Continuous Renal Replacement Therapy

Prof. Bancha Satirapoj, MD
Division of Nephrology
Department of Medicine
Phramongkutklao Hospital and College of Medicine

Outline

- Timing to initiation of kidney replacement therapy and modalities
- Principle and indication for CRRT
- How to order CRRT in critically illness

Large RCTs on optimal timing of KST in AKI

	ELAIN	AKIKI	IDEAL-ICU	FST	STARRT-AKI
No. of patients	231	620	477	118	2,927
Design and countries	Single-center, Germany	Multicenter (31), France	Multicenter (29), France	Multicenter, Thailand	Multicenter (168), 15 countries
Recruitment period	2013-2015	2013-2016	2012-2016	2016-2017	2015-2019
Mean age, y	67	66	69	67	65
Male sex	63%	66%	61%	49%	68%
Setting	95% surgical (mostly cardiac and abdominal)	80% sepsis	Septic shock	Mixed, 68% medical	67% medical
KST modality	CVVHDF 30 mL/kg/h with citrate with transition to SLEDD or IHD	Physician discretion (IHD and CRRT by center [randomized by center])	Physician discretion (IHD and CRRT by center [randomized by center])	CVVH	Physician discretion (IHD and CRRT by center [randomized by center])
Criteria for early KST	Within 8 h of stage 2 and NGAL ≥ 150 ng/mL	Within 6 h of stage 3	Within 12 h of stage 3	Any AKI with absence of response to FST	Within 12 h of stage 2
Criteria for late KST	Within 12 h of stage 3 and NGAL ≥ 150 ng/mL	Urgent criteria: severe hyperkalemia (>6 mmol/L), severe pulmonary edema refractory to diuretics, severe acidosis (pH < 7.15), serum urea > 40 mmol/L, oligoanuria > 72 h	48 h of stage 3	No response to FST and serum urea > 100 mg/dL; severe hyperkalemia (>6 mmol/L), severe metabolic acidosis (pH < 7.15); severe pulmonary edema	AKI for 72 h or conventional criteria: serum K^+ ≥ 6.0 mmol/L, pH ≤ 7.20, or serum HCO_3 ≤ 12 mmol/L, severe respiratory failure (PaO_2/FiO_2 ≤ 200), and clinical perception of volume overload

Bouchard J, et al. Am J Kidney Dis. 2022; 79(3):417-426.

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Time difference: early vs late KST	20 h (6 vs 26 h)	55 h (2 vs 57 h)	44 h (8 vs 52 h)	19 h (2 vs 21 h)	25 h (6 vs 31 h)
Primary outcome	90-d mortality: 39% (early) vs 55% (late); $P = 0.03$	60-d mortality: 49% (early) vs 50% (late)	90-d mortality: 58% (early) vs 54% (late)	28-d mortality: 62% (early) vs 58% (late)	90-d mortality: 44% (early) vs 44% (late)
Mortality rate in patients on KST in late group	NA	62%	68%	NA	NA
Patients never receiving KST (delayed group)	9.2%	49%	38%	25%	38%
Dialysis dependence	13% (early) vs 15% (late) at 90 d	2% (early) vs 5% (late) at 60 d	2% (early) vs 3% (late)	12% (early) vs 17% (late) at 28 d	10.4% (early) vs 6.0% (late); RR, 1.74 (95% CI, 1.24-2.43)

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Setting	95% surgical (mostly cardiac and abdominal)	80% sepsis	Septic shock	Mixed, 68% medical	67% medical
Additional findings	In early group, greater renal recovery at 90 d (54% vs 39%, P = 0.02), shorter KST duration (9 vs 25 d, P = 0.04), and shorter LOS (51 vs 82 d, P < 0.001)	In early group, higher rates of CRBSI (10% vs 5%, P = 0.03) and hypophosphatemia (22% vs 15%, P = 0.03)	Higher rate of hyperkalemia in delayed group (0% vs 4%, P = 0.03)	FST predicted need for KST: 75% of nonresponders required dialysis in late group; 86% of responders who were not enrolled in the trial avoided KST	In early group, higher rates of hypotension and hyophosphatemia (8.7% vs 5.6%, P = 0.001) and hypophosphatemia (7.5% vs 4.2%, P < 0.001)

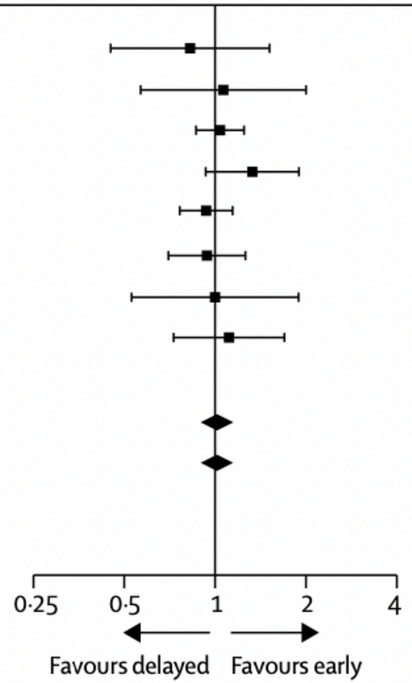
Bouchard J, et al. Am J Kidney Dis. 2022; 79(3):417-426.

Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials

Early RRT might provide the benefit of shorter MV or RRT support in the surgical population and in AKI patients with high plasma NGAL.

A

	28-day mortality, n/N (%)		Risk ratio (95% CI)	Weight (%)
	Delayed RRT	Early RRT		
Combes et al, 2015	10/22 (45%)	11/20 (55%)	0·83 (0·45–1·51)	3·1
Wald et al, 2015	15/52 (29%)	13/48 (27%)	1·07 (0·57–2·00)	2·9
Gaudry et al, 2016	134/308 (44%)	129/308 (42%)	1·04 (0·87–1·25)	34·2
Zarbock et al, 2016	48/119 (40%)	34/112 (30%)	1·33 (0·93–1·90)	9·1
Barbar et al, 2018	102/241 (42%)	111/245 (45%)	0·93 (0·76–1·14)	28·2
Lumlertgul et al, 2018	35/60 (58%)	36/58 (62%)	0·94 (0·70–1·26)	13·3
Srisawat et al, 2018	9/18 (50%)	10/20 (50%)	1·00 (0·53–1·89)	2·8
Geri et al, 2019	13/17 (76%)	11/16 (69%)	1·11 (0·73–1·70)	6·4
Total	**366/837 (44%)**	**355/827 (43%)**		
Random-effects one-step model			1·01 (0·91–1·13)	
Random-effects two-step model			1·01 (0·91–1·13)	
I^2=0·0%				
τ^2=0·0				



The timing of RRT initiation does not affect survival in critically ill patients with severe AKI in the absence of urgent indications for RRT.

Gaudry S, et al. Lancet. 2020; 395(10235):1506-1515.
Chen et al. Ann. Intensive Care 2020: 10:30.

KDIGO: Initiate RRT

- Life-threatening changes in fluid, electrolyte, and acid-base balance exist
- Consider the broader clinical context, the presence of conditions, and trends of laboratory tests > single BUN and creatinine thresholds alone

KDIGO. Kidney Int Supplements. 2012: 2: 8–12.

Controversies in AKI: KDIGO Conference

- Optimal timing for short-term KST remains unknown
- KST initiation should be considered when metabolic and fluid demands exceed the kidney's capacity
- Risk of complications, global prognosis, potential for recovery, and patient preferences should be considered when taking the decision

Ostermann M, et al. Kidney Int. 2020;98(2):294-309.

Controversies in AKI: KDIGO Conference

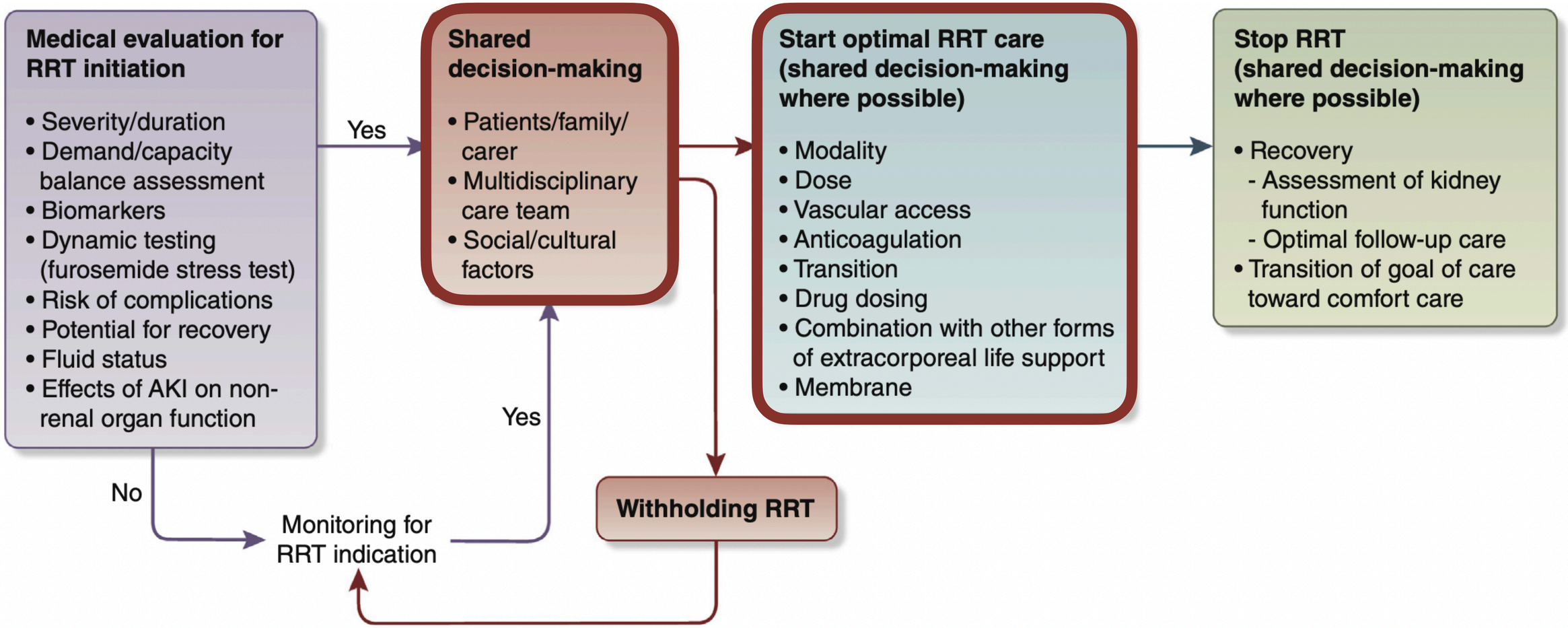


Figure 3 | Schematic diagram of renal replacement therapy (RRT) decisions in acute kidney injury (AKI).

Ostermann M, et al. Kidney Int. 2020;98(2):294-309.

Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial

- **More-delayed strategy: RRT initiation was postponed until mandatory indication (hyperkalemia or metabolic acidosis or pulmonary edema) or until BUN to 140 mg/dL**

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
More-delayed strategy	1·34 (0·96–1·89)	0·13	1·65 (1·09–2·50)	0·018
Simplified Acute Physiology Score III	1·03 (1·02–1·05)	<0·0001	1·03 (1·01–1·05)	0·0005

Severe AKI patients with oliguria > 72 h or BUN > 112 mg/dL would mandate immediate RRT.

Gaudry S, et al. Lancet. 2021; 397(10281):1293-1300.

RRT modality in critically ill patients with AKI–A network meta-analysis of RCTs

Renal recovery (RR with 95% CI)			
CRRT	1.19 (0.90, 1.59)	1.05 (0.83, 1.35)	1.21 (0.89, 1.65)
	HRRT	0.88 (0.61, 1.28)	1.01 (0.69, 1.48)
		IRRT	1.15 (0.80, 1.64)
			PD
Short-term mortality (RR with 95% CI)			
CRRT	0.88 (0.73, 1.07)	0.96 (0.85, 1.07)	0.91 (0.75, 1.10)
	HRRT	0.91 (0.75, 1.10)	1.03 (0.82, 1.29)
		IRRT	0.95 (0.77, 1.17)
			PD
Fluid removal volume (mL/day, WMD with 95%CI)			
CRRT	−99 (−300, 102)	−95 (−369, 178)	**−769 (−1065, −474)**
	HRRT	3 (−325, 332)	**−671 (−987, −354)**
		IRRT	**−674 (−1017, −331)**
			PD

No difference in the renal recovery or short-term mortality was observed among the four RRT modalities

PD was associated with less fluid removal volume

Zhou X, et al. J Crit Care. 2021; 64:82-90.

