CRITCARE BITES

RENAL REPLACEMENT THERAPY IN THE ICU

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SICM
Society of Intensive Care Medicine
SINGAPORE

MAD FOR MEDICINE

CONTENT

- Acute kidney injury
- Mechanisms of fluid and solute removal
- Intermittent vs continuous RRT
- Indication and timing of RRT initiation
- Dosing of renal replacement therapy
- Pre vs post filter fluid replacement
- Vascular access
- Regional citrate anticoagulation
- Pressure alarms
- Discontinuation of renal replacement therapy
- Special populations: Acute brain injury, hyponatremia, liver failure

ACUTE KIDNEY INJURY

SIGNIFICANCE OF ACUTE KIDNEY INJURY

- Incidence: 1-25% in critically ill patients with ~4% requiring renal replacement therapy, mortality up to 60%[1]
- Associated with high mortality rates – Stratified mortality according to RIFLE classification[2]
  - 5-10% with no renal dysfunction
  - 9-27% at risk
  - 26 to 40% with failure
- Among hospital survivors, 1-year renal recovery was incomplete in approximately 1/3 of patients, and 19% remained RRT-dependent[3]

1. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294:813–818.
2. Mehta RL, Pascual MT, Soroko S, et al. Spectrum of acute renal failure in the intensive care unit: PICARD experience. Kidney Int 2004;66:1613-21
3. De Corte W, Dhondt A, Vanholder R, et al. Long-term outcome in ICU patients with acute kidney injury treated with renal replacement therapy: a prospective cohort study. Crit Care. 2016;20:256

Table 2 | Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

KDIGO 2012 DEFINITION AND CLASSIFICATION OF AKI

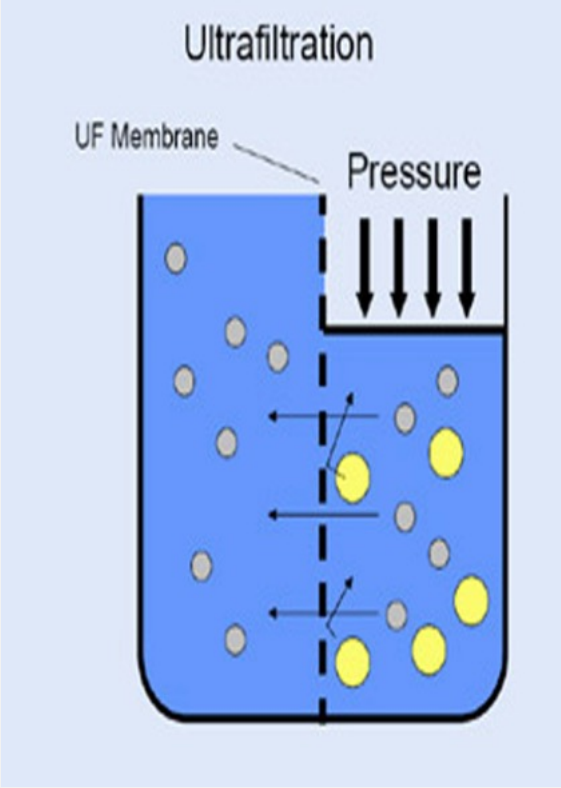
CAUSES OF AKI

Pre-Renal	Renal	Post-Renal
-Shock -Cardio-renal syndrome -Hepato-renal syndrome -Abdominal compartment syndrome	-Acute tubular necrosis -Acute interstitial nephritis -Glomerulonephritis -Drugs -Rhabdomyolysis -Tumour lysis -Multiple myeloma -Contrast nephropathy -HUS, TTP -Venous congestion	-Stones -Tumour -Bladder obstruction

MECHANISMS OF FLUID AND SOLUTE REMOVAL

MECHANISMS OF FLUID REMOVAL

- Ultrafiltration: Process by which plasma water is forced across a semipermeable membrane by hydrostatic pressure



MECHANISMS OF SOLUTE REMOVAL

- Convection (haemofiltration):
  - Transmembrane pressure drives plasma water across a semipermeable membrane
  - This process **drags solutes** with the plasma
  - Removal of middle molecules (e.g. inflammatory cytokines)
  - Requires high UF rates (>1L/hr) to produce significant enough solute clearance
- Diffusion (haemodialysis):
  - Solute removal across a membrane driven by a **concentration gradient** of solute between the blood on one side of the membrane and electrolyte solution (dialysate) on the other side of the membrane
  - Concentration gradient maintained by **countercurrent flow**
  - Removal of small molecules

