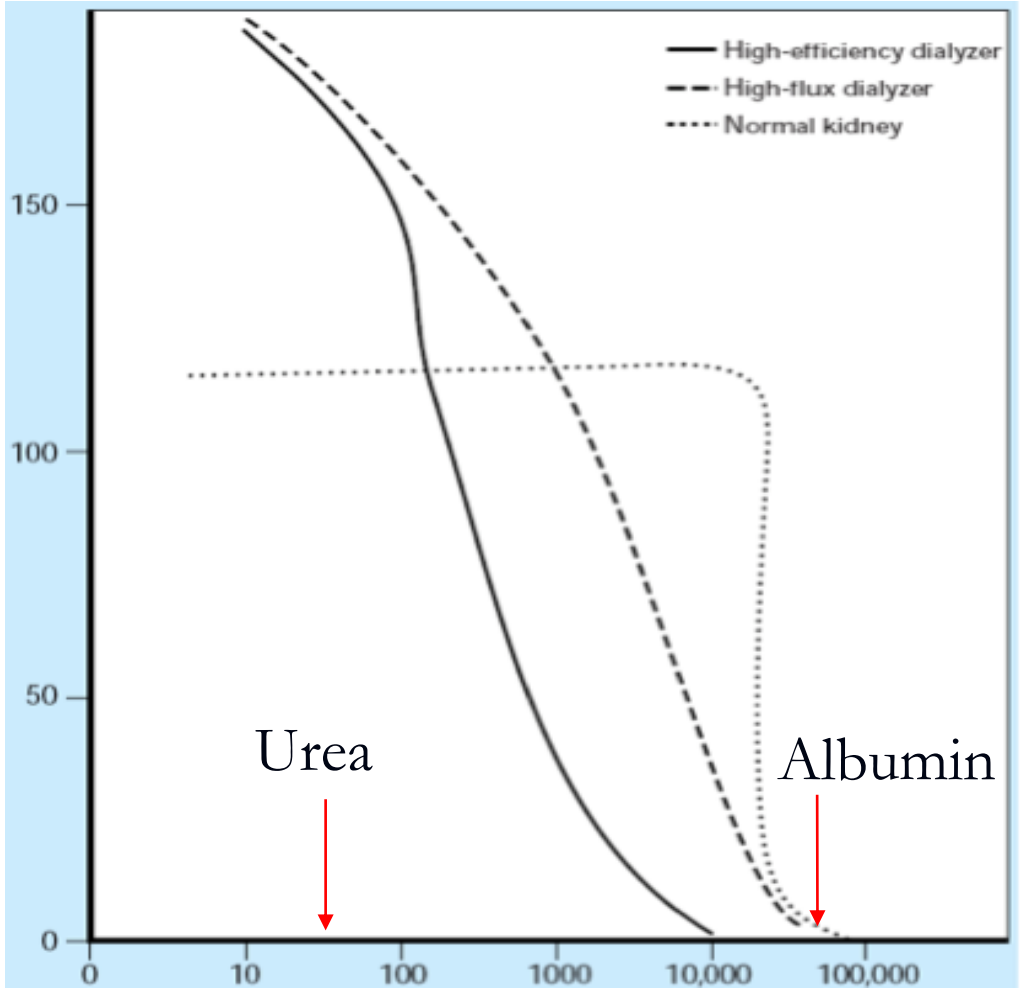
Which molecule?