RRT modality in critically ill patients with AKI–A network meta-analysis of RCTs

Hypotension (RR with 95%CI)			
CRRT	1.08 (0.41,2.85)	1.09 (0.86,1.39)	**0.30 (0.18,0.52)**
	HRRT	1.01 (0.37,2.76)	**0.28 (0.09,0.85)**
		IRRT	**0.28 (0.15,0.50)**
			PD
Length of ICU stay (days, WMD with 95%CI)			
CRRT	−1.9 (−5.9, 2.2)	1.6 (−2.1, 5.2)	**−10.0 (−16.4, −3.6)**
	HRRT	3.4 (−2.0, 8.8)	**−8.1 (−15.7, −0.6)**
		IRRT	**−11.6 (−18.9, −4.2)**
			PD
Length of in-hospital stay (days, WMD with 95%CI)			
CRRT	−6.5 (−16.5, 3.4)	1.2 (−4.1, 6.6)	−2.9 (−12.2, 6.4)
	HRRT	7.8 (−3.5, 19.1)	3.7 (−9.9, 17.2)
		IRRT	−4.1 (−14.8, 6.6)
			PD

PD was associated with lower incidence of hypotension compared with the extracorporeal modalities,

No superiority of one particular RRT modality over another in critically ill patients with AKI.

Zhou X, et al. J Crit Care. 2021; 64:82-90.

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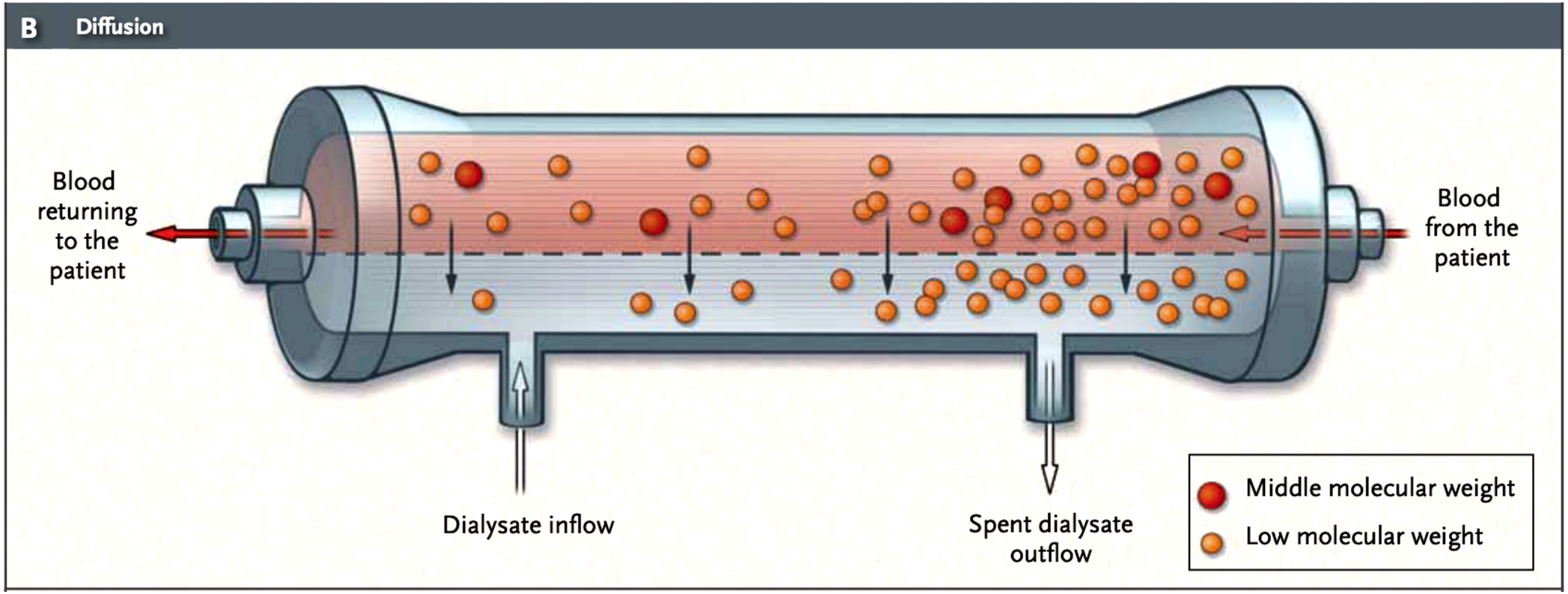
Definition of Terms

- **SCUF- Slow Continuous Ultrafiltration**
- **CAVH- Continuous Arteriovenous Hemofiltration**
- **CAVHD- Continuous Arteriovenous Hemodialysis**
- **CVVH- Continuous Venovenous Hemofiltration**
- **CVVH-D- Continuous Venovenous Hemodialysis**
- **CVVHDF- Continuous Venovenous Hemofiltration with Dialysis**

Mechanism of Solute Clearance

- Minimal solute clearance (Ultrafiltration)
- Convective clearance (Hemofiltration)
- Diffusive clearance (Hemodialysis)
- Combined (Hemodiafiltration)

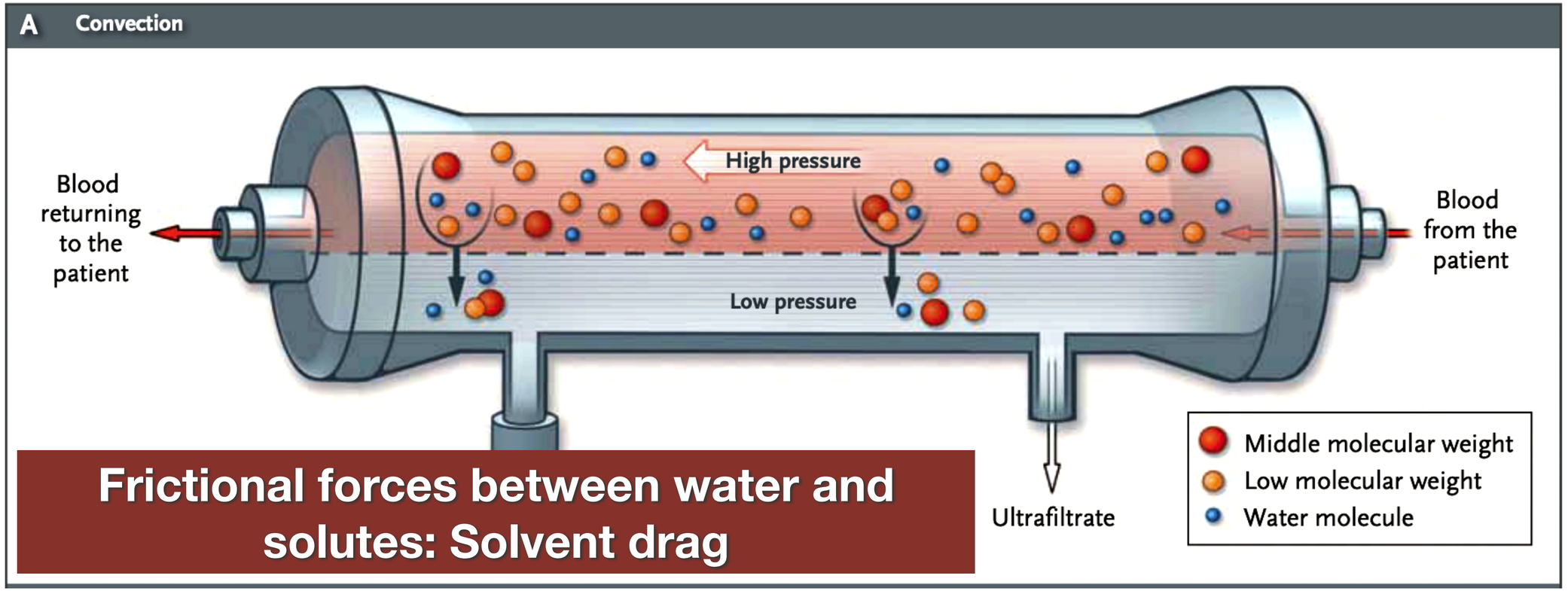
Hemodialysis



Diffusion across a concentration gradient

Tolwani A. N Engl J Med 2012;367:2505-14.

Hemofiltration



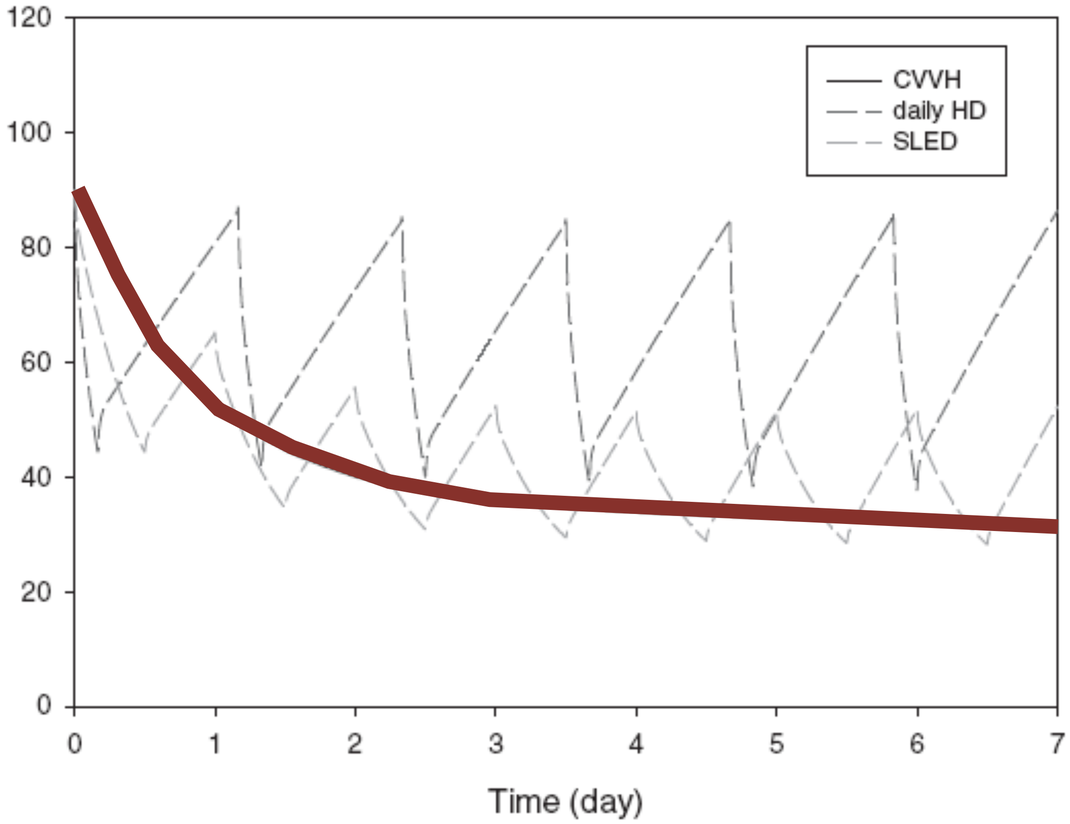
Convection based on a pressure gradient
'Transmembrane pressure gradient'

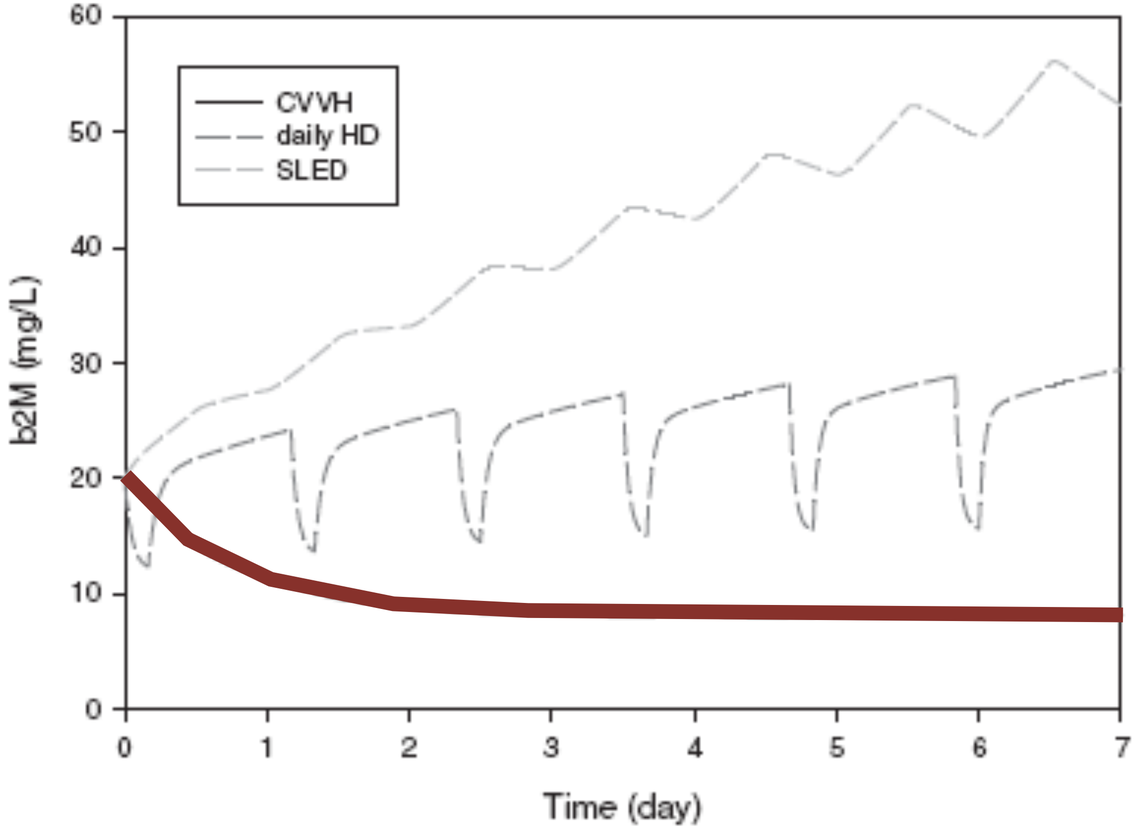
Tolwani A. N Engl J Med 2012;367:2505-14.