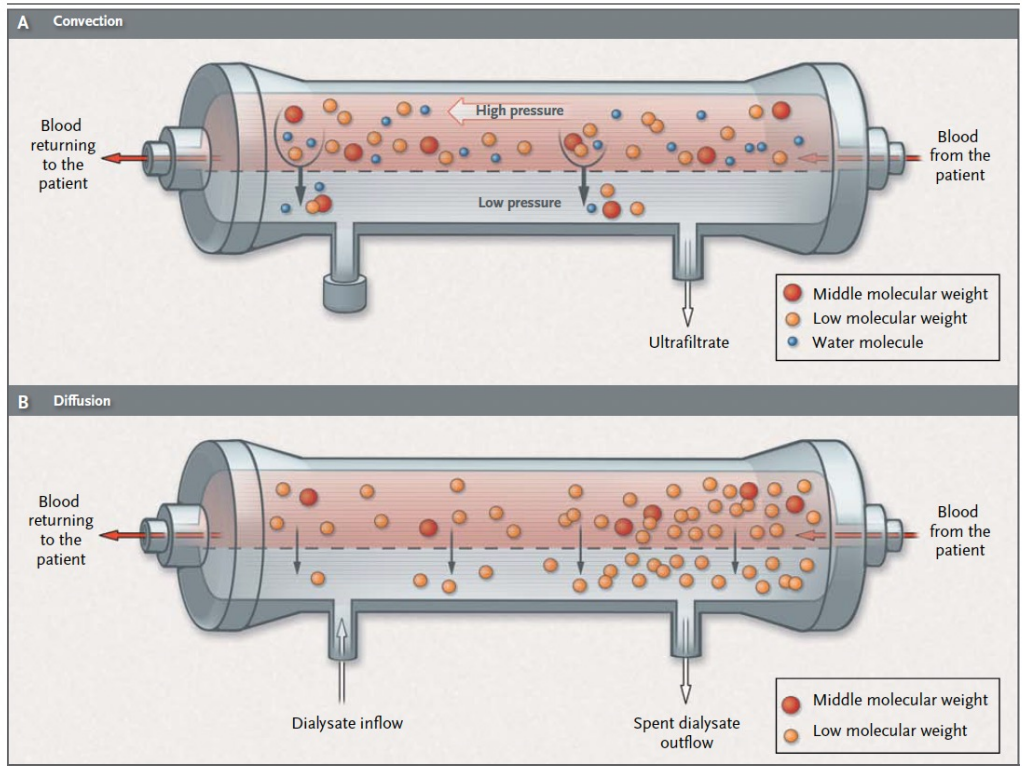
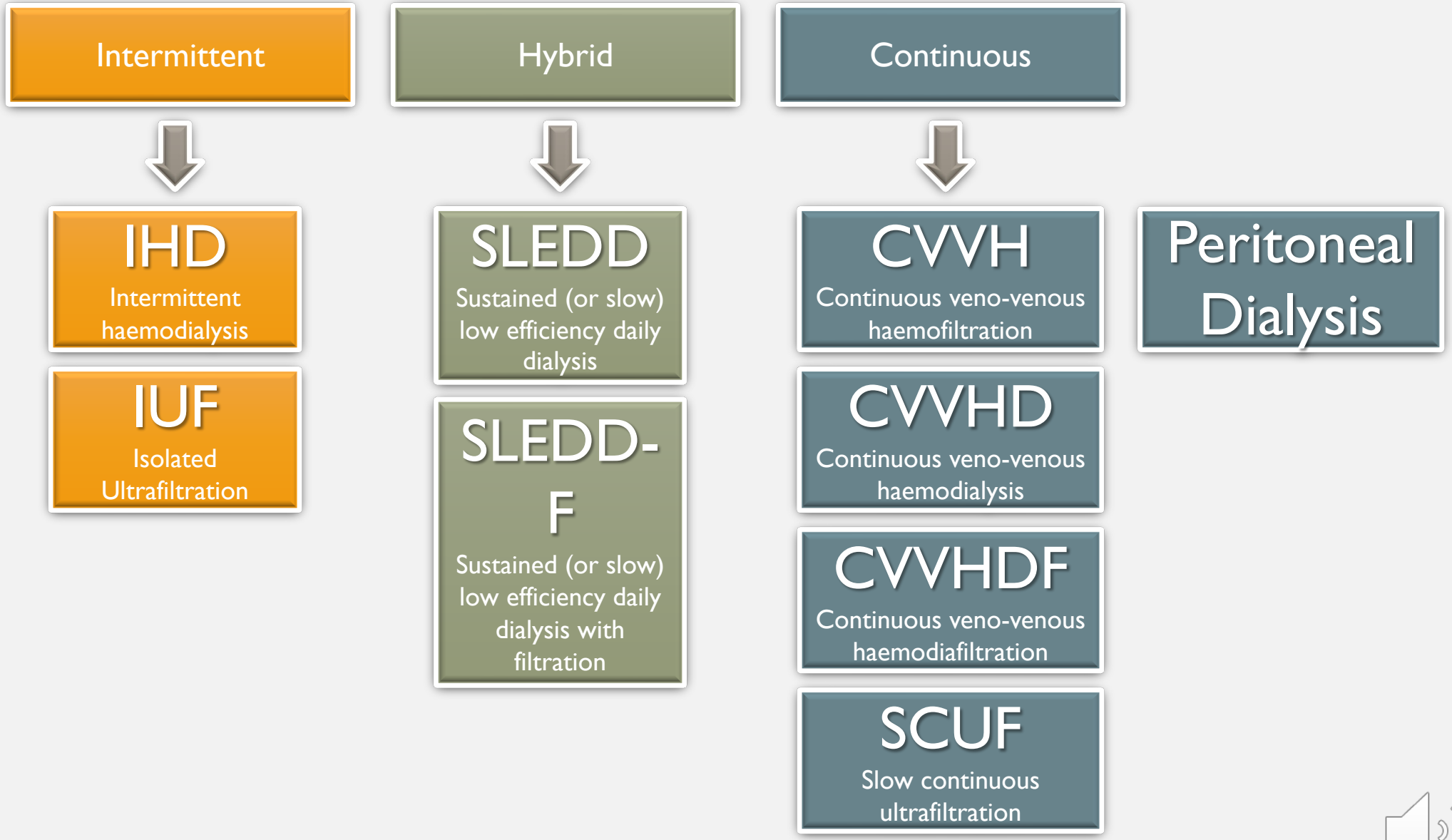


Figure 1. Transport of Solutes across a Semipermeable Membrane.

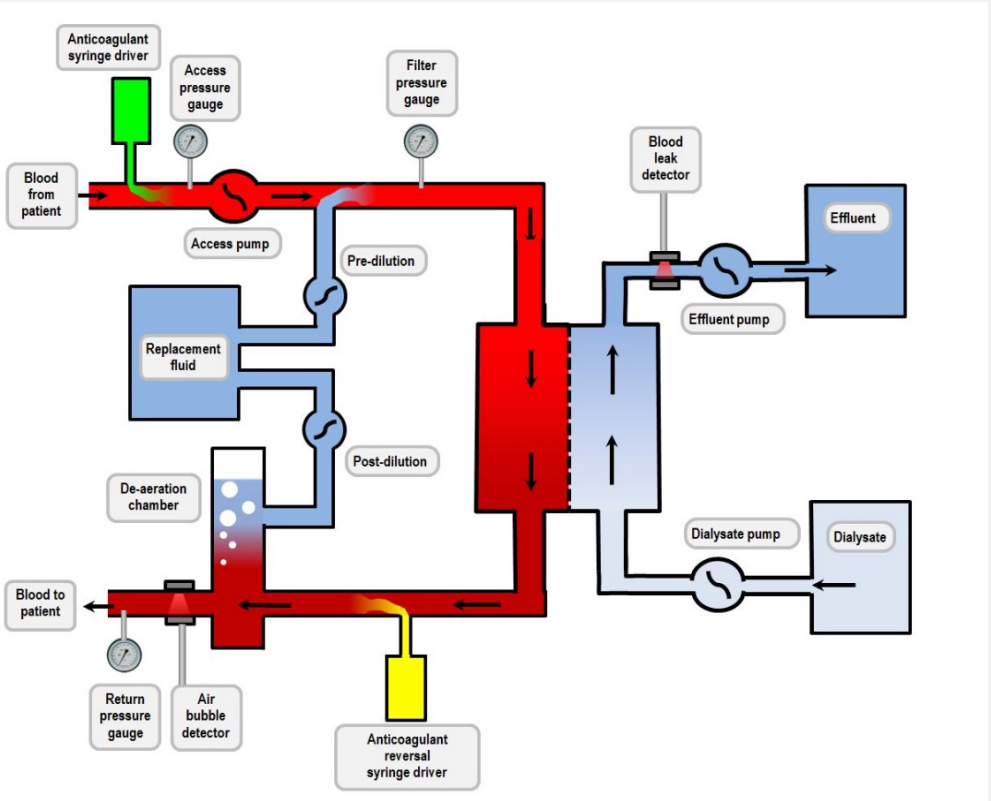
As shown in Panel A, convection occurs when solutes are transported across a semipermeable membrane with plasma water in response to a hydrostatic pressure gradient that is created on the blood side of the hemofilter. Convection enhances removal of low- and middle-molecular-weight molecules. As shown in Panel B, in diffusion, movement of solute across a semipermeable membrane is driven by a concentration gradient between the blood and the dialysate. Solutes move from the side with the higher concentration of particles to the side with the lower concentration. Diffusion is best for clearing low-molecular-weight solutes such as urea and creatinine.