- Urea 60 Da
- Creatinine 113 Da
- ®2 Microglobulin 12 kDa

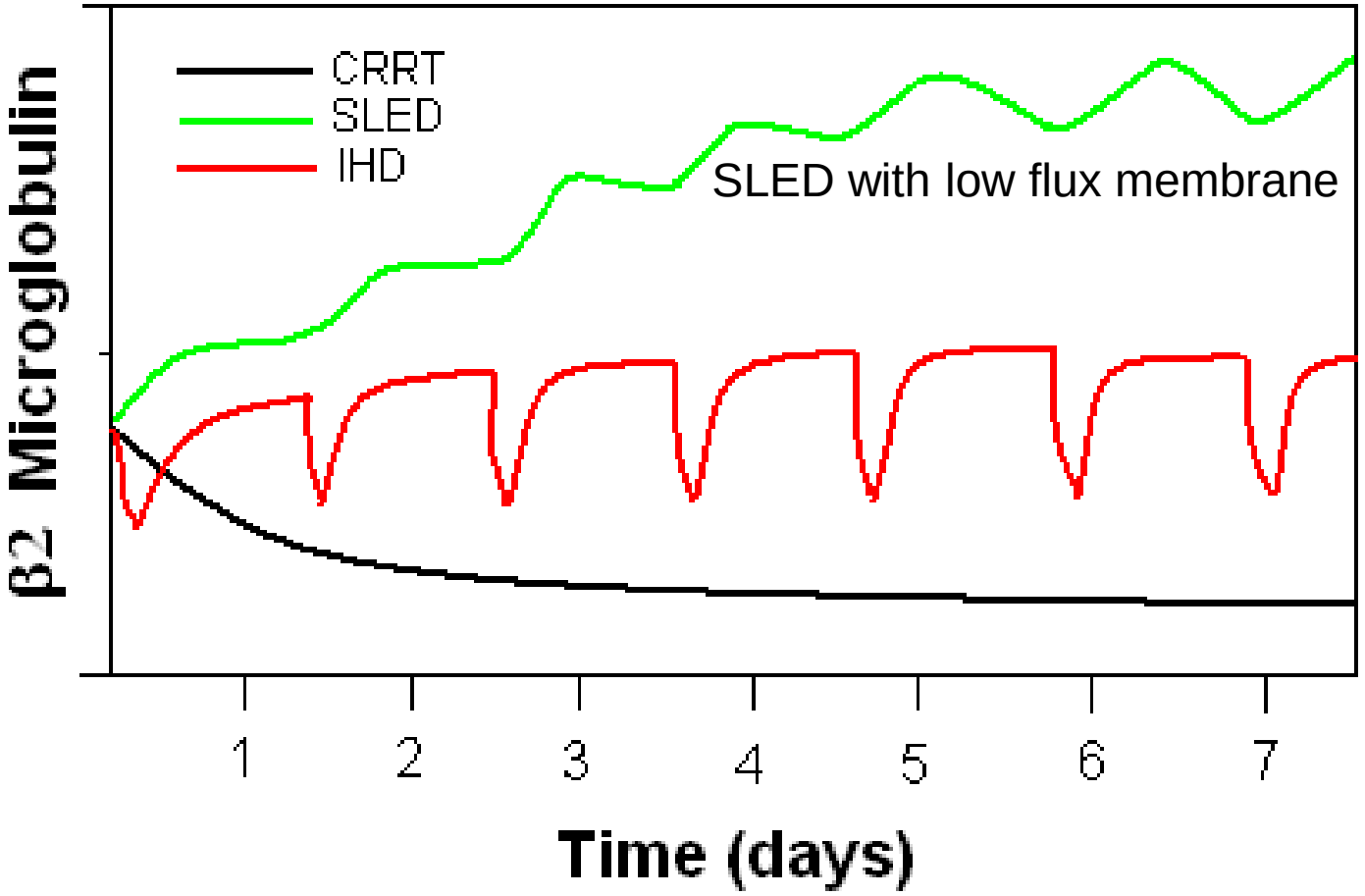
- Albumin 60 kDa
- Cytokines 6-70 kDa

Diffusion limited clearance on HD

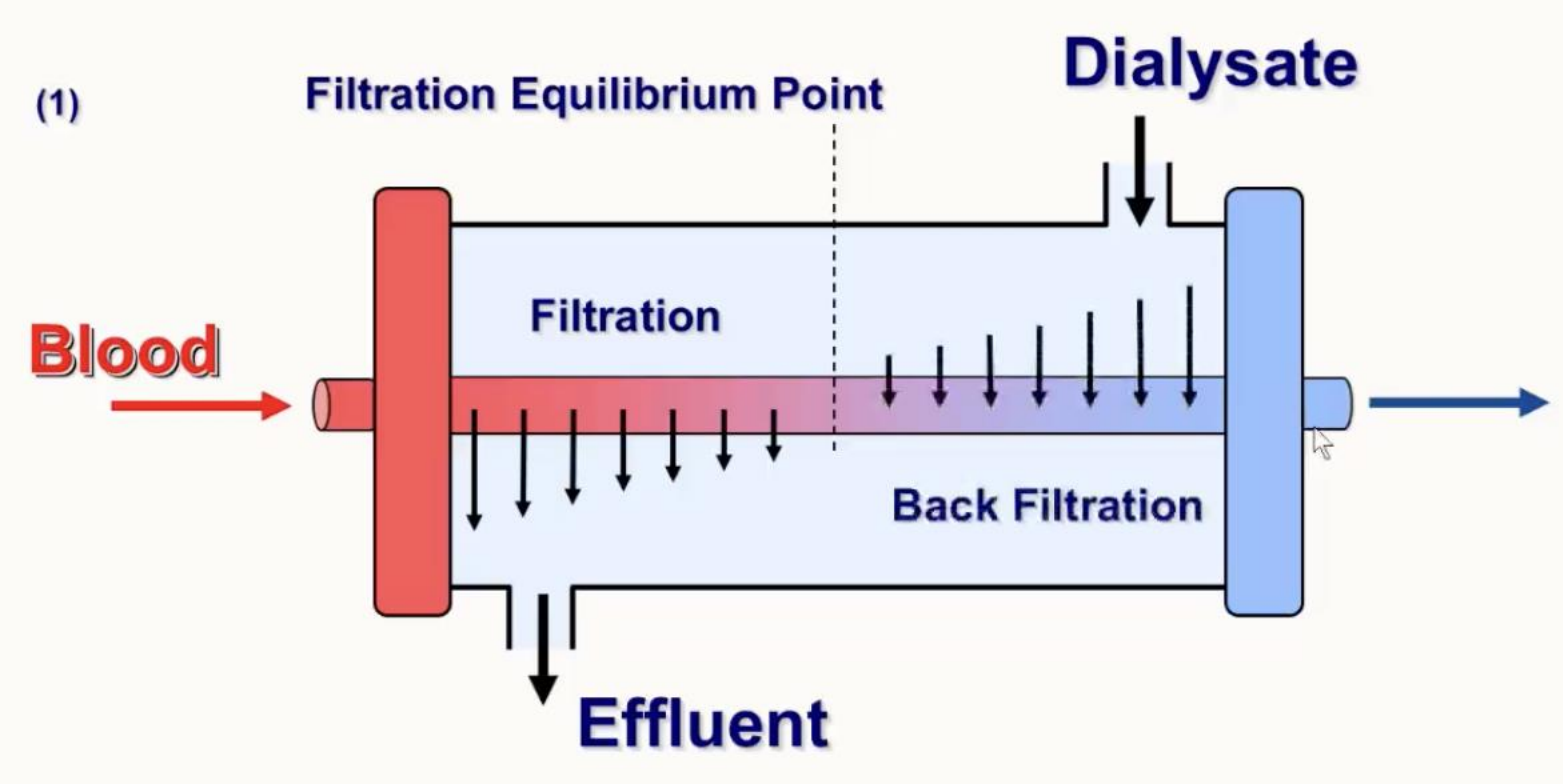




®2 Microglobulin on RRT



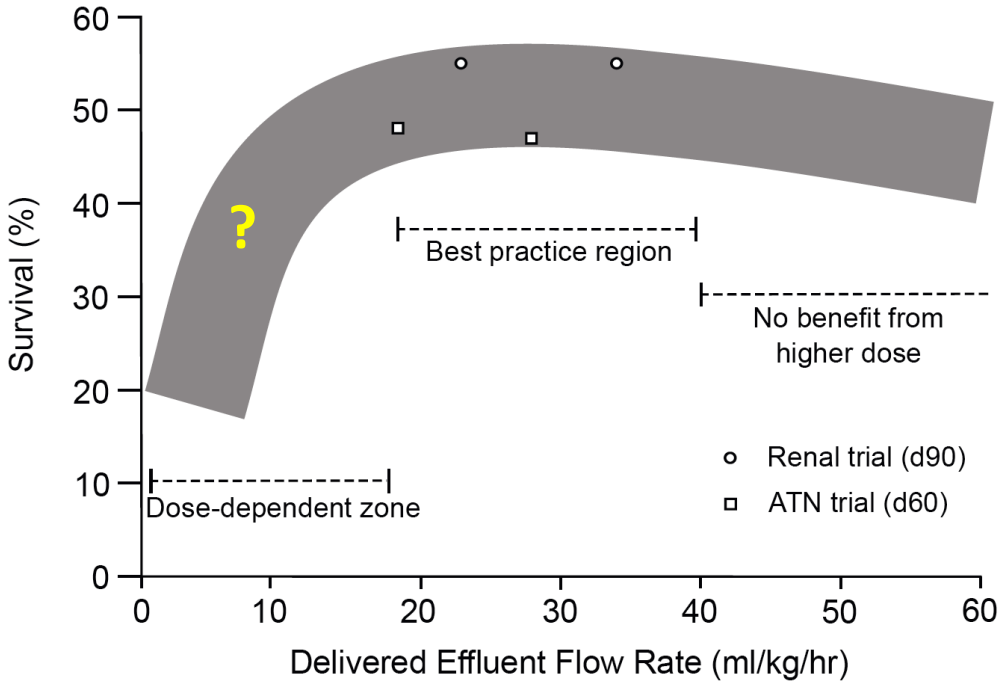
Balanced back filtration can add convection to CVVHD



How low can you go?