CRRT modalities

CRRT	RF or Dialysate	Urea clearance	Middle molecule	Treatment
SCUF	No	1-4	+	Fluid remove
CVVH	RF	22-24	+++	Fluid remove with AKI
CVVHD	Dialysate	24-30	-	AKI
CVVHDF	RF + Dialysate	36-38	+++	AKI with severe sepsis

Uremia Control and large molecule clearance





Liao, Z et al. Artificial Organs 2003; 27: 802-807

CRRT: hemodynamic Stability

1. Rate of fluid removal is much slower in CRRT
   - UF rate below the rate of interstitium-to-plasma flow (refilling)
2. Slower rate of urea clearance allows for equalization of urea concentrations between compartments and decreased water shifts and cell edema
3. Magnitude of sodium removal less than the amount of sodium removed with hemodialysis
4. Decrease in core temperature and peripheral vasoconstriction
5. Convective removal of inflammatory mediators, especially septic shock

Jorge Cerda, Claudio Ronco. Seminars in Dialysis. 2009: 114–122

Continuous Renal Replacement Therapy

- **Potential setting in AKI**
- **Using CRRT > standard intermittent RRT, for hemodynamically unstable patients. (2B)**
- **Using CRRT > intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (2B)**

KDIGO. Kidney Int Supplements. 2012: 2: 8–12.

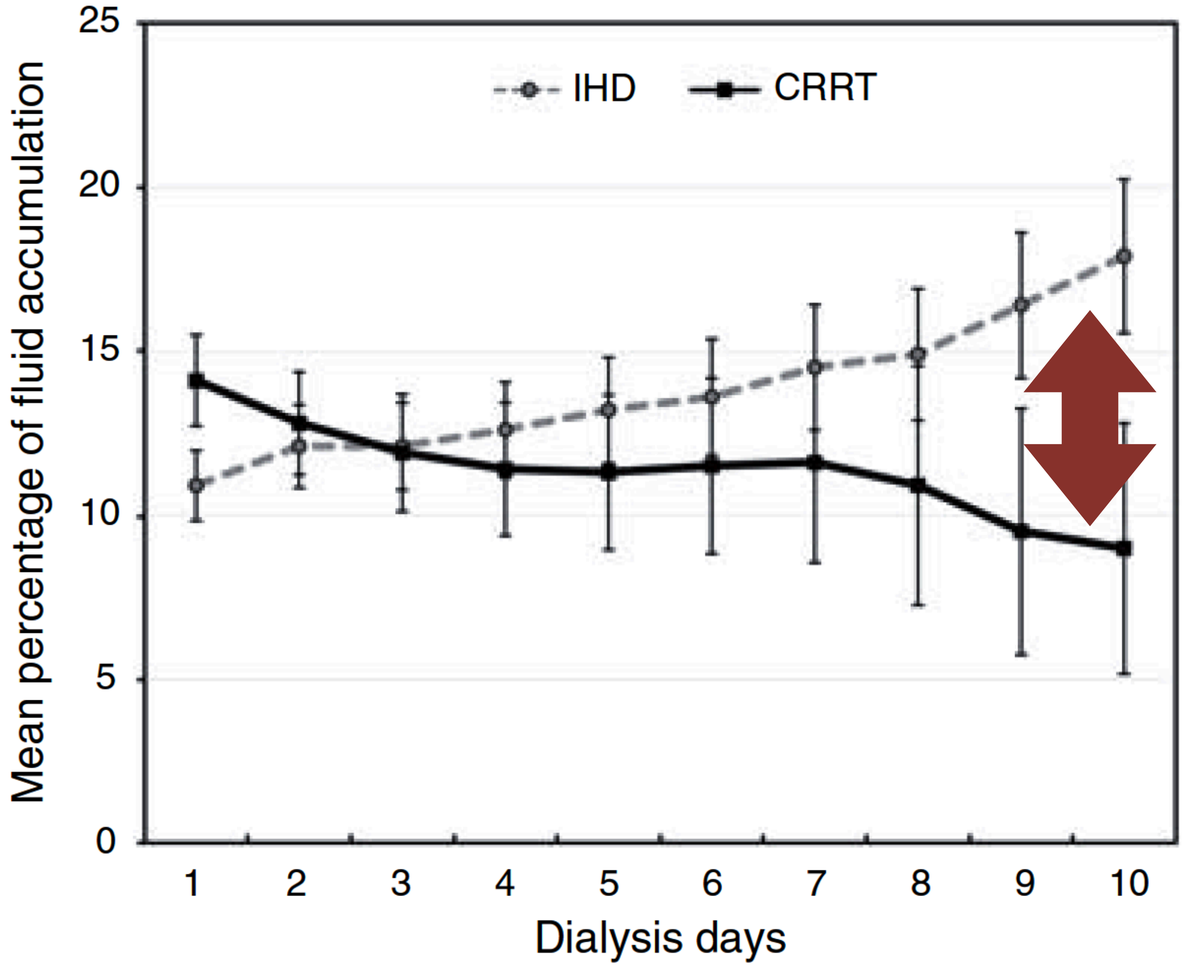
คู่มือการรักษาด้วยการฟอกเลือดและการกรองพลาสมาสำหรับผู้ป่วยโรคไต พ.ศ. 2561

น้ำหนัก	คำจำกัดความ
++	**“ควรทำเป็นอย่างยิ่ง/ต้องทำ” (strongly recommend)** ความมั่นใจของคำแนะนำให้ทำอยู่ในระดับสูง เพราะมาตรการดังกล่าวมีประโยชน์อย่างยิ่งต่อผู้ป่วยและคุ้มค่า (cost effective)
+	**“น่าทำ/ควรทำ” (recommend)** ความมั่นใจของคำแนะนำให้ทำอยู่ในระดับปานกลาง เนื่องจากมาตรการดังกล่าวอาจมีประโยชน์ต่อผู้ป่วยและอาจคุ้มค่าในภาวะจำเพาะ
+/-	**“อาจทำหรือไม่ทำ” (neither recommend nor against)** ความมั่นใจยังไม่เพียงพอในการให้คำแนะนำ เนื่องจากมาตรการดังกล่าวยังมีหลักฐานไม่เพียงพอในการสนับสนุนหรือคัดค้านว่าอาจมี หรืออาจไม่มีประโยชน์ต่อผู้ป่วยและอาจไม่คุ้มค่า แต่ไม่ก่อให้เกิด อันตรายต่อผู้ป่วยเพิ่มขึ้น ดังนั้น การตัดสินใจกระทำขึ้นอยู่กับปัจจัยอื่นๆ
-	**“ไม่น่าทำ” (against)** ความมั่นใจของคำแนะนำห้ามทำอยู่ในระดับปานกลาง เนื่องจากมาตรการดังกล่าวไม่มีประโยชน์ต่อผู้ป่วยและไม่คุ้มค่า หากไม่จำเป็น
--	**“ไม่ควรทำ” (strongly against)** ความมั่นใจของคำแนะนำห้ามทำอยู่ในระดับสูง เพราะมาตรการดังกล่าวอาจเกิดโทษหรือก่อให้เกิดอันตรายต่อผู้ป่วย

1.3 CRRT or SLED (+/IV)

- ภาวะสมองบวมหรือมีความเสี่ยงที่จะเกิดภาวะสมองบวม เช่น ภาวะตับวายเฉียบพลัน เส้นเลือดในสมองอุดตันเฉียบพลัน สมองขาดออกซิเจน เนื่องจากหัวใจหยุดเต้น (Hypoxic ischemic encephalopathy)
- ความผิดปกติทางเมตาบอลิกที่ยังเกิดต่อเนื่องที่ไม่สามารถแก้ไขได้ด้วยวิธีการฟอกเลือดชนิดชั่วคราว ได้แก่ ภาวะเลือดเป็นกรดอย่างรุนแรง ภาวะโพแทสเซียมในเลือดสูง
- ปริมาณสารน้ำในร่างกายเกินที่ไม่สามารถขจัดออกด้วยการใช้ยา หรือวิธีการฟอกเลือดชนิดชั่วคราว โดยเฉพาะในผู้ป่วยที่มีส่วนเกินมากกว่าร้อยละ 10 ของน้ำหนักเดิม
- มีความจำเป็นที่จะต้องควบคุมปริมาณน้ำและสมดุลกรดด่างรวมถึงเกลือแร่ในเลือดอย่างต่อเนื่อง

Fluid accumulation over time in patients on continuous renal replacement therapy and on intermittent hemodialysis



Bouchard J, et al. Kidney International (2009) 76, 422–427.

1.4 Continuous Renal Replacement Therapy (+/IV)

- ผู้ที่ยังมีความดันโลหิตต่ำแม้จะได้รับยากระตุ้นความดันโลหิตในขนาดสูง และจำเป็นต้องได้รับการบำบัดทดแทนไตควรได้รับการพิจารณาว่าน่าจะได้ประโยชน์จากวิธีการบำบัดทดแทนไตชนิดต่อเนื่อง (CRRT)
  - Dopamine> 15 ug/kg/min or
  - Epinephrine or norepinephrine > 0.1 ug/kg/min