N Engl J Med 2012; 367:2505-2514
DOI: 10.1056/NEJMct1206045

INTERMITTENT VS CONTINUOUS


Intermittent
Hybrid
Continuous
IHD
Intermittent haemodialysis
IUF
Isolated Ultrafiltration
SLEDD
Sustained (or slow) low efficiency daily dialysis
SLEDD-F
Sustained (or slow) low efficiency daily dialysis with filtration
CVVH
Continuous veno-venous haemofiltration
CVVHD
Continuous veno-venous haemodialysis
CVVHDF
Continuous veno-venous haemodiafiltration
SCUF
Slow continuous ultrafiltration
Peritoneal Dialysis

CONTINUOUS RENAL REPLACEMENT THERAPY



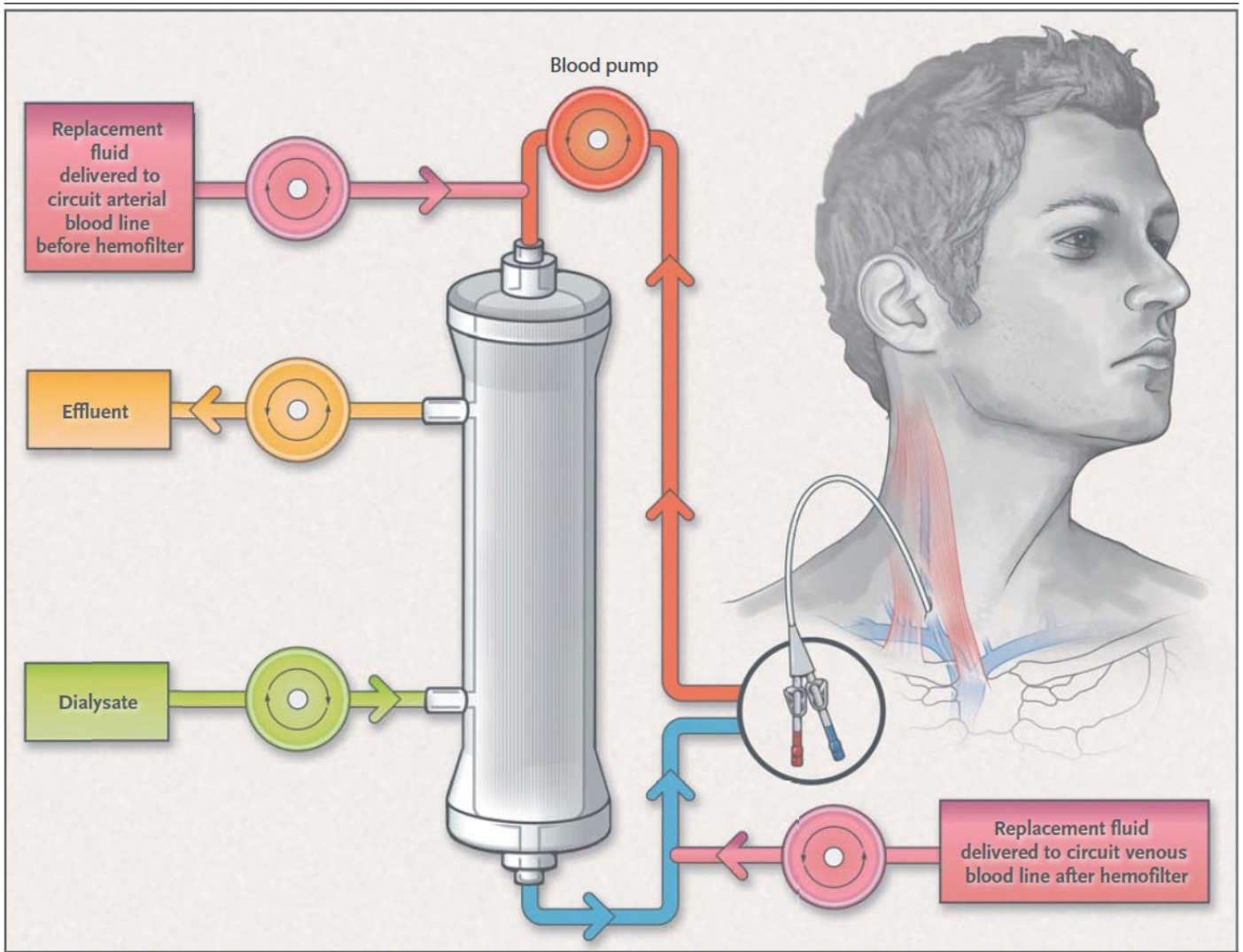


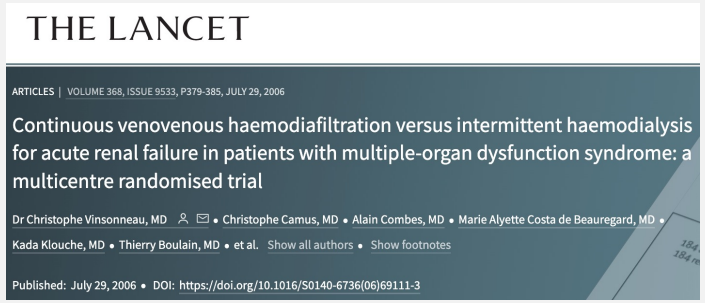
Figure 2. Circuit Components in Continuous Renal-Replacement Therapy.

Continuous renal-replacement therapy requires a central double-lumen venovenous catheter, an extracorporeal circuit and hemofilter, a blood pump, and an effluent pump. Depending on the type of continuous renal-replacement therapy, dialysate, replacement fluid pumps, or both are required. In continuous venovenous hemofiltration, solutes and plasma water are forced across the semipermeable membrane by high ultrafiltration rates (convection). Simultaneously, replacement fluid is infused into the blood with the use of a replacement pump. The replacement fluid replenishes both the volume and electrolytes removed. Replacement fluid can be infused before or after the hemofilter. In continuous venovenous hemodialysis, solutes and plasma move across the semipermeable membrane into the dialysate compartment of the hemofilter by means of diffusion and ultrafiltration. The flow of dialysate is in the opposite direction from the flow of blood. In continuous venovenous hemodiafiltration, solutes and plasma water are removed by diffusion, convection, and ultrafiltration.

PROS AND CONS

	Pros	Cons
Intermittent	Flexible timing allows for down time – scans, procedures, physio etc Rapid fluid, solute, toxin removal Minimisation of anticoagulant exposure Cheaper	Hypotension Cerebral edema (dialysis disequilibrium)
Continuous	Haemodynamic stability Stable and predictable volume and solute control Stable ICP	Anticoagulation requirements Higher potential for filter clotting Hypothermia Expensive Immobility and transport issues

EVIDENCE



Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, Pallot JL, Chiche JD, Taupin P, Landais P, Dhainaut JF; Hemodiafe Study Group. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. Lancet. 2006 Jul 29;368(9533):379-85. doi: 10.1016/S0140-6736(06)69111-3. PMID: 16876666.

Rate of survival at 60-days did not differ between the groups (32% IHD group vs 33% in the CRRT group [95 % CI -8.8 to 11.1,])

Rabindranath K, Adams J, Macleod AM, Muirhead N. Intermittent versus continuous renal replacement therapy for acute renal failure in adults. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD003773. doi: 10.1002/14651858.CD003773.pub3. PMID: 17636735.

CRRT did not differ from IHD in in-hospital mortality, ICU mortality, number of surviving patients not requiring RRT, haemodynamic instability, hypotension or need for escalation of pressor therapy.