- Where is the inflection point of the Dose-response curve?
- What is the relationship between prescribed and delivered dose in trials and the real world?
- How do we ensure high quality CRRT is delivered?

CRRT: Dose-response



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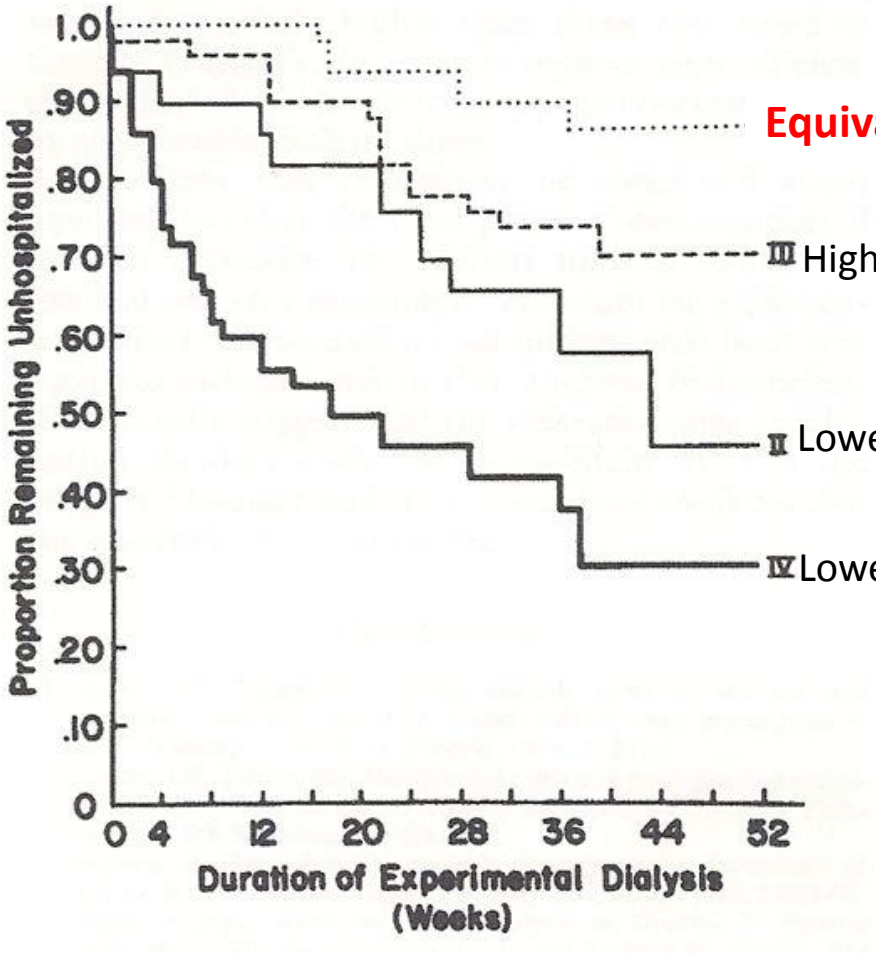
Prowle *et al*. *Critical Care* 2011, **15**:207
http://ccforum.com/content/15/2/207