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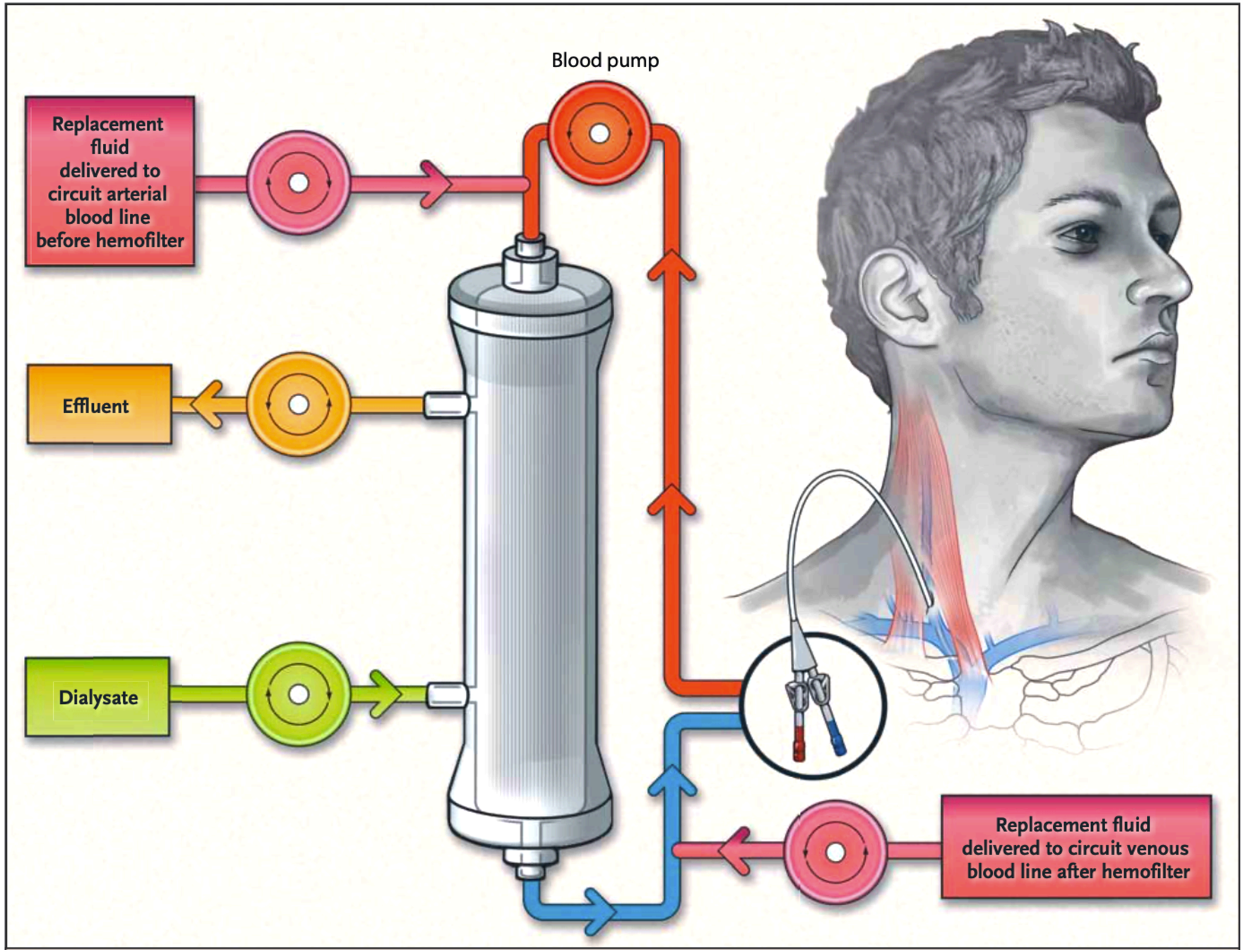


Dialysis catheter

Tolwani A. N Engl J Med 2012;367:2505-14.

Temporary vascular access function by saline dilution

Catheter type	Blood flow rate (mL/min)	Recirculation (%)
Femoral		
>20 cm	233	8.5
<20 cm	248	26.3
Jugular	226	0.4

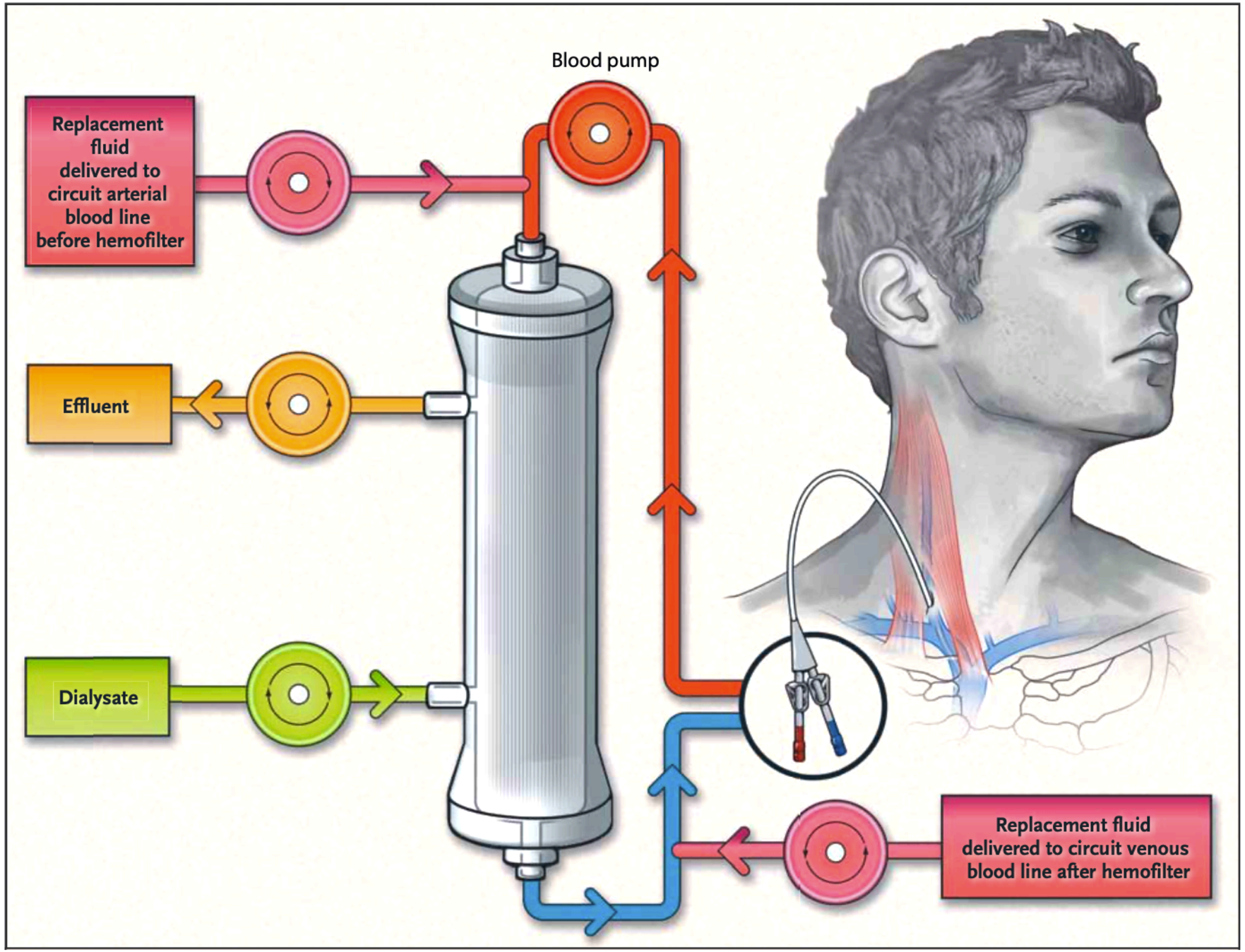
Little et al, AJKD 2000

Catheter type	Length (cm)
Right internal jugular vein	13.5-16
Left internal jugular vein	16-20
Femoral vein	20-24

Choosing a vein for insertion of a dialysis catheter in patients with AKI

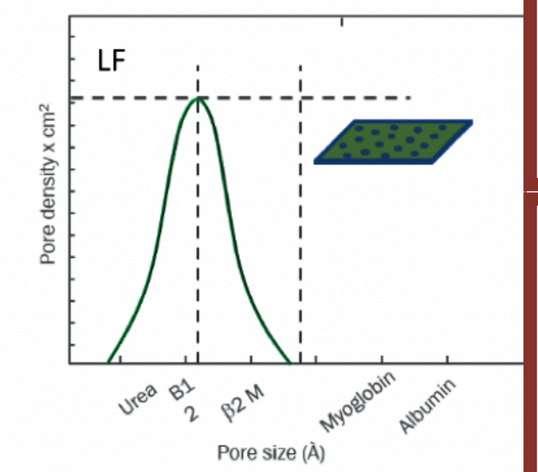
- First choice
  - Right jugular vein
- Second choice
  - Femoral vein
- Third choice
  - Left jugular vein
- Last choice
  - Subclavian vein with preference for the dominant side

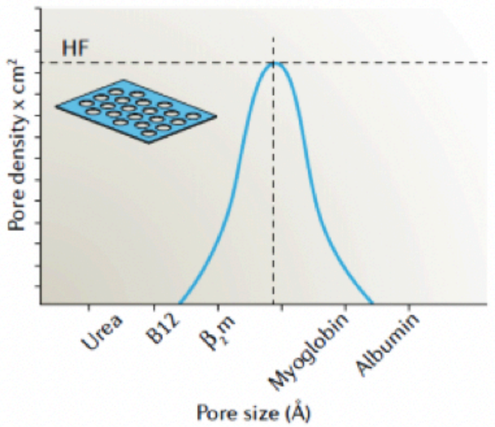
KDIGO. Kidney Int Supplements. 2012: 2: 8–12.

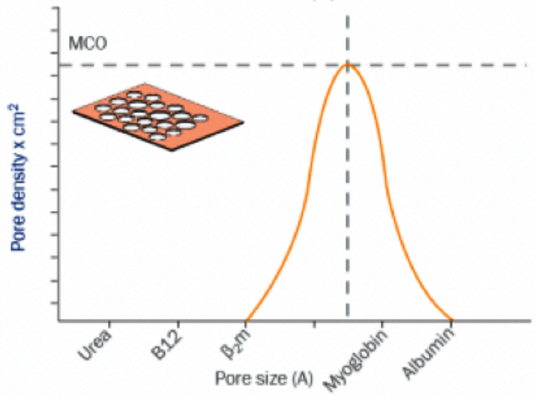


Dialysis Dialyzers

Tolwani A. N Engl J Med 2012;367:2505-14.







Urea (60 Da)

Phosphate (96 Da)

Small Molecules
<500 Da

PTH (9,500 Da)

Beta 2 microglobulin (12 kDa)

Cystatin C (13 kDa)

Myoglobin (17 kDa)

Kappa free-light-chains (23 kDa)

Complement factor D (24 kDa)

Interleukin-6 (25 kDa)

Conventional middle molecules
500 Da - <25 kDa

Alpha 1 macroglobulin (33 kDa)

YKL-40 (40 kDa)

Lambda free-light-chains (45 kDa)

Large middle molecules
25 kDa - 45 kDa

Albumin (67 kDa)