CRRT associated with higher MAP and higher risk of filter clotting

GUIDELINES

5.6.2: We suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients. (2B)

5.6.3: We suggest using CRRT, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (2B)

PRESCRIBING INTERMITTENT DIALYSIS

Intermittent Haemodialysis (IHD)	Slow Low Efficiency Dialysis (SLED)
Qb: 200-250ml/min Qd: 500ml/min Duration 4H	Qb: 150ml/min Qd: 300ml/min Duration: 6-8H

<u>Dialysis Disequilibrium</u>

- Rapid osmotic shifts between blood and brain compartments can result in cerebral edema and raised ICP, causing neurological complications
- Tends to occur during or shortly after dialysis initiation, especially in patients with very high urea or hypernatremia
- Risk is reduced with SLED/CRRT, initial shorter dialysis durations (especially if using IHD), using smaller surface area dialysers, limit urea reduction ratio to 40%

INDICATION AND TIMING OF RRT INITIATION

INDICATIONS FOR RRT

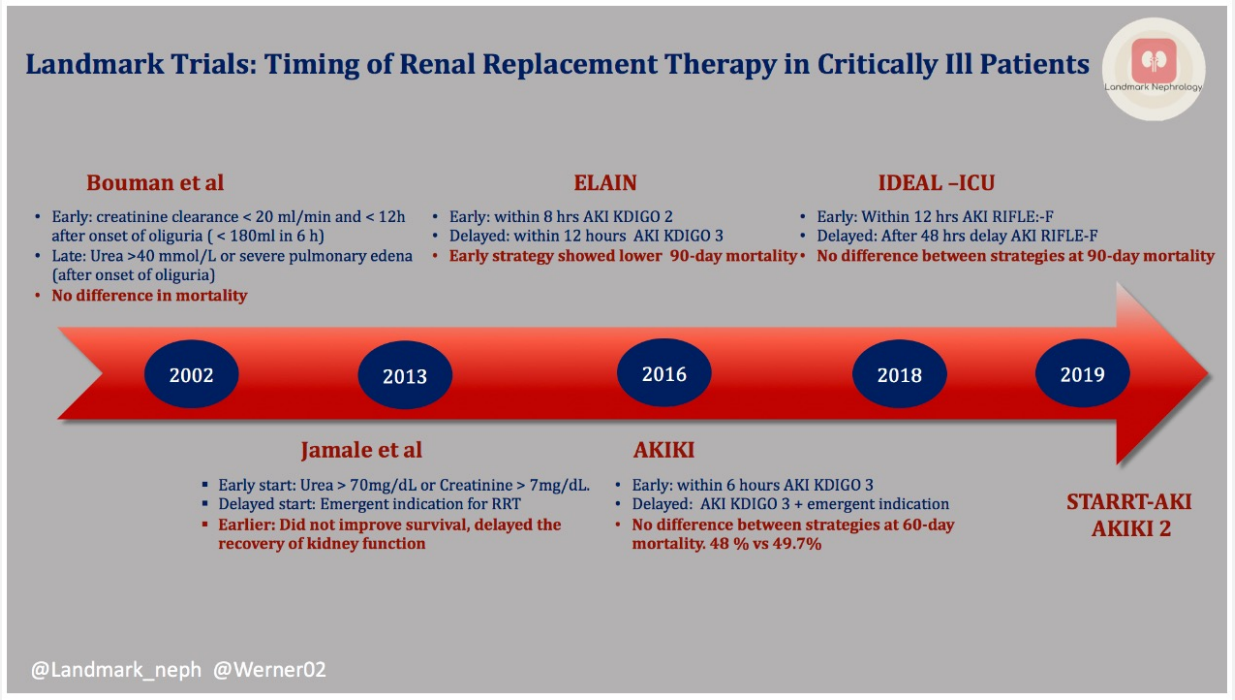
Table 2. Indications and Contraindications for Continuous Renal-Replacement Therapy in Critically Ill Patients with Acute Kidney Injury.

Indications
Classic indications
Hyperkalemia
Severe metabolic acidosis
Diuretic-resistant volume overload
Oliguria or anuria
Uremic complications
Some drug intoxications
Potential indications
Hemodynamic instability
Disrupted fluid balance (due to cardiac failure or multiorgan failure)
Increased catabolic states (e.g., rhabdomyolysis)
Sepsis
Increased intracranial pressure
Electrolyte abnormalities
Contraindications
Advance directives indicating that the patient does not want dialysis
The patient or his or her health care proxy declines continuous renal-replacement therapy
Inability to establish vascular access
Lack of appropriate infrastructure and trained personnel for continuous renal-replacement therapy

N Engl J Med 2012; 367:2505-2514
DOI: 10.1056/NEJMct1206045

TIMING OF RRT INITIATION

5 landmark studies: ELAIN (2016), AKIKI (2016), IDEAL-ICU (2018), STARRT-AKI (2020), AKIKI 2 (2021)



- ELAIN showed mortality benefit with early RRT – essentially a very early vs early study in a predominantly surgical population
- AKIKI, IDEAL-ICU, STARRT-AKI were neutral – These studied patients with sepsis/septic shock, and from a timeline point of view examined the middle of the spectrum – no difference between early and slight delay
- AKIKI 2 showed harm with prolonged delay of RRT – It essentially studied the very late end of the spectrum (delay vs very delayed), and showed increased HR for death at 60 days (in multivariable analysis)

Study	Design (year)	Sample Size	Entry criteria	Groups	Outcome
Early versus delayed initiation of RRT on mortality in critically ill patients with AKI (ELAIN) [6]	Single centre RCT (2016)	231	KDIGO stage 2 AKI, NGAL > 150 ng/mL, ≥ 1 of: severe sepsis, vasopressor use, fluid overload or progression of other organ dysfunction	Early, RRT started within 8 h OR Late, RRT started 12 h after developing Stage 3 AKI*	90 Day Mortality. Early = 39.3%, Late = 57.4% (p = 0.03)
Artificial kidney initiation in kidney injury (AKIKI) study group [7]	Multicentre RCT (2016)	620	KDIGO Stage 3 AKI and mechanical ventilation or catecholamine infusion or both	Early, RRT started within 6 h OR Late, RRT started if oliguria persisted > 72 h*	60 Day Mortality. Early = 48.5%, Late = 49.7% (p = 0.79)
Initiation of dialysis early versus delayed in the intensive care unit (IDEAL-ICU) study [8]	Multicentre RCT (2018)	488	Septic shock and meeting RIFLE 'F' criteria	Early, RRT started within 12 h OR Late, RRT started after 48 h	90 Day Mortality. Early = 58%, Late = 54% (p = 0.38)
Standard versus accelerated initiation of RRT in AKI (STARRT-AKI) trial [9]	International Multicentre RCT (2020)	2927	KDIGO Stage 2 or 3 AKI	Accelerated RRT, within 12 h OR Standard, RRT started after 72 h*	90 Day Mortality, Accelerated = 43.9%, Standard = 43.7% (p = 0.92)
Comparison of two delayed strategies for RRT initiation for severe AKI (AKIKI 2): a multicentre, open-label, randomised, controlled trial [10]	Multicentre RCT (2021)	278	KDIGO Stage 3 AKI and mechanical ventilation or catecholamine infusion or both. Oliguria or anuria for > 72 h or BUN 112 – 140 mg/dL	Delayed group, RRT start in < 12 h. More delayed group, RRT postponed until BUN ≥ 140 mg/dL or urgent indication	RRT-free days Delayed = 12 days More delayed = 10 days HR# for death 60 days 1.65 (95% CI 1.09–2.50) for more delayed group

Cove ME, MacLaren G, Brodie D, Kellum JA. [illegible]ising the timing of renal replacement therapy in acute kidney injury. Crit Care. 2021 May 31;25(1):184. doi: 10.1186/s13054-021-03614-5. PMID: 34059096; PMCID: PMC8165519.