What happens if you give very little RRT? Historic Data from ESRD



Equivalent to 9 ml/kg/hr continuous

III Higher dose shorter sessions

II Lower dose longer sessions

IV Lower dose shorter sessions

Effect of the Hemodialysis Prescription on Patient Morbidity — Report from the National Cooperative Dialysis Study N Engl J Med 1981; 305:1176-1181

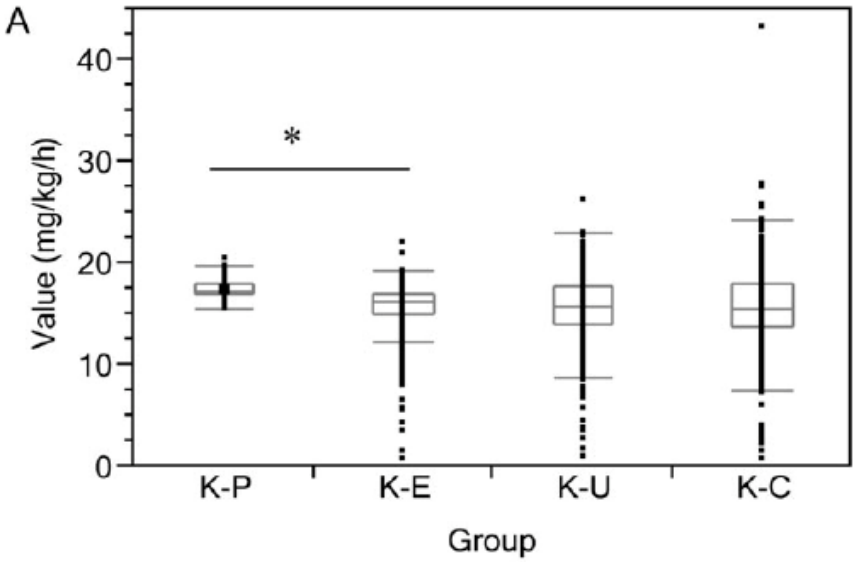
RENAL Study doses achieved

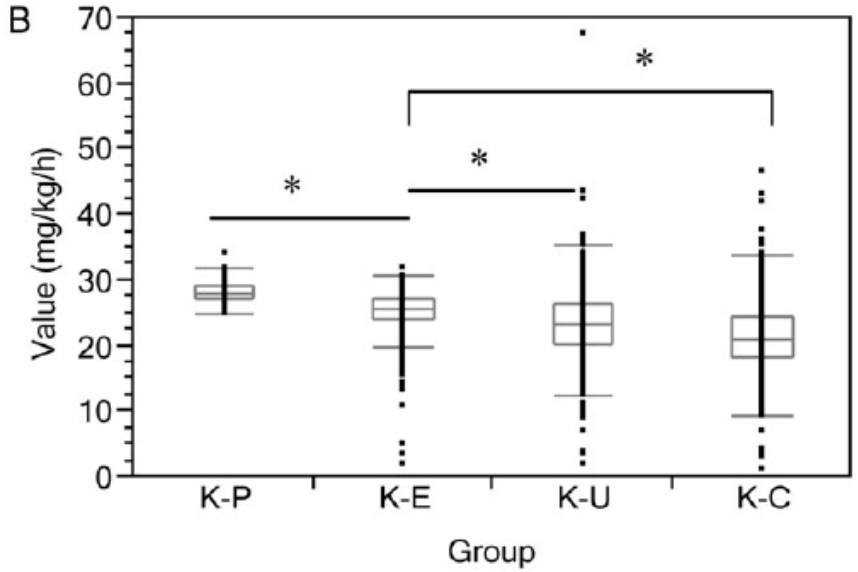
	Higher Intensity Q1 Median Q3 / n(%)	**Lower Intensity** Q1 Median Q3 / n(%)	**P value**[1]
Days of study treatment	2.00 3.00 7.00	2.00 3.00 7.00	0.35
Daily effluent (ml/kg/hr)	29.83 36.31 39.51	19.72 23.38 24.98	<0.001
Percent of dose delivered	0.75 0.91 0.99	0.79 0.94 1.00	<0.001

CRRT Dose: "You can't always get what you want"

Table 2. CVVHDF clearance comparisons

	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	<0.001
Estimated clearance (K_E)	15.79 ± 2.47	25.10 ± 3.16	<0.001
Urea clearance (K_U)	15.55 ± 3.07	23.31 ± 5.30	<0.001
Creatinine clearance (K_C)	15.67 ± 3.88	21.62 ± 5.5	<0.001