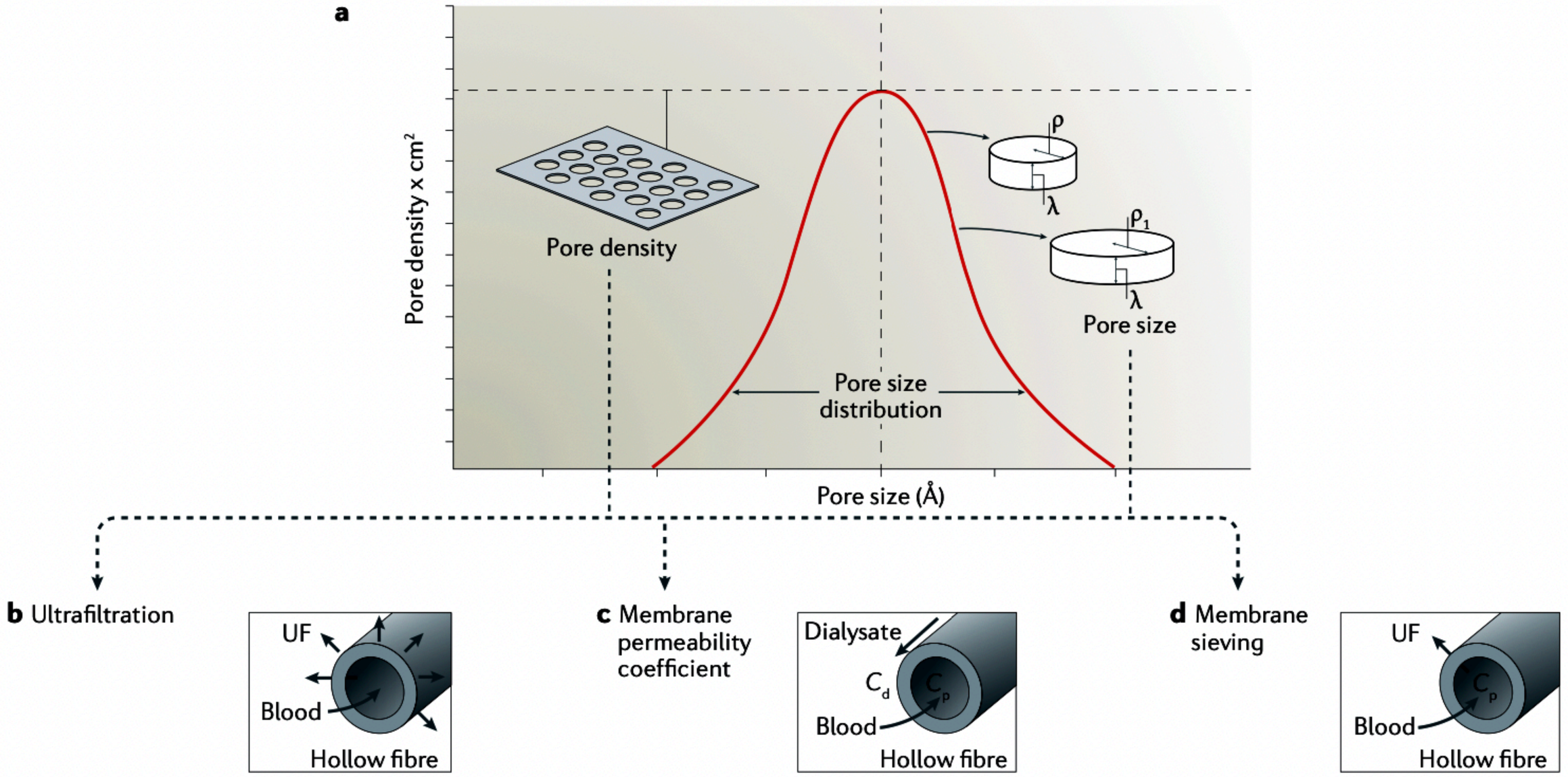
Essential proteins

Low Flux

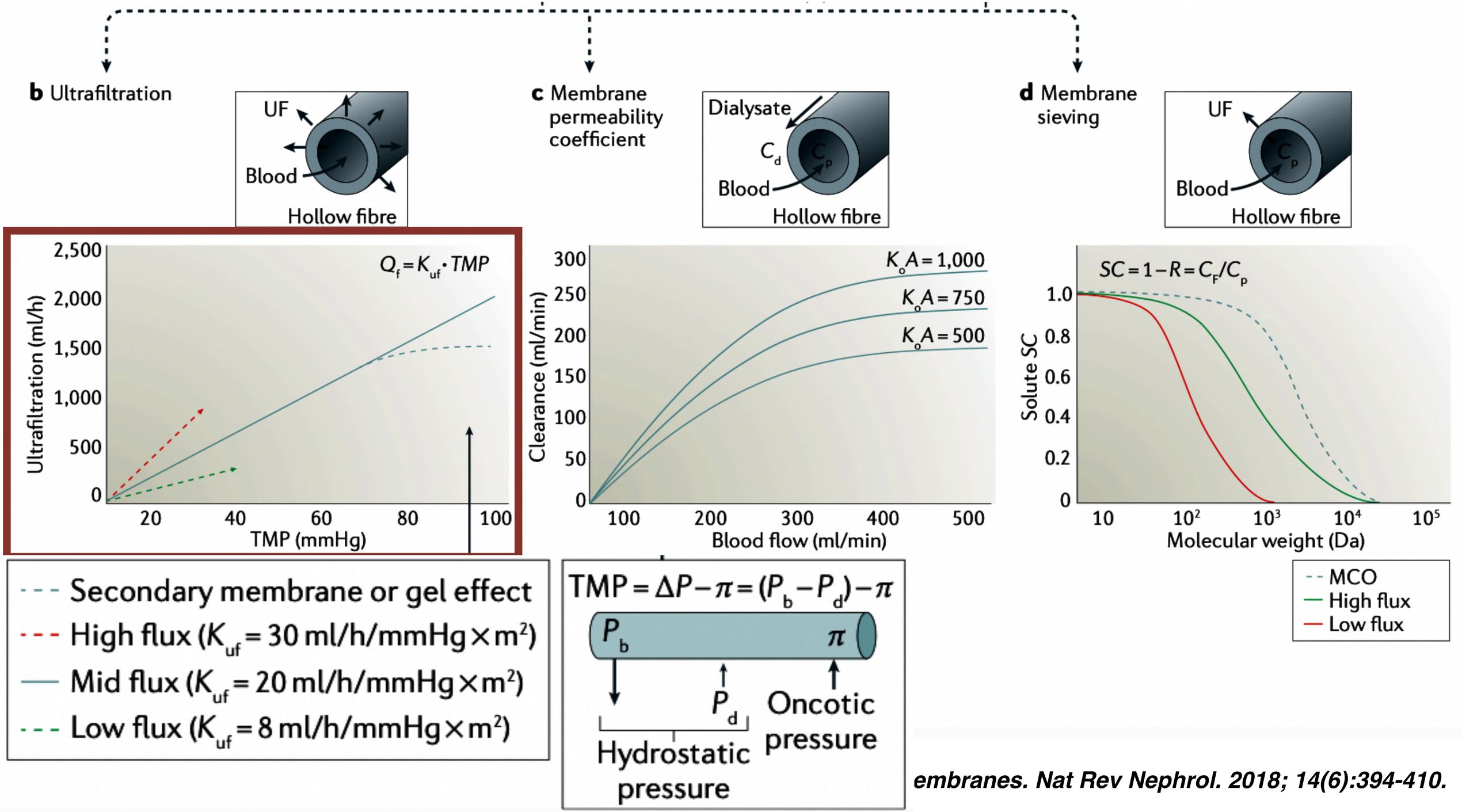
High Flux

HDx

García-Prieto A, et al. Clin Kidney J. 2023 Feb 20;16(7):1071-1080.



Ronco C, Clark WR. Haemodialysis membranes. Nat Rev Nephrol. 2018; 14(6):394-410.



embranes. Nat Rev Nephrol. 2018; 14(6):394-410.

Classification of HD membranes

Table 1: Classification of HD membranes in Europe and Japan.

(A) Classification of HD membranes in Europe

Category	UF coefficient (mL/h/mmHg/m^2)[a]	β2-microglobulin		Albumin sieving coefficient[a]
		Sieving coefficient[a]	Clearance (mL/min)[b]	
Low flux	<12		<10	0
High flux	14–40	<0.7–0.8	20–80	<0.01
MCO	40–60	0.99	>80	<0.01
Protein-leaking	>40	0.9–1	>80	0.01–0.03
High cut-off	40–60	1		<0.2

García-Prieto A, et al. Clin Kidney J. 2023 Feb 20;16(7):1071-1080.

Classification of HD membranes

(B) Classification of HD membranes in Japan

Class type	Category	β2-microglobulin clearance (mL/min)[c]
I	Low flux	<10
II	High flux	<30
III		<50
IV	Super high flux	<70
V		>70

[a] *In vitro*.

[b] For conventional HD with with a blood flow rate of 200 to 400 mL/min.

[c] For conventional HD at a blood flow rate of 200 mL/min and a dialysate flow rate of 500 mL/min.

García-Prieto A, et al. Clin Kidney J. 2023 Feb 20;16(7):1071-1080.

KDIGO Clinical Practice Guideline for AKI 2012

- Use dialyzers with a biocompatible membrane for IHD and CRRT in patients with AKI (2C)
  - Less complement activation
  - Less cytokine activation
  - Decrease oxidative stress

KDIGO. Kidney Int Supplements. 2012: 2: 8–12.

Solute Clearance in CRRT

Type of Therapy	Solute Transport	Replacement Fluid	Blood Flow	Ultrafiltrate Flow	Dialysate Flow
			ml/min	*ml/hr*	
Continuous venovenous hemofiltration	Convection	Yes	50–300	500–4000	0
Continuous venovenous hemodialysis	Diffusion	No	50–300	0–350†	500–4000
Continuous venovenous hemodiafiltration	Convection and diffusion	Yes	50–300	500–4000	500–4000

* Rates of blood flow, ultrafiltrate flow, and dialysate flow are representative of typical rates used in clinical practice.
† Ultrafiltration in continuous venovenous hemodialysis is used for regulation of the patient's fluid volume and not for convective purposes.

Tolwani A. N Engl J Med 2012;367:2505-14.

Blood flow rate

- A change in the blood flow rate: no affect solute clearance
  - BFR > effluent flow rate
  - Limited solute clearance by effluent flow rate
- BFR does not affect hemodynamic stability

- High BFR (>300 mL/min) increased pressure alarms, resulting in pump stoppage and blood stasis, which increases the risk of clotting

Faster Blood Flow Rate Does Not Improve Circuit Life in Continuous Renal Replacement Therapy: A Randomized Controlled Trial

Nigel Fealy, RN, MN[1–3]; Leanne Aitken, RN, PhD, FACCCN[2,4–6]; Eugene du Toit, PhD[7]; Serigne Lo, PhD, AStat[8]; Ian Baldwin, RN, PhD, FACCCN[1,3]

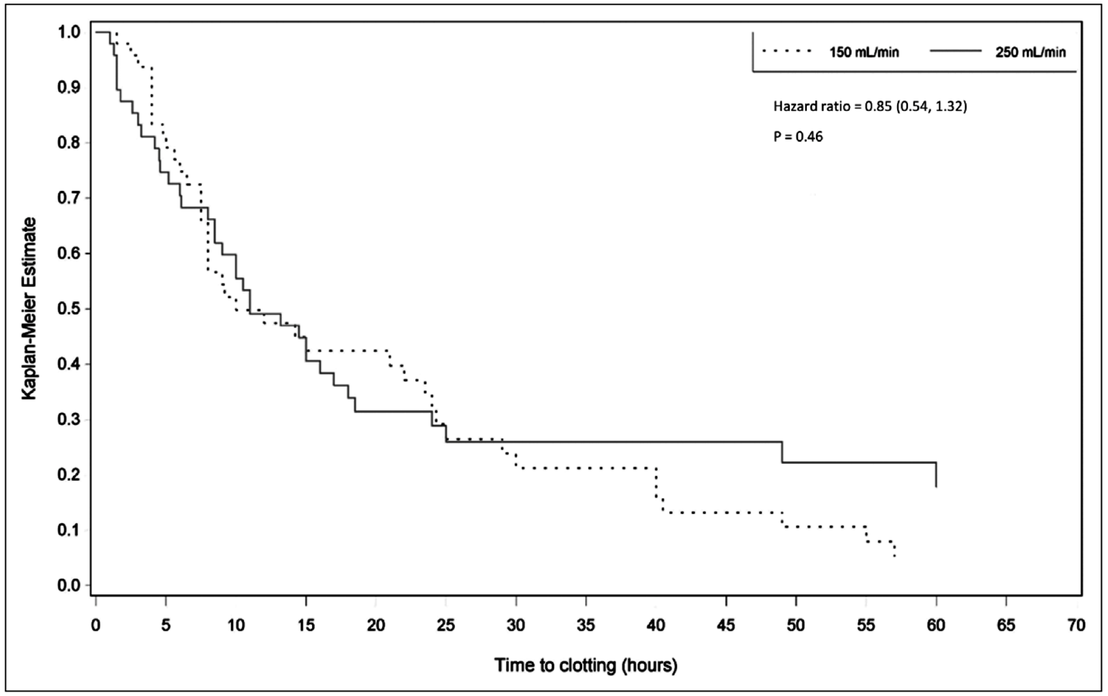
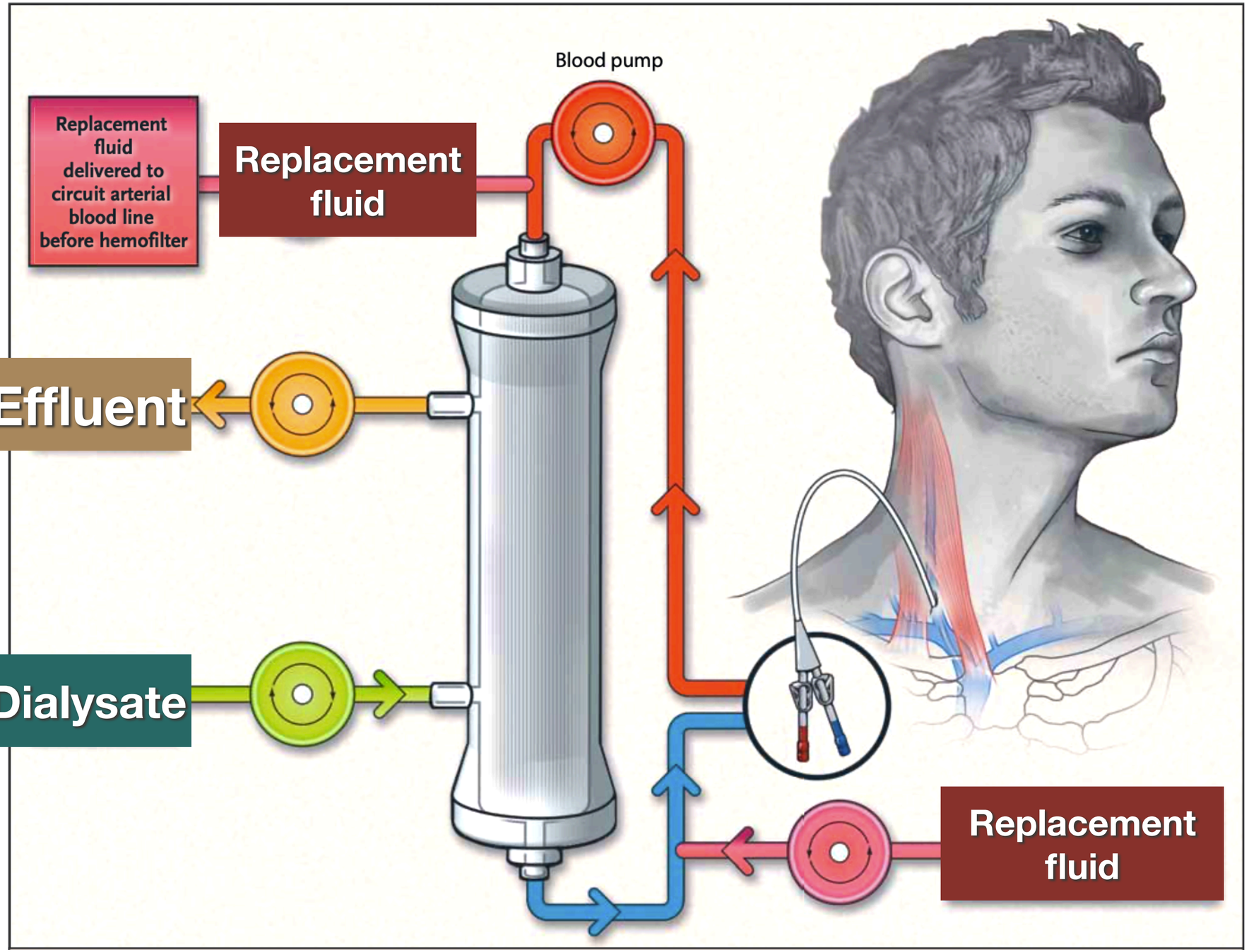