PRACTICAL APPROACH

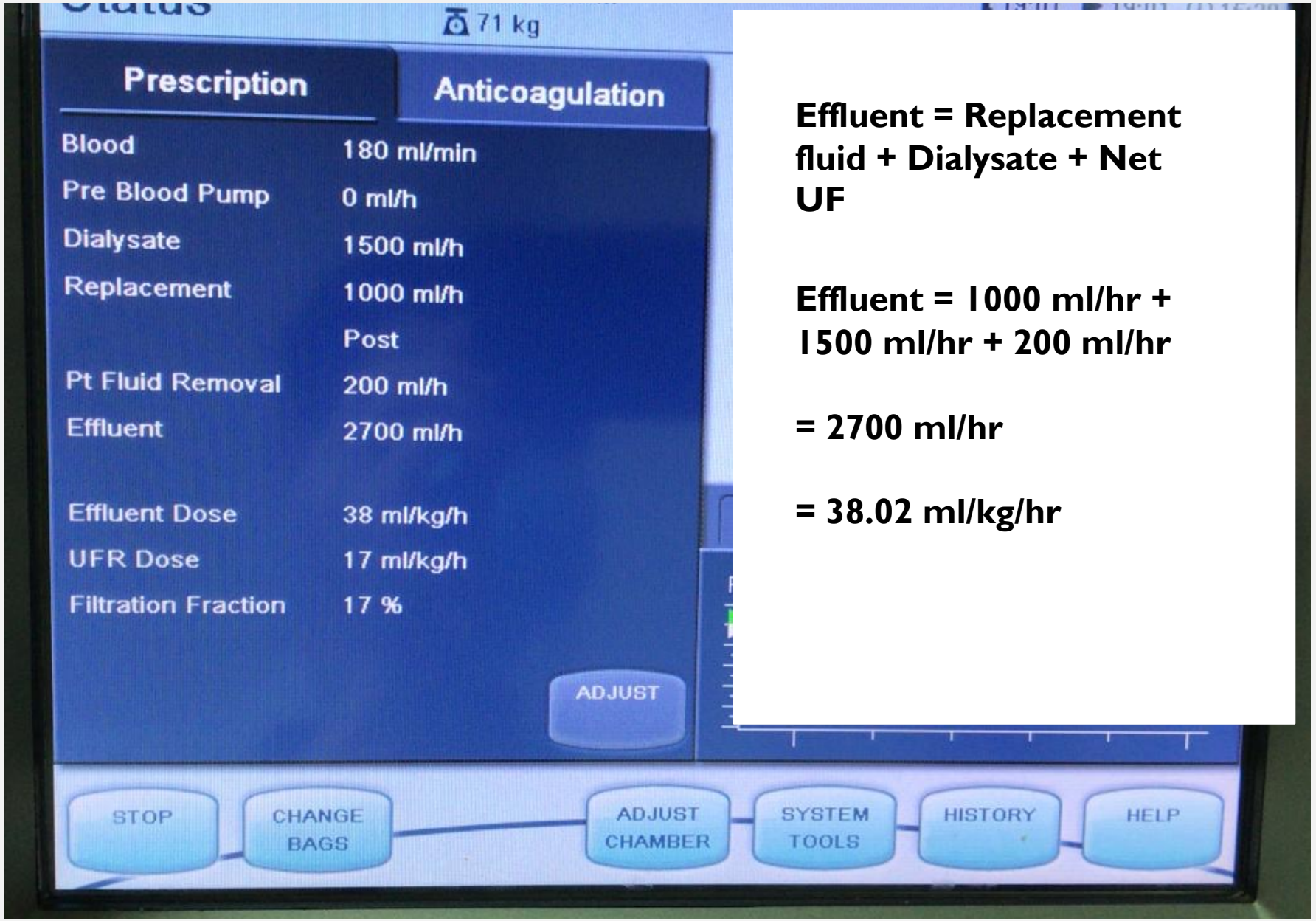
- Evidence tells us that there is no rush for early initiation, but probably harmful to continue waiting beyond 72 hours of severe AKI
- Bearing in mind the limitations of aggregate data – decisions for RRT initiation still needs to be contextualized to the patient (e.g. underlying disease processes, expected trajectory, practical considerations)
- Additional adjuncts to personalize decisions/further stratify patients
  - Frusemide stress test[1,2]
  - Renal biomarkers (e.g. neutrophil gelatinase associated lipocalin (NGAL))[3]
  - Scoring systems

1. Chen, JJ., Chang, CH., Huang, YT. *et al.* Furosemide stress test as a predictive marker of acute kidney injury progression or renal replacement therapy: a systemic review and meta-analysis. *Crit Care* **24**, 202 (2020). https://doi.org/10.1186/s13054-020-02912-8
2. McMahon BA, Chawla LS. The furosemide stress test: current use and future potential. Ren Fail. 2021 Dec;43(1):830-839. doi: 10.1080/0886022X.2021.1906701. PMID: 33971784; PMCID: PMC8118439.
3. Meersch M, Zarbock A, Küllmar M. Renal biomarkers for the initiation of renal replacement therapy-is this the future? J Thorac Dis. 2018 Sep;10(Suppl 26):S3229-S3232. doi: 10.21037/jtd.2018.08.44. PMID: 30370122; PMCID: PMC6186579.

DOSING OF RRT

WHAT IS DOSING IN CRRT?

- Conceptual: Volume of blood purified measured in terms of clearance rate of a representative marker solute
- Kt/V used in CKD but has limitations in AKI (esp in ICU patients) – wide variations of urea and volume in the ICU patients
- Practical: **Effluent rate** in ml/kg/hr → **Dialysate + Replacement fluid + Net UF**



Effluent = Replacement fluid + Dialysate + Net UF

Effluent = 1000 ml/hr + 1500 ml/hr + 200 ml/hr

= 2700 ml/hr

= 38.02 ml/kg/hr

OPTIMAL DOSING

- Early studies showed possible benefit of high dosing but refuted in more recent studies
- 2012 KDIGO guidelines 2012 for CRRT – **20-25 ml/kg/h;** however prescribe at higher dose of 25-30mk/kg/h in view of actual delivered dose < prescribed dose because:
  - Vascular access factors: Recirculation, malfunction
  - Haemofilter factors: Clogging, clotting
  - Prescription factors: Pre vs post-dilution, QB/QD ratio
  - Downtime: Procedures, alarms, bag/filter changes
- Landmark trials: ATN (NEJM 2008), RENAL (NEJM 2009)
- ? Higher doses for septic ATN – IVOIRE study looking at high volume haemofiltration did not demonstrate benefit

OPTIMAL DOSING

ORIGINAL ARTICLE

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

The VA/NIH Acute Renal Failure Trial Network*

Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, Finkel K, Kellum JA, Paganini E, Schein RM, et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008;359:7–20.