Nephrol Dial Transplant (2012) 27: 952–956

In-Depth Review

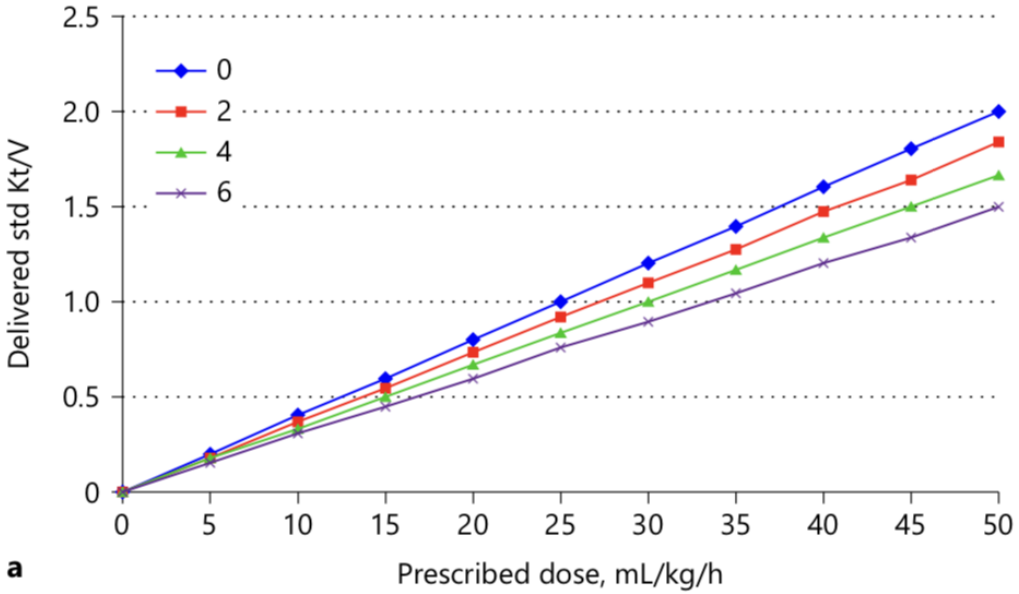
Blood Purification

Blood Purif 2017;44:140–155
DOI: 10.1159/000475457

Received: January 12, 2017
Accepted: April 4, 2017
Published online: June 7, 2017

Quantification and Dosing of Renal Replacement Therapy in Acute Kidney Injury: A Reappraisal

William R. Clark[a] Martine Leblanc[b] Zaccaria Ricci[c] Claudio Ronco[d, e]



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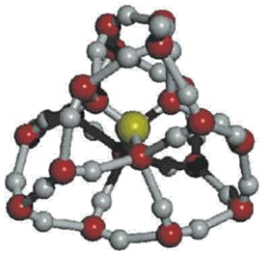
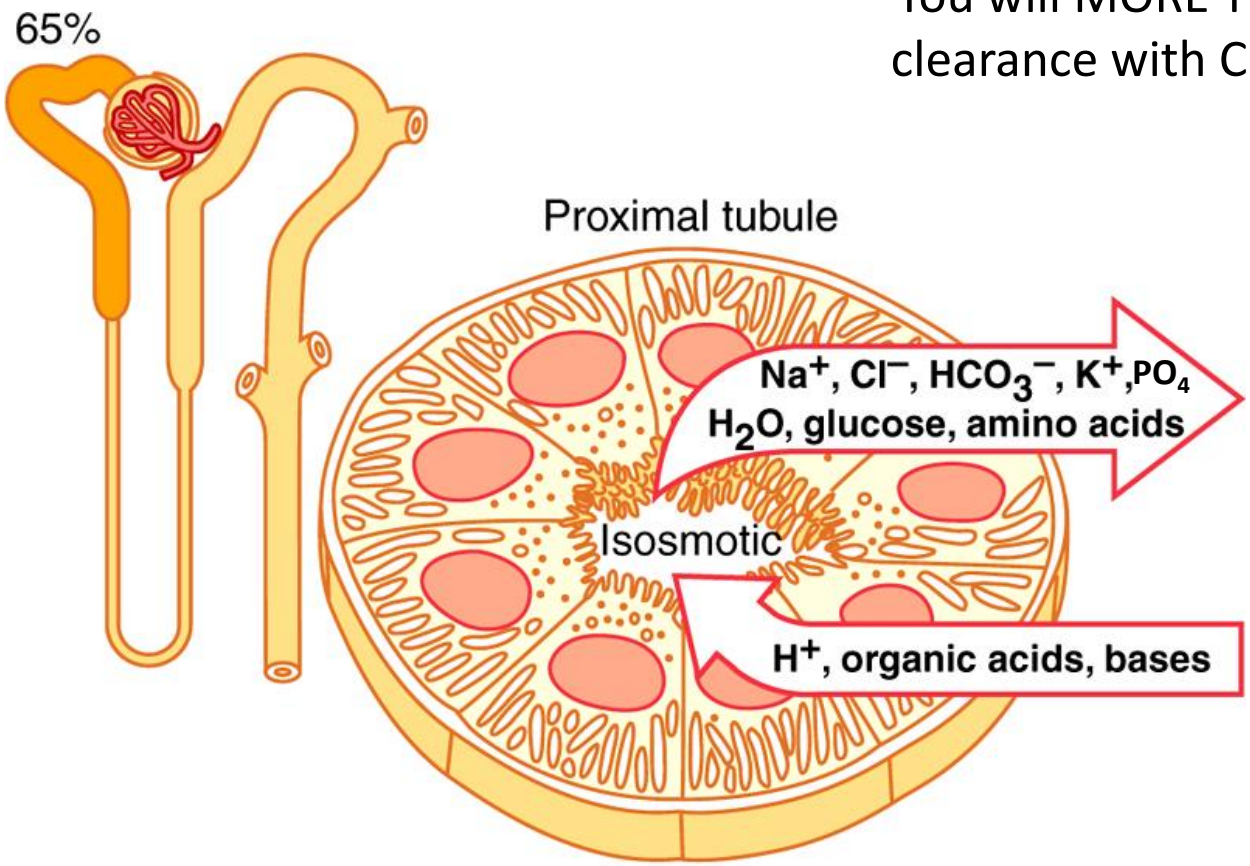
Can you have too much of a good thing?