Figure 2. Kaplan-Meier estimate of the probability of continuous renal replacement therapy circuit survival for the first circuit–clotted circuits only.

There was no difference in circuit life whether using blood flow rates of 250 or 150mL/min during CRRT.

Fealy N, et al. Crit Care Med. 2017;45(10):e1018-e1025.



Tolwani A. N Engl J Med 2012;367:2505-14.

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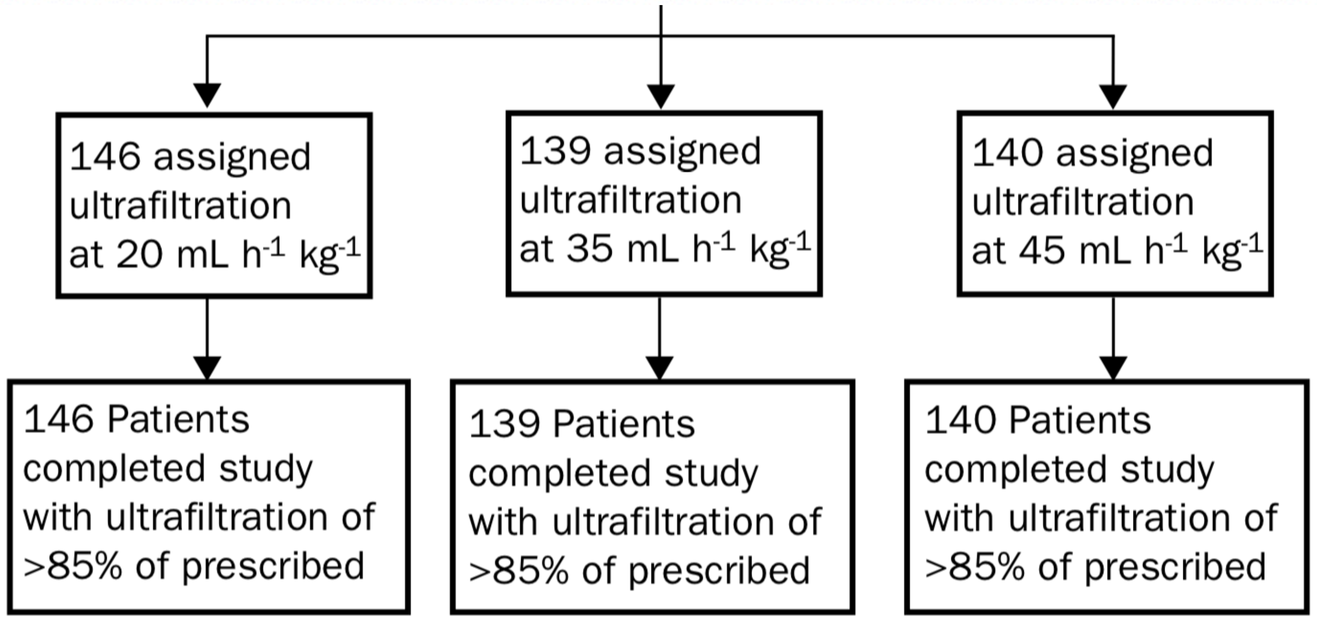
Tolwani A. N Engl J Med 2012;367:2505-14.

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



Ronco et al : Lancet 2000; 355: 26–30

Results of Cox's proportional hazards regression

Variable	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Sex (female)	0·90 (0·69–1·19)	0·89 (0·66–1·20)
Weight	1·01 (0·99–1·03)	1·00 (0·99–1·02)
Age	1·00 (0·98–1·01)	1·00 (0·98–1·01)
Causes of acute renal failure		
Presence of sepsis	1·71 (1·20–2·44)	0·55 (0·34–0·89)
BUN at start of continuous haemofiltration	1·06 (1·05–1·07)	1·05 (1·04–1·07)
APACHE II score	1·13 (1·09–1·18)	1·11 (1·04–1·19)
Trial groups		
Group 1	1·0	1·0
Group 2	0·55 (0·40–0·77)	0·51 (0·36–0·72)
Group 3	0·57 (0·41–0·78)	0·49 (0·35–0·69)

Increase in the rate of ultrafiltration improved survival and ultrafiltration should reach at least 35 mL/kg/day

BUN=blood urea nitrogen.

Ronco et al : Lancet 2000; 355: 26–30

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*

- **Less intensive therapy**
  - **Hemodialysis and SLED were given three times per week,**
  - **CRRT was provided with a flow rate of 20 mL/kg per hour.**

ATN trial

The VA/NIH Acute Renal Failure Trial Network. N Engl J Med 2008;359:7-20

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*

RENAL trial

Bellomo R; et al N Engl J Med. 2009; 361(17):1627-38.

Randomized clinical trials examining CRRT dose

Study	*N*	CRRT dose	Participants	Mortality	AKI recovery
Ronco (2000)	425	CVVH 20 versus 35 versus 45 ml/kg/h	75% post-surgical, 12% septic	59% vs 43% versus 42% ($p < 0.002$)	
Bouman (2002)	106	CRRT 20 versus 48 ml/kg/h	58% post-cardiac surgery, 100% respiratory failure, 100% inotrope or pressors	31.2% versus 25.7% (p = ns)	No difference
Saudan (2006)	206	CVVHF 25 ml/kg/h versus CVVHDF 42 ml/kg/h	60% septic	61% versus 41% ($p = 0.03$)	
Tolwani (2008)	200	CVVHDF 20 versus 35 ml/kg/h	54% septic, 77.5% respiratory failure	44% versus 51% (p = ns)	
Palevsky (ATN) (2008)	1124	CVVHDF 20 versus 35 ml/kg/h IHD 3/week HD versus 6/week HD	63% septic, 80.6% respiratory failure	51.5% versus 53.6% ($p = 0.47$)	No difference
Bellomo (RENAL) (2009)	1508	CVVHDF 25 versus 40 ml/kg/h	49.4% septic, 73.9% respiratory failure	44.7% versus 44.7% ($p = 0.99$)	No difference

Neyra JA, Tolwani A. CRRT prescription and delivery of dose. Semin Dial. 2021; 34(6):432-439.

Intensity of continuous renal replacement therapy for AKI

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)
	Assumed risk	Corresponding risk	
	Less intensive CRRT	Intensive CRRT	
Mortality at day 30 Follow-up: 30 days	**Study population**		**RR 0.88** (0.81 to 1.1)
	430 per 1000	**420 per 1000** (412 to 523)	
Adverse events: hypophosphataemia	**Study population**		**RR 1.21** (1.11 to 1.31)
	540 per 1000	**654 per 1000** (600 to 708)	

Cochrane Library

Trusted evidence.
Informed decisions.
Better health.

Increased risk of hypophosphataemia with more intense CRRT.

[Intervention Review]

Cochrane Database of Systematic Reviews 2016, 10. Art. No.: CD010613.

KDIGO Clinical Practice Guideline for AKI 2012

- Delivering a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI (1A)
- Delivering an effluent volume of 20–25 ml/kg/h for CRRT in AKI (1A)
  - Usually require a higher prescription of effluent volume (Not Graded)
  - In order to ensure delivery of this flow rate, we prescribe an effluent flow rate of at least 25-30 mL/kg per hour

BW 70 kg = 1750-2100 mL/hr

KDIGO. Kidney Int Supplements. 2012: 2: 8–12.

KDIGO Clinical Practice Guideline for AKI 2012

- Dose of RRT to be delivered should be prescribed before starting each session of RRT (Not Graded)
- Frequent assessment of the actual delivered dose in order to adjust the prescription (1B)
- Provide RRT to achieve the goals of electrolyte, acid-base, solute, and fluid balance that will meet the patient's needs (Not Graded)

KDIGO. Kidney Int Supplements. 2012: 2: 8–12.

Calculation of total effluent fluid rate according to CRRT modality

CRRT modality	Total effluent dose (ml/kg/h)
CVVH or CVVHF	[Pre-Filter Replacement Fluid Rate (ml/h) + Post-Filter Replacement Fluid Rate (ml/h) + Fluid Removal Rate (ml/h)]/Patient Current Weight (kg)
CVVHD	[Dialysate Fluid Rate (ml/h) + Fluid Removal Rate (ml/h)]/Patient Current Weight (kg)
CVVHDF	[Pre-Filter Replacement Fluid Rate (ml/h) + Post-Filter Replacement Fluid Rate (ml/h) + Fluid Removal Rate (ml/h) + Dialysate Fluid Rate (ml/h)]/ Patient Current Weight (kg)

Neyra JA, Tolwani A. CRRT prescription and delivery of dose. Semin Dial. 2021; 34(6):432-439.

Fluid removal rate

Effluent dosing under different CRRT

Simulation of effluent dosing under different CRRT modalities

CVVHDF: total ultrafiltration rate (2000 ml/h)[a] + dialysate rate (2000 ml/h) + fluid removal rate (100 ml/h) = effluent dose of 30.4 ml/kg per h → 26.8 ml/kg per h after predilution adjustment (30.4×0.88)[b] assuming 50% of replacement fluid as prefilter (preblood pump =1000 ml/h)

CVVH: total ultrafiltration rate (4000 ml/h)[a] + fluid removal rate (100 ml/h) = effluent dose of 30.4 ml/kg per h → 23.7 ml/kg per h after predilution adjustment (30.4×0.78)[b] assuming 50% of replacement fluid as prefilter (preblood pump =2000 ml/h)

CVVHD: dialysate rate (4000 ml/h) + fluid removal rate (100 ml/h) = effluent dose of 30.4 ml/kg per h

Plasma flow rate (ml/h), blood flow rate (ml/min) ×60 (min/h) × (1-HCT); where HCT is the current hematocrit of the patient (HCT 30% for the case of our patient). CVVHDF, continuous veno-venous hemodiafiltration; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis.

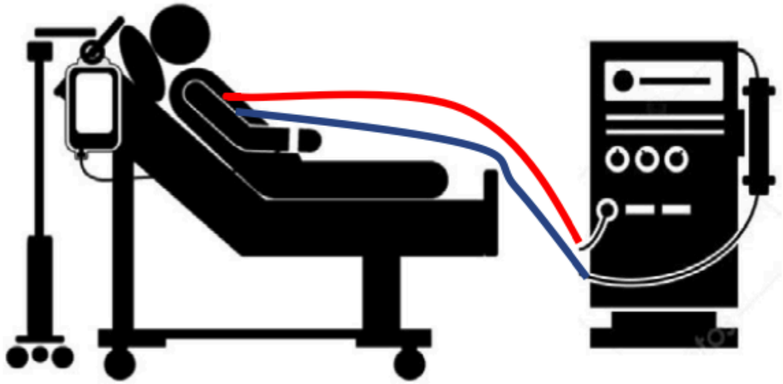
[a]Total ultrafiltration rate (ml/h) = preblood pump or prefilter replacement fluid rate + postfilter replacement fluid rate.