ATN VA/NIH trial

-35ml/kg/h vs 20ml/kg/h

-No differences in mortality, duration of RRT, rate of renal recovery or non-renal organ failure

ORIGINAL ARTICLE

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*

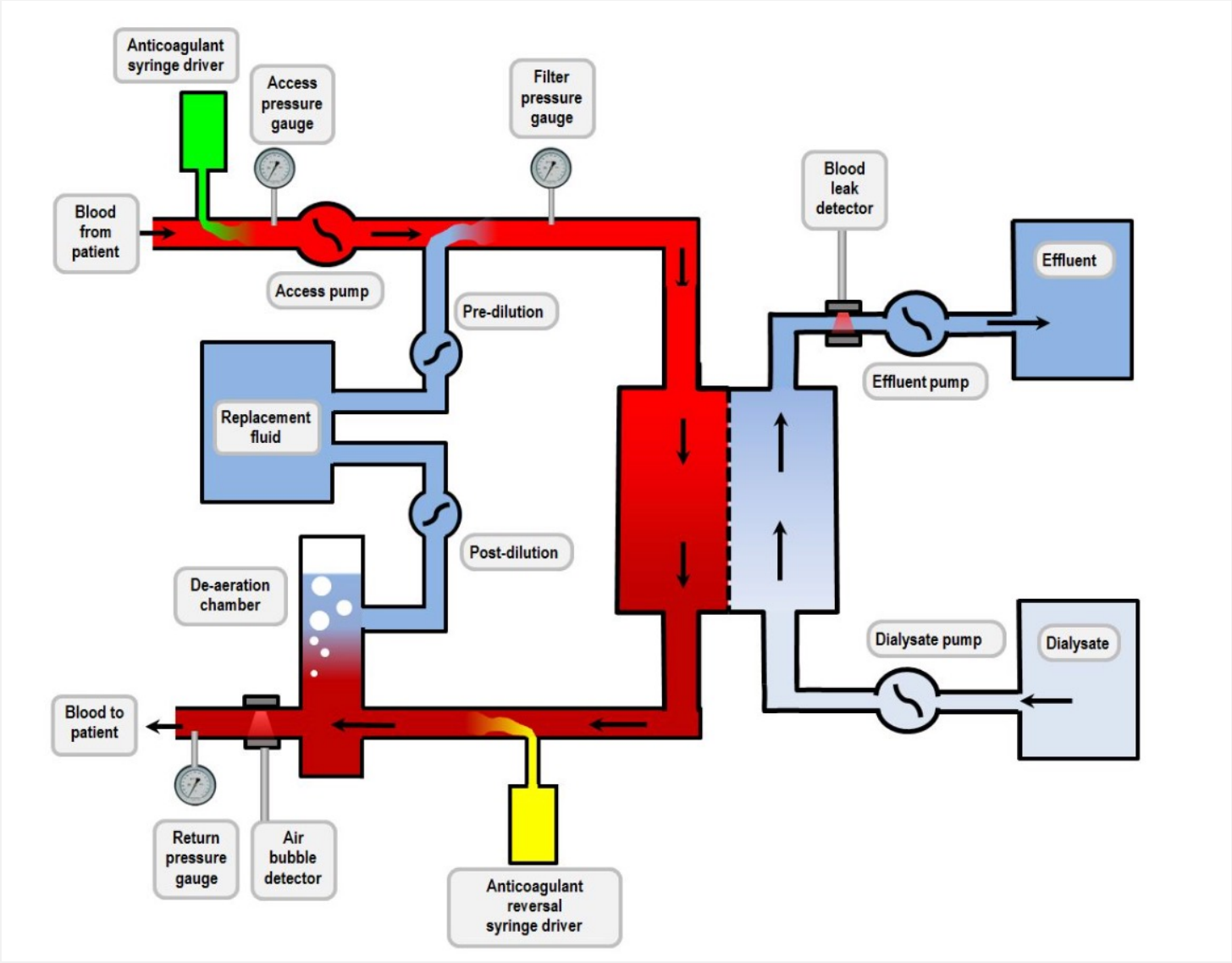
Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009; 361: 1627–1638

RENAL Trial

-40ml/kg/h vs 25ml/kg/h

-No differences in mortality or duration of RRT. Hypophosphatemia more common in high intensity group

PRE VS POST FILTER FLUID REPLACEMENT


Anticoagulant syringe driver
Access pressure gauge
Filter pressure gauge
Blood leak detector
Blood from patient
Access pump
Pre-dilution
Effluent
Effluent pump
Replacement fluid
Post-dilution
De-aeration chamber
Dialysate pump
Dialysate
Blood to patient
Return pressure gauge
Air bubble detector
Anticoagulant reversal syringe driver

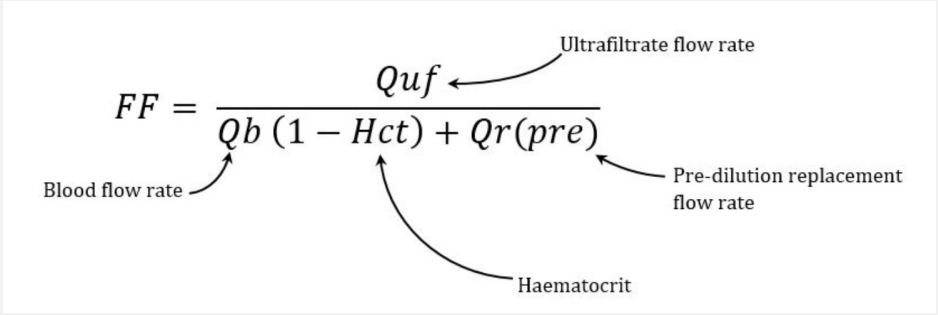
PRE VS POST FILTER FLUID REPLACEMENT

- In convective modalities (CVVHF, CVVHDF), fluid replacement can either be given pre or post filter

	Pre-Filter	Post-Filter
Pros	-Prolong filter life/less clotting risk -UF rate is not limited by blood flow rate	-Increased efficiency -Prevents clotting in de-aeration chamber
Cons	-Less efficient because of increased dilution factor (although arguably the prolonged filter life might increase the overall efficiency)	-Decreased filter life because of higher end-filter haematocrit -Constrained by Qb and Quf (to keep filtration fraction <0.2-0.25)

FILTRATION FRACTION

- Filtration fraction is the percentage of plasma that is being removed from blood during UF – ratio of filtration rate to plasma flow rate
- Indication of how concentrated blood is in the filter
- Filtration fraction = Qtotal / (Qp + Qpre-dil)



- Filtration fraction > 25% associated with filter clotting

DILUTION FACTOR

- When pre-filter fluid is administered, the blood gets diluted before reaching the filter, resulting in reduced effectiveness of solute clearance
- This concept is termed dilution factor – mathematically computed as:
  Qb (1 – Hct) / [Qb (1 – Hct) + Qr (pre)]
- Effective delivered dose = dilution factor x prescribed effluent dose x hours of RRT

VASCULAR ACCESS

VASCULAR ACCESS

5.4.2: When choosing a vein for insertion of a dialysis catheter in patients with AKI, consider these preferences (Not Graded):

- First choice: right jugular vein
- Second choice: femoral vein;
- Third choice: left jugular vein;
- Last choice: subclavian vein with preference for the dominant side.

Right IJ – 16cm (R atrium)

Left IJ – 20cm

Right femoral – 24cm (IVC)

Left femoral – 24cm (IVC)

KDIGO 2012 Guidelines

VASCULAR ACCESS

- Good vascular access plays an important role in prevention of circuit clotting
- Practical considerations: Site in the neck if prone positioning anticipated
- Jugular and femoral sites: no difference in terms of infectious complications except in obese patients (BMI > 28 kg/m^2)[1]
- Left jugular vein access associated with greater rates of catheter dysfunction[2]

1. Parienti JJ et al. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. JAMA. 2008;299:2413–22
2. Parienti JJ et al. Catheter dysfunction and dialysis performance according to vascular access among 736 critically ill adults requiring renal replacement therapy: a randomized controlled study. Crit Care Med. 2010;38:1118–25.