- Even 35ml/kg/hr will probably only achieve a CKD stage 4 GFR equivalent.
- However CRRT isn't native renal function.
  - No tubular function
- Abrupt changes in solutes and electrolytes may be harmful.
- CRRT is expensive

PO_4



- 80-95% of Phosphate is resorbed in PCT
  - ∴ PO_4 Clearance 5-10 ml/min
  - You will MORE THAN DOUBLE clearance with CRRT 20ml/min



Hall: Guyton and Hall Textbook of Medical Physiology, 12th Edition
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Adverse Effects in RENAL/ATN

Table 4. Summary of Complications Associated with Study Treatment.

Complication	Higher-Intensity CRRT	Lower-Intensity CRRT	P Value
Hypophosphatemia*			
No. of patients/total no.(%)	461/708 (65.1)	396/733 (54.0)	<0.0001
No. of episodes	1495	1059	—
Hypokalemia*			
No. of patients/total no. (%)	168/718 (23.4)	180/737 (24.4)	0.34
No. of episodes	297	308	0.93
Arrhythmia			
No. of patients/total no. (%)	303/722 (42.0)	337/741 (45.5)	0.18
No. of episodes	545	617	0.27
Arrhythmia requiring treatment			
No. of patients/total no. (%)	240/722 (33.2)	267/741 (36.0)	0.26
No. of episodes	388	413	0.71
Arrhythmia causing hemodynamic instability			
No. of patients/total no. (%)	200/722 (27.7)	181/741 (24.4)	0.15
No. of episodes	299	257	0.10
Disequilibrium			
No. of patients/total no. (%)	3/722 (0.4)	0/743	0.08
No. of episodes	3	0	—
One or more other serious adverse events			
No. of patients/total no. (%)	4/722 (0.6)	5/743 (0.7)	0.77
No. of episodes	4	5	—
Filters used daily — no.	0.93±0.86	0.84±0.81	<0.001

Table 4. Summary of Complications Associated with Study Therapy.*

Event	Intensive Strategy (N=563)	Less-Intensive Strategy (N=561)	P Value
	no. of patients (%)		
Any serious adverse event†	287 (51.0)	280 (49.9)	0.72
Not related to study therapy	207 (72.1)	202 (72.1)	
Possibly or probably related to study therapy	48 (16.7)	51 (18.2)	
Definitely related to study therapy	32 (11.1)	27 (9.6)	
Nonfatal only‡	137 (47.7)	128 (45.7)	
Catheter-related complications			
Insertion-related complications	28 (5.0)	31 (5.5)	0.68
Late catheter-related complications	48 (8.5)	38 (6.8)	0.27
Hypotension			
Requiring vasopressor support	81 (14.4)	56 (10.0)	0.02
Requiring discontinuation of treatment	55 (9.8)	49 (8.7)	0.55
Requiring other intervention	212 (37.7)	168 (29.9)	0.006
Other treatment-related complications			
Any nonhypotensive complication	216 (38.4)	194 (34.6)	0.19
Electrolyte disturbance	144 (25.6)	116 (20.7)	0.05
Hypokalemia	42 (7.5)	25 (4.5)	0.03
Hypophosphatemia	99 (17.6)	61 (10.9)	0.001
Other	99 (17.6)	85 (15.2)	0.27

IVOIRE Study

- AKI 2 Septic shock
- 35 vs 70 ml/kg/h CVVH

- HVHF
  - Higher Antibiotic clearances
  - More Hyperkalaemia
  - More Hypophosphataemia

Intensive Care Med (2013) 39:1535–1546
DOI 10.1007/s00134-013-2967-z

ORIGINAL

Olivier Joannes-Boyau
Patrick M. Honoré
Paul Perez
Sean M. Bagshaw
Hubert Grand
Jean-Luc Canivet
Antoine Dewitte

High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial

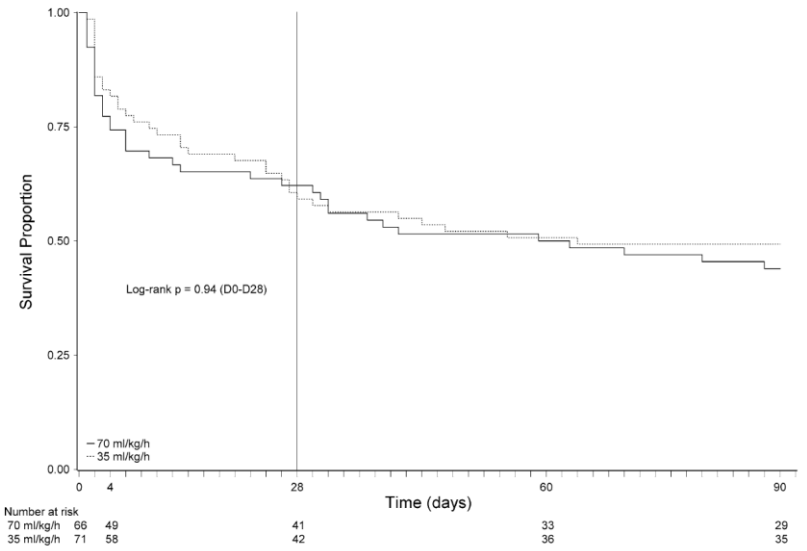


Fig. 2 Survival of participants in the IVOIRE (hIgh VOlume in Intensive caRE) trial. Participants in the HVHF group and SVHF group underwent haemofiltration at 70 mL/kg/h and 35 mL/kg/h of fluid exchange for 96 h, respectively

Does one size fit all?