[b]Dilution factor for predilution: Plasma flow rate (ml/h)/[Plasma flow rate (ml/h) + prefilter replacement fluid rate (ml/h)] = 0.88 for our patient (1000 ml/h prefilter replacement fluid in CVVHDF) and 0.78 (assuming 2000 ml/h of prefilter replacement fluid in CVVH).

Dilution factor x0.88 for 1 L and x0.78 for 2 L

Neyra JA, et al. Kidney360. 2020; 2(2):371-384.

Factors that affect solute clearance during CRRT



Causes of loss of CRRT filter efficiency

- Loss of filter surface area due to clotting or air
- Loss of permeability due to clogging, clotting, adsorption (solute fouling on the membrane surface)
- Concentration polarization

Prescribed CRRT dose

- Consensual recommended effluent dose of 25-30 ml/kg/h on average

Treatment Interruptions

- **Intended**
- Procedures
- Mobilization
- Recirculation
- **Unintended**
- Catheter problems
- Filter change
- Bag changes

Delivered CRRT dose

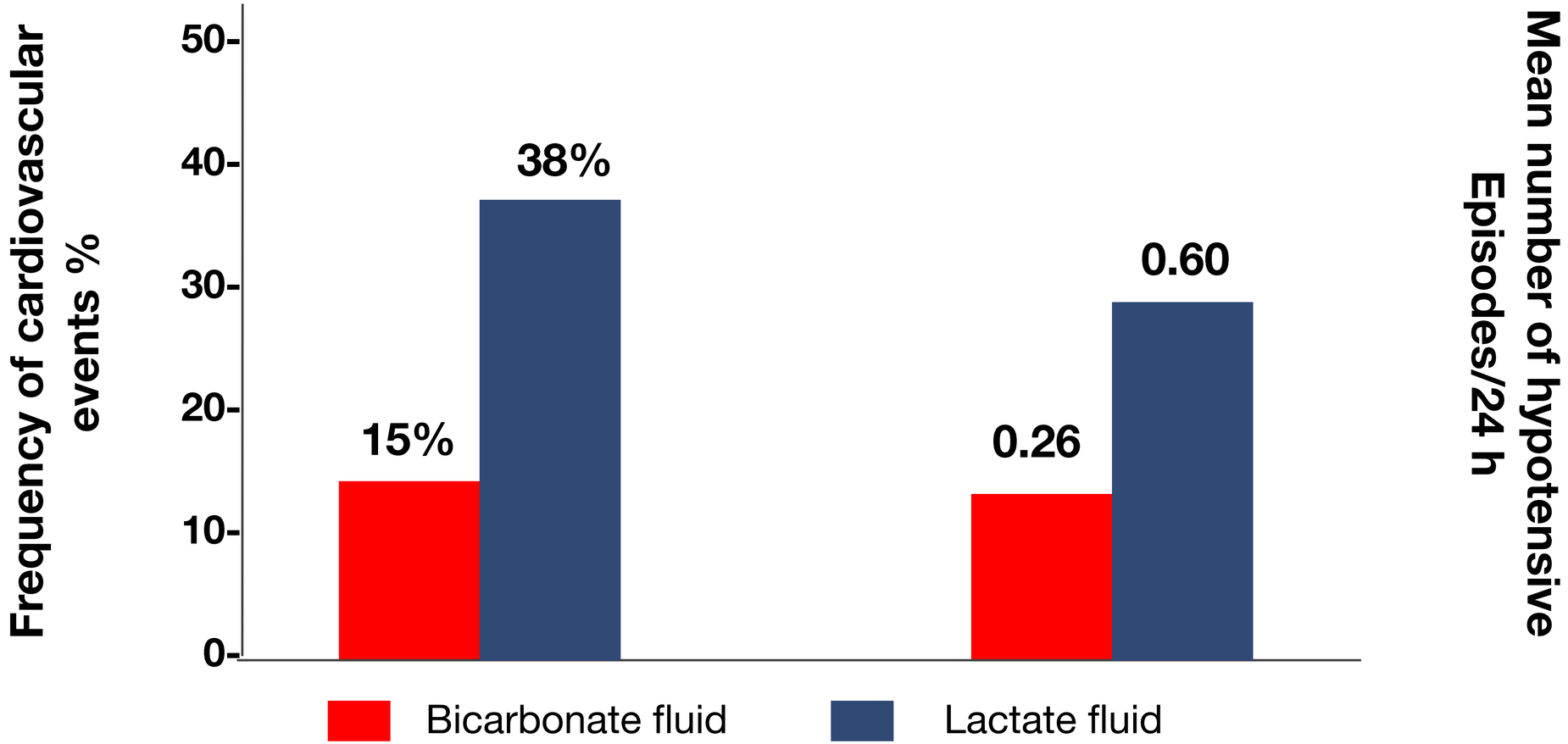
- Consensual recommendation ≥80% of prescribed CRRT dose

Neyra JA, Tolwani A. Semin Dial. 2021; 34(6):432-439.

Effects of bicarbonate- and lactate-buffered replacement fluids on cardiovascular outcome in CVVH patients

Barenbrock, M, et al. Kidney Int 2000; 58:1751.

Frequency of CVS events and hypotensive episodes before the end of the study with AKI



No differences in survival or recovery of renal function related to the buffer selection

Barenbrock, M, et al. Kidney Int 2000; 58:1751.

Composition of solutes in dialysate, and CRRT solutions

Table 1. Composition of solutes in serum, dialysate, and CRRT solutions

Analyte	Normal Serum Concentration[a]	Standard IHD Dialysate	Commercially Available Phosphate-Free CRRT Solutions[b]	Commercially Available Phosphate-Containing CRRT Solution
Sodium, mEq/L	136–145	137[c]	130[d], 140	140
Potassium, mEq/L	3.5–5.0	2, 3[c]	0, 2, 3, 4	4
Calcium, mEq/L	2.3–2.5[e]	2, 2.5, 3[c]	0[d], 2.5, 3	0[d], 2.5
Magnesium, mmol/L	0.66–1.07	0.75	1, 1.5	1.5
Chloride, mEq/L	98–106	104–106	106–120.5	114.5, 122
Acetate, mEq/L	—[f]	4	0	0
Lactate, mEq/L	0.7–1.8	0	0–3	0
HCO_3, mEq/L	23–28	35[c]	25[d], 35	22[d], 32
Dextrose, mg/dl	70–99[g]	100	100	0
Phosphate, mmol/L	1.12–1.45[h]	0	0	1.2

- dZero calcium and lower sodium and bicarbonate concentration are used during citrate anticoagulation. eSerum ionized calcium (usual units in laboratory reports are mmol/L [divide mEq/L by two] or mg/dl [multiply mEq/L by two]). fSerum acetate is not clinically measured. gSerum glucose. hSerum phosphate is measured as mg/dl. The normal serum phosphorus concentration is 3.4–4.5 mg/dl (1.12–1.45 mmol/L).

Vijayan A. Clin J Am Soc Nephrol. 2022; 17(5):631-633.

Replacement fluid

Ca	1.75	mmol/L
Mg	0.5	mmol/L
Na	140	mmol/L
Cl	109.5	mmol/L
HCO3	35	mmol/L
Osmol	287	mOsm/L

CRRT: Replacement fluid

Formula	0.45%NaCl	3%NaCl	7.5%NaHCO3	Sterile water	Na (mEq/L)	HCO3 (mEq/L)
1	900	50	50	-	138	44
2	925	-	75	-	137	66
3	-	100	100	800	138	88
4	-	-	150	850	132	132
5	880	80	40		143	35

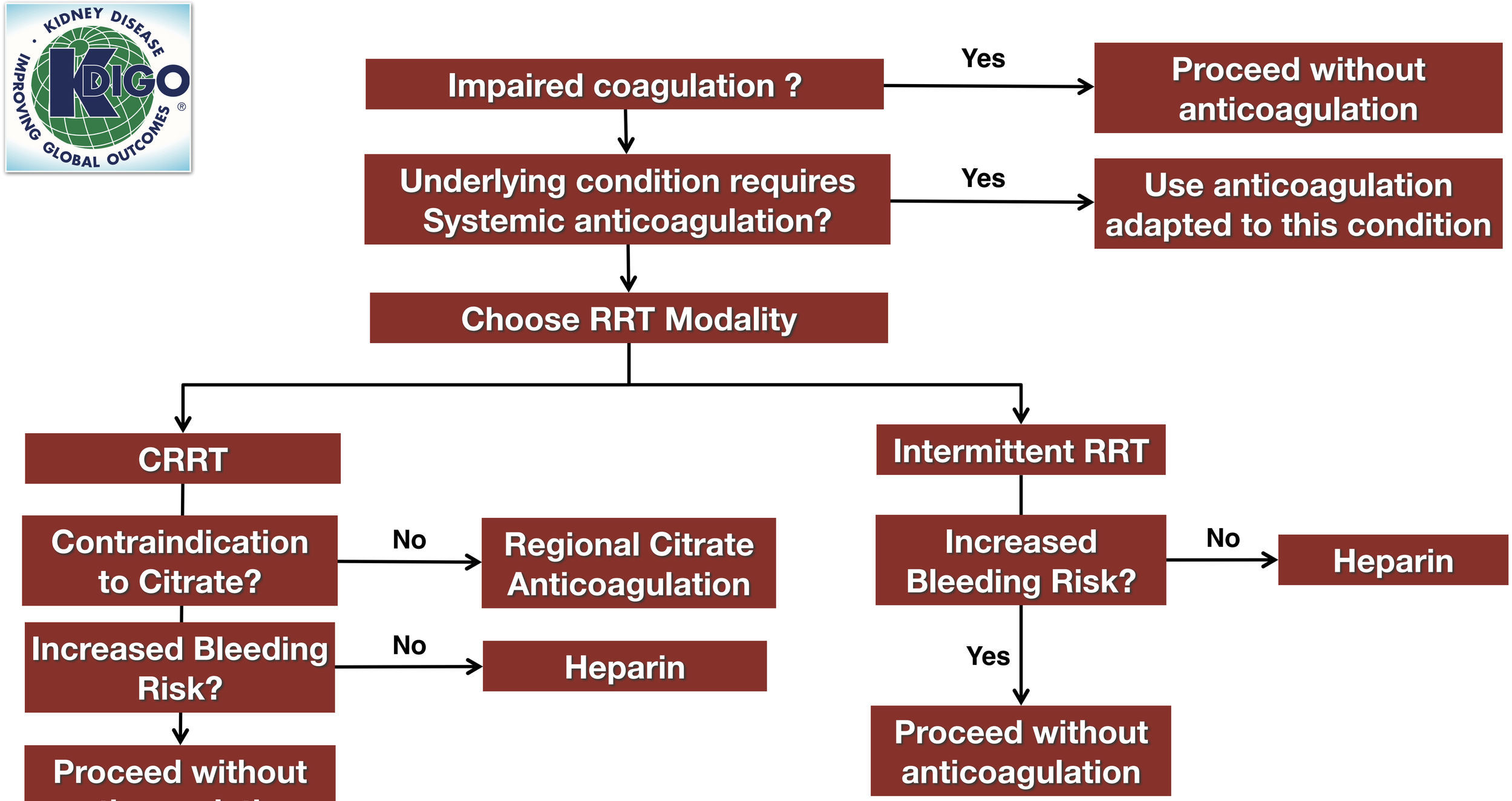
KDIGO Clinical Practice Guideline for AKI 2012

- Using bicarbonate > lactate, as a buffer in dialysate and replacement fluid
  - RRT in patients with AKI (2C)
  - AKI and circulatory shock (1B)
  - AKI and liver failure and/or lactic acidemia (2B)

KDIGO. Kidney Int Supplements. 2012: 2: 8–12.