REGIONAL CITRATE ANTICOAGULATION

WHY ANTICOAGULATION?

- Prevention of clotting of filter
  - Achieve adequate RRT
  - Prevent blood loss for filter clotting
- However must be balanced against bleeding risks
- Besides anticoagulation, other methods to reduce filter clotting include:
  - Ensuring good vascular access
  - Filtration fraction <20-25%
  - Pre-filter fluid replacement

ANTICOAGULATION OPTIONS

- Systemic vs regional: Regional generally preferred because anticoagulation effect confined to extracorporeal circuit
- Citrate vs Heparin

	Heparin Preferred in IHD Instances when systemic anticoagulation is necessary	Citrate Preferred in CRRT
Pros	• No monitoring involved (LMWH) • Single dose during IHD • Less costly, widely available	• Less bleeding risks • Prolongs filter life • Avoids risk of HIT
Cons	• Bleeding risk • Monitoring required in view of narrow TI (UF) • Heparin Induced Thrombocytopenia • Systemic – risk of accumulation • Monitoring of anti-Xa levels challenging	• Accumulation causing toxicity – metabolic disturbances, arrhythmias • Increased complexity • Strict protocol • Cost • Contraindicated in liver impairment and severe lactic acidosis

CITRATE VS HEPARIN: EVIDENCE

Citrate vs. heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized study

Monchi M, Berghmans D, Ledoux D, et al. Citrate vs. heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized study. Intensive Care Med 2004; 30: 260–265.

Improved filter lifespan and lower blood transfusion rates in RCA vs heparin anticoagulation

Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients

DEMETRIOS J. KUTSOGIANNIS, R.T. NOEL GIBNEY, DANIEL STOLLERY, and JUN GAO

Kutsogiannis DJ, Gibney RT, Stollery D, et al. Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. Kidney Int 2005; 67: 2361–2367

Improved filter lifespan and lower bleeding risk in RCA vs heparin anticoagulation

JAMA | Original Investigation

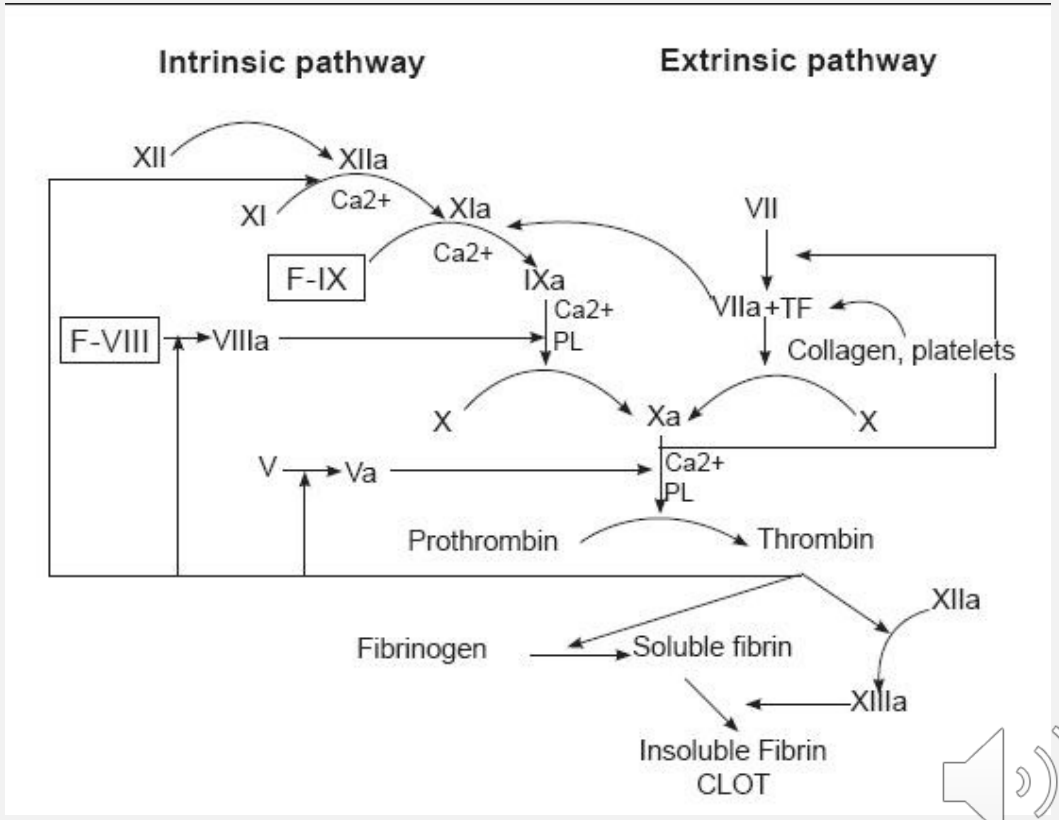
Effect of Regional Citrate Anticoagulation vs Systemic Heparin Anticoagulation During Continuous Kidney Replacement Therapy on Dialysis Filter Life Span and Mortality Among Critically Ill Patients With Acute Kidney Injury
A Randomized Clinical Trial

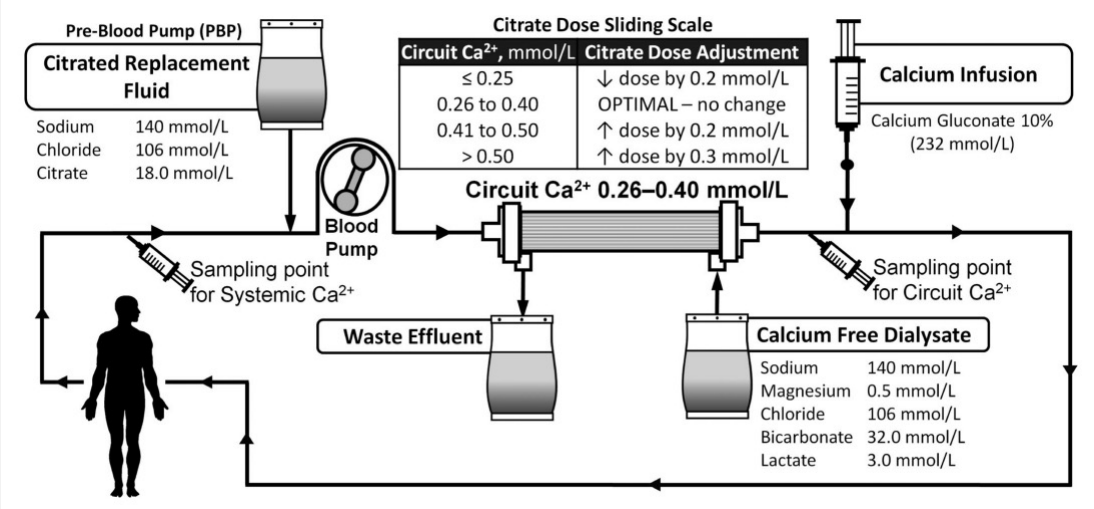
Zarbock A, Küllmar M, Kindgen-Milles D, et al. Effect of Regional Citrate Anticoagulation vs Systemic Heparin Anticoagulation During Continuous Kidney Replacement Therapy on Dialysis Filter Life Span and Mortality Among Critically Ill Patients With Acute Kidney Injury: A Randomized Clinical Trial. *JAMA.* 2020;324(16):1629–1639. doi:10.1001/jama.2020.18618