Dealing with weight?

ATN study

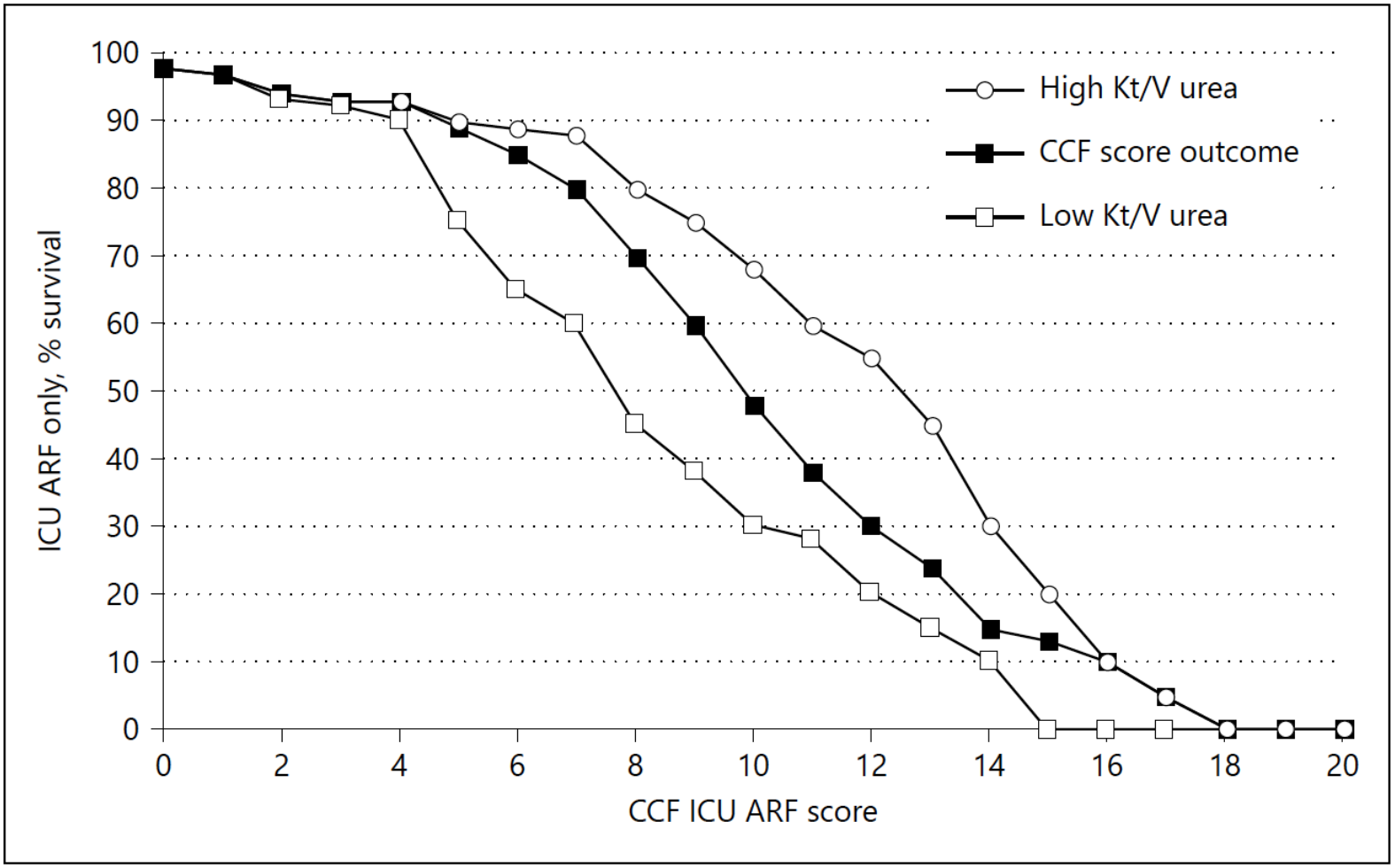
- EXCLUDED BW >120kg
- In obese patients (>30% above ideal body weight) dose was based on *adjusted body weight*, calculated as ideal body weight plus 25% of the difference between ideal and actual weight.