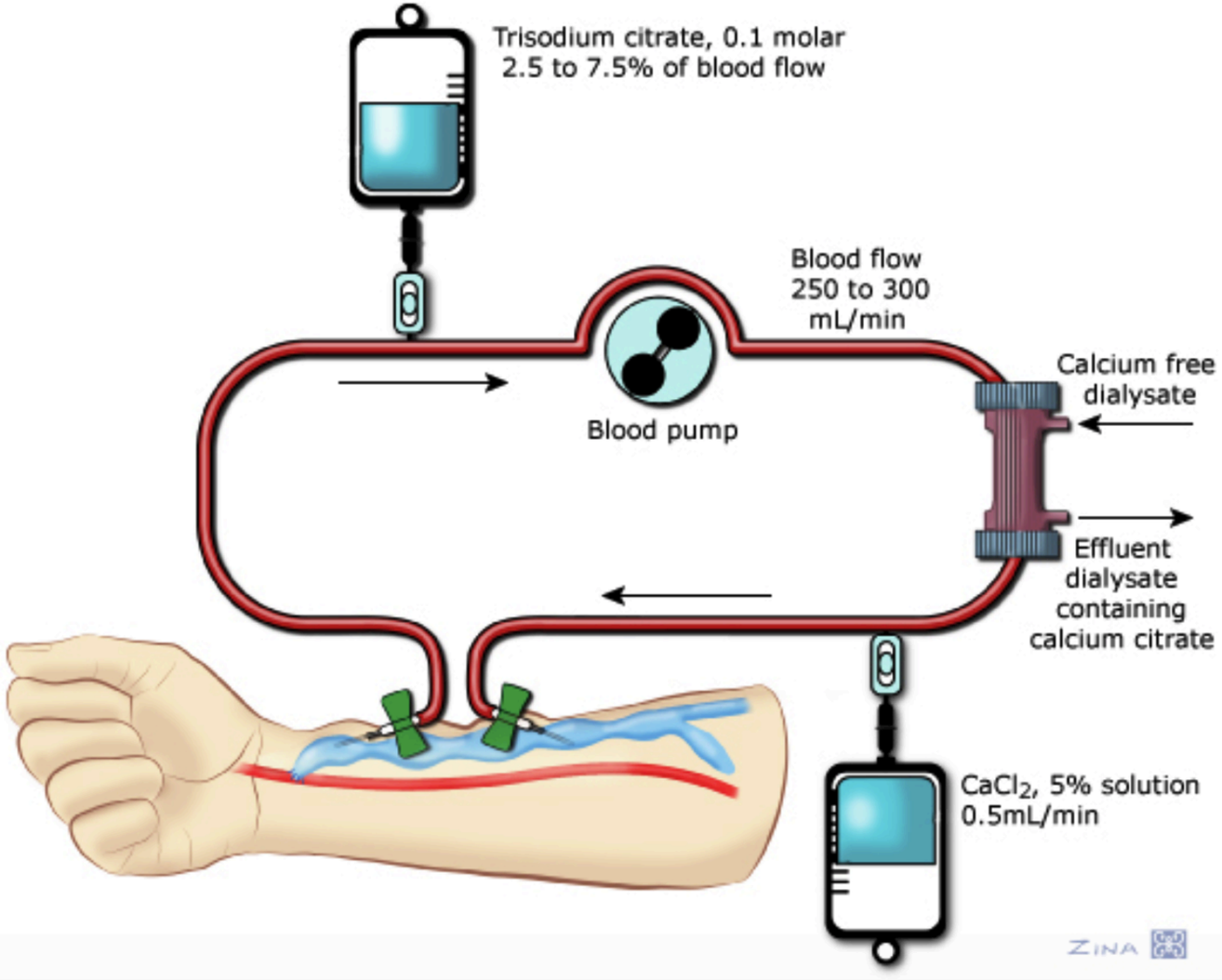
Anticoagulation with RRT

- Prevent clotting of the filter and/or reduction in membrane permeability
- Adequate RRT
- Blood loss in the clotted filter



KDIGO. Kidney Int Supplements. 2012: 2: 8–12.

Regional citrate anticoagulation



Different anticoagulants in AKI patients

Anticoagulant	Advantage	Disadvantage
Citrate	Strict regional anticoagulation – reduced bleeding risk	• Risk of accidental overdose with potentially fatal consequences • Insufficient citrate metabolism in patients with reduced liver function and shock states resulting in accumulation with metabolic acidosis and hypocalcemia • Other metabolic complication (acidosis, alkalosis, hypernatremia, hypocalcemia, hypercalcemia) • Increased complexity • Requires strict protocol

Set target post-filter Ca2+ to 0.25–0.35 mmol/L

KDIGO. Kidney Int Supplements. 2012: 2: 8–12.

Metabolic complications of citrate utilization with continuous RRT

Table 8. Metabolic complications of citrate utilization with continuous RRT

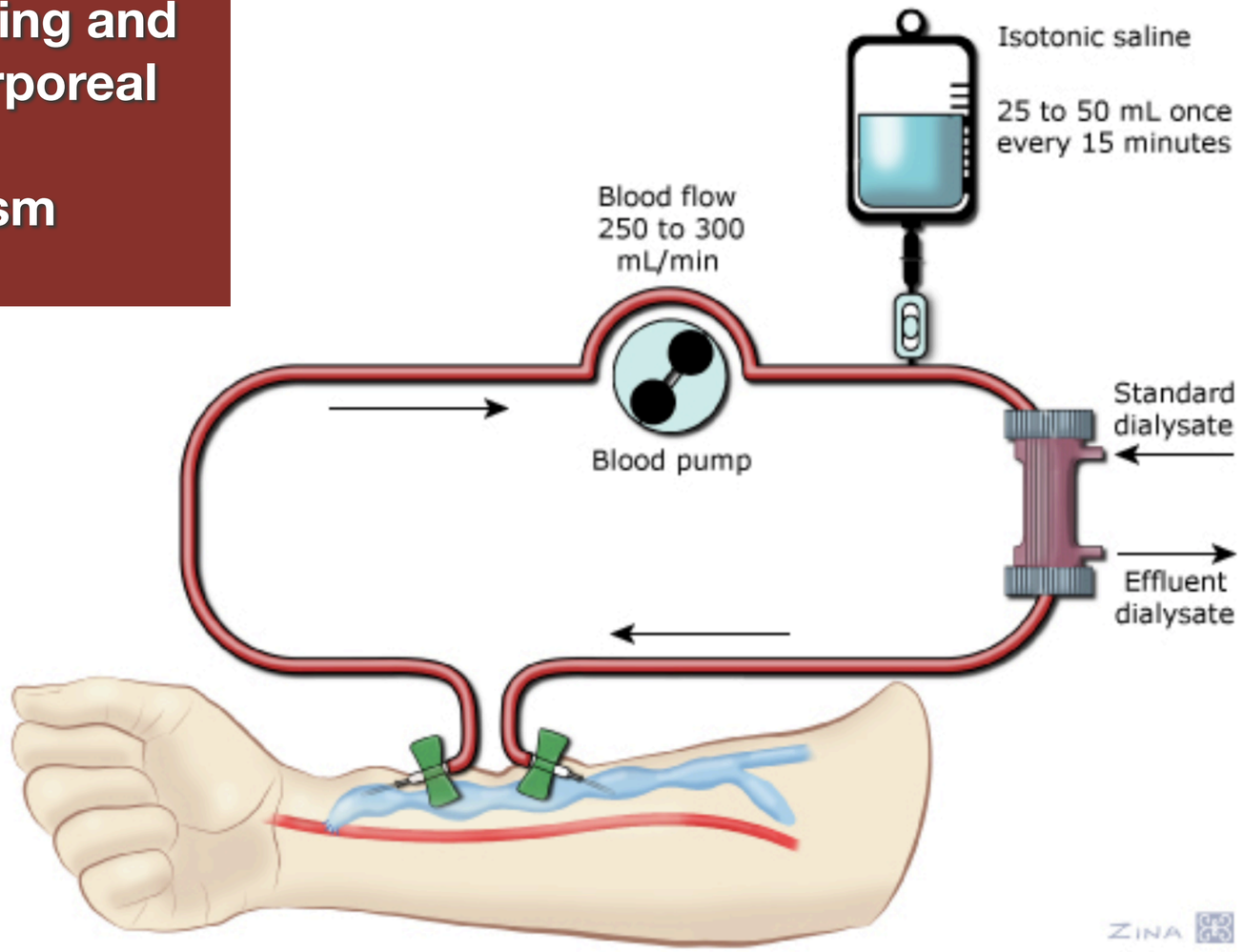
Complication	Mechanism	Diagnosis	Management
Citrate excess	Metabolic conversion of citrate to bicarbonate resulting in excess buffer	Metabolic alkalosis Total Ca^{++}/iCa^{++} <2.5	Decrease blood flow rate Increase dialysate flow rate, or decrease buffer concentration in other CRRT solutions
Citrate toxicity	Decreased metabolic conversion of citrate resulting in accumulation of citrate-calcium complexes in blood	Anion gap metabolic acidosis Total Ca^{++}/iCa^{++} >2.5 Escalating Ca^{++} infusion rate	Decrease blood flow rate, or increase dialysate flow rate, or discontinue citrate
Citrate deficit	Metabolic conversion of citrate to bicarbonate resulting in insufficient buffer	Metabolic acidosis Total Ca^{++}/iCa^{++} <2.5	Increase blood flow rate Decrease dialysate flow rate Increase buffer concentration in other CRRT solutions

Ca^{++}, calcium; iCa^{++}, ionized calcium; CRRT, continuous RRT.

Neyra JA, et al. Kidney360. 2020; 2(2):371-384.

Normal saline flushing

Labor (frequent monitoring and flushing of the extracorporeal circuit)
Risk for air embolism
Low efficiency



Different anticoagulants in AKI patients

Anticoagulant	Advantage	Disadvantage
Saline flush	No bleeding complication	Risk for air embolism Low efficiency

KDIGO. Kidney Int Supplements. 2012: 2: 8–12.

Filtration fraction (FF)

- Ratio of ultrafiltration rate (Quf) to plasma water flow rate is determined by blood flow (Qb) rate and patient hematocrit (Hct):
- $$FF = \frac{Quf}{Qb \times (1 - Hct)}$$
- FF > 0.25-0.30: increase risk of filter clot
- Filter clotting and coating with accumulated proteins

Jorge Cerda, Claudio Ronco. Seminars in Dialysis. 2009: 114–122

Filtration fraction (FF)

- **BFR 150 mL/min, Hct 40%**
- **UF 2500 mL/hr = DFR 1000 + post-RF 1000 + fluid loss rate =500 mL/hr**

Filtration fraction (FF)

- **BFR 150 mL/min, Hct 40%**
- **UF 2500 mL/hr = DFR 1000 + pre-RF 1000 + fluid loss rate =500 mL/hr**

Filtration fraction (FF)

- **BFR 200 mL/min, Hct 40%**
- **UF 2500 mL/hr = DFR 1000 + post-RF 1000 + fluid loss rate =500 mL/hr**

Prevention of clot and Anticoagulation

- Change CVVH to CVVHD and CVVHDF
- Pre-dilution method
- Increase BFR 150-200 ml/min
- Catheter and blood line position
- Pressure monitoring
- Air-blood interface

Follow treatment

- Clinical evaluation of AKI : urine output/volume status
- Lab evaluation
- Na+, K+, Cl-, HCO3-, Ca 2+ and blood sugar every 6-12 hr
- BUN, Cr, Mg2+, PO4, CBC and PT/PTT every 24 hr
- Ratio of urea nitrogen in effluent and blood (EUN/BUN) every 24 hr

Outline

- Timing to initiation of kidney replacement therapy
- Modalities for acute kidney replacement therapy
- Principle and indication for CRRT
- How to order CRRT in critically illness

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ORDERS FOR ONE DAY		ORDERS FOR CONTINUATION		
Date	Orders	Date	Orders	Date off
	CRRT ORDER ☐ **CVVH** ☐ **CVVHD** ☐ **CVVHDF** ☐..... Vascular access: ..... BFR: ..... mL/min DFR: ..... mL/h FLR: ..... mL/h Net UF.....L/d **Total dose.....mL/kg/h** **Replacement fluid:** ☐ Pre-dilution ..... mL/h ☐ Post-dilution ..... mL/h **Anticoagulant Rx:** ☐ Heparin .....U/h ☐ NSS 100 mL IV q 2 h ☐ Citrate ..... **Dialysate solution:** ☐ Accusol-35 5 L ☐ 0.45 NaCl ..... mL ☐ 3% NaCl ..... mL ☐ Sterile water ..... mL ☐ 7.5% NaHCO3 ..... mL ☐ KCL ..... mEq/L ☐ 10%Ca gluconate ..... amp iv in 24 h ☐ 50%MgSO4 ..... g iv drip in 24 h ☐ Others: ..... **Lab monitoring:** - Serum electrolytes, Ca, Mg, PO4, ABG and Lactate q .....h - CBC, BUN, Cr, PT and PTT q 24 h **Signature**			

DEPARTMENT OF MEDICINE
PHRAMONGKUTKLAO HOSPITAL

NEPHROLOGY
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Intelligence Dialysis Center
Nephrology Unit
Phramongkutklao Hospital and College of Medicine