RENAL

- EXCLUDED body weight <60 kg or >100kg

Am J Kidney Dis 1996;28(suppl 3): S81-

Cleveland Clinic 1990s AKI - IHD data



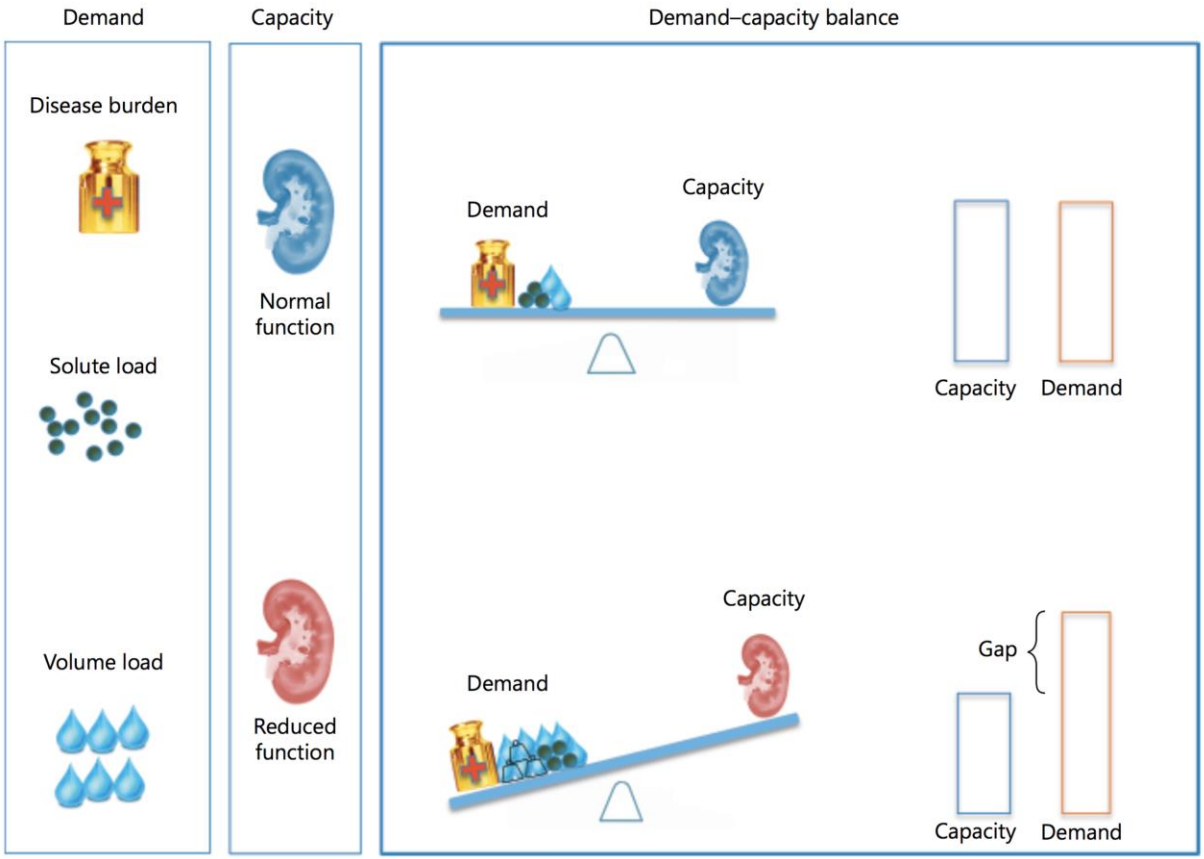
ADQI Consensus

Blood Purification

Blood Purif 2016;42:224–237
DOI: 10.1159/000448506

Published online: August 26, 2016

Patient Selection and Timing of Continuous Renal Replacement Therapy



CRRT Dose

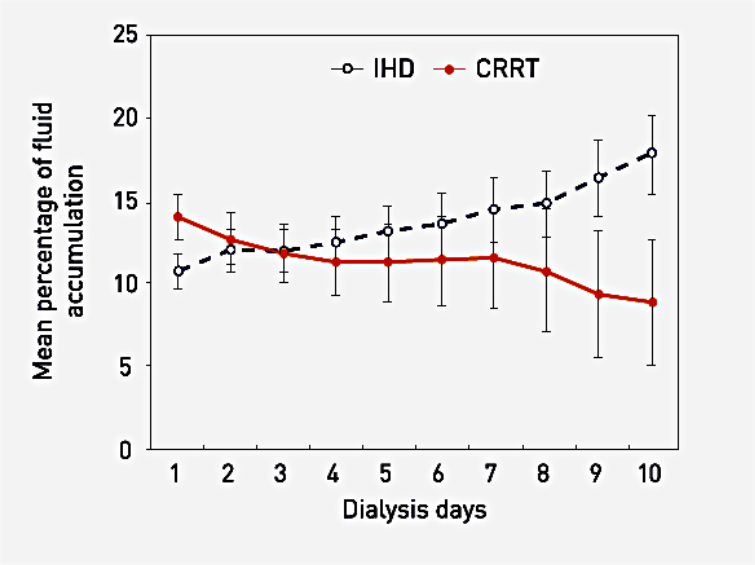
- Give a dose of > 20-25 ml/kg/hr CRRT to replicate results seen in high quality clinical trials
  - Leeway to avoid under-dosing
  - No evidence to support higher doses in unselected patients
  - Inflection point of DR curve not clearly defined
  - How to deal with extremes of weight

CRRT dose 2

- Urea dose does not equal middle molecule dose
  - This may be much less for diffusive vs. convective clearance
    - Circuit dose may vary
- Conversely molecules with tubular reabsorption may have higher clearance on CRRT compared to native renal function
  - Native dose may vary
- Filter downtime may result in semi-intermittent therapy where does is not longer directly related to effluent flow

Finally – salt & water

- Dose conventionally concentrates on solute not solvent
- In ESRD daily HD may be beneficial as fluid control rather than solute control
- Continuous therapy is associated with less positive FB



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