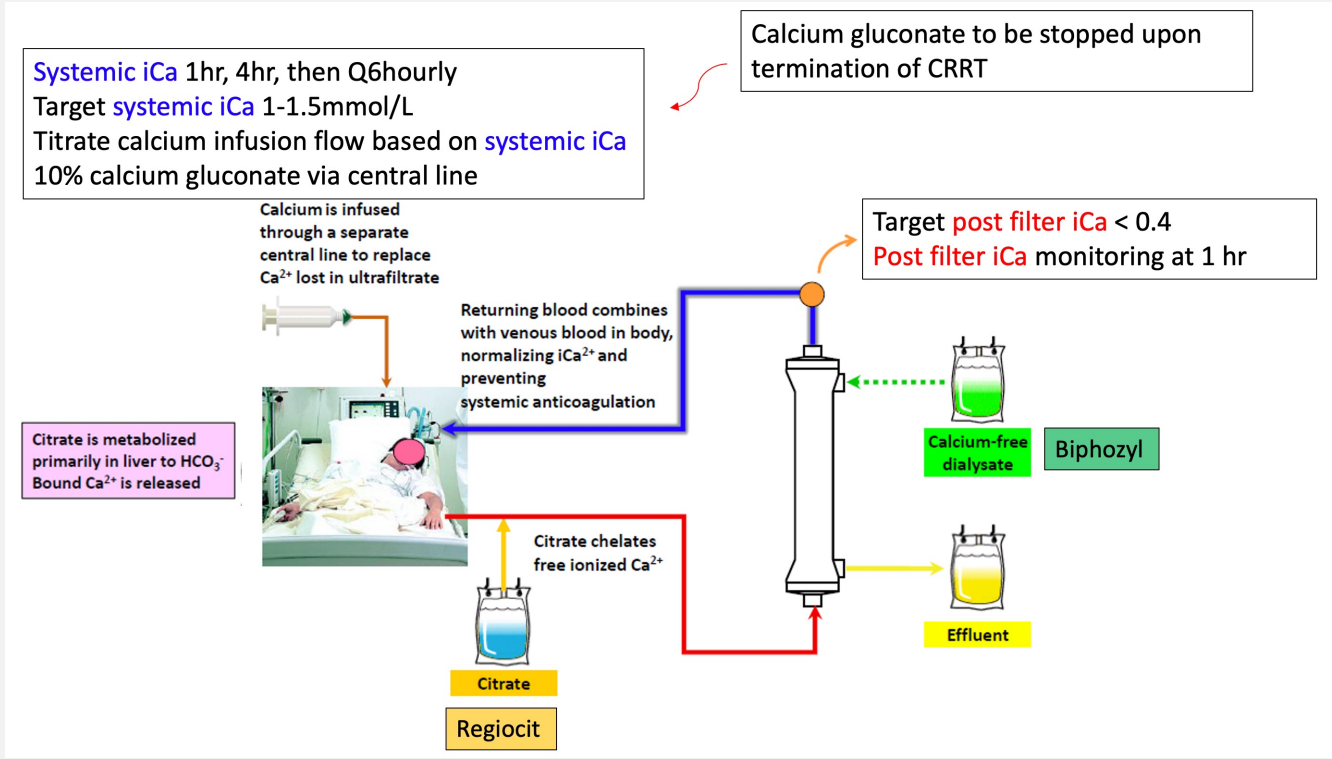
RICH Trial
Improved filter lifespan in RCA vs heparin anticoagulation; underpowered for mortality benefit

REGIONAL CITRATE ANTICOAGULATION

- Calcium required for generation of thrombin (activation of factors II, IX, X)
- Citrate infused before the filter
- Citrate binds to ionized calcium in the CRRT circuit, inactivating clotting pathway
- Calcium-citrate complexes removed by circuit (60%) and metabolism by liver and muscle
- Calcium infused systemically to maintain systemic calcium levels (as calcium is lost in effluent)
- Magnesium also chelated hence need to check levels and replace



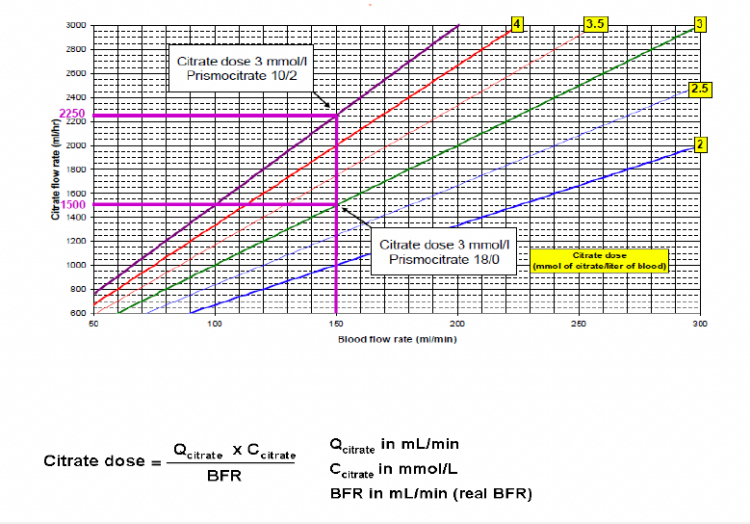




Poh CB, Tan PC, Kam JW, Siau C, Lim NL, Yeon W, Cui HH, Ding HT, Song XY, Yan P, Chea KL, Liu JS, Chionh CY. Regional Citrate Anticoagulation for Continuous Renal Replacement Therapy - A Safe and Effective Low-Dose Protocol. Nephrology (Carlton). 2020 Apr;25(4):305-313. doi: 10.1111/nep.13656. Epub 2019 Sep 16. PMID: 31469465.

REGIONAL CITRATE ANTICOAGULATION

- Usually start at 2.5-3.0 mmol/L citrate dose
- Target post filter iCa <0.4
- Target systemic iCa 1-1.2 mmol/L
- Citrate dosing (refer to chart)



$$\text{Citrate dose} = \frac{Q_{citrate} \times C_{citrate}}{BFR}$$

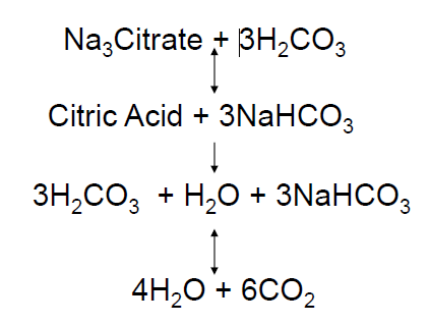
$Q_{citrate}$ in mL/min
$C_{citrate}$ in mmol/L
BFR in mL/min (real BFR)

Regiocit Flow Chart with Prismaflex

Regiocit 18/0	Citrate Dose (mmol/L of blood)				
Blood Flow Rate (ml/min)	**2.0**	**2.5**	**3.0**	**3.5**	**4.0**
100	670	840	1000	1170	1340
110	740	920	1100	1290	1470
120	800	1000	1200	1400	1600
130	890	1090	1300	1520	1740
140	940	1170	1400	1640	1870
150	1000	1250	1500	1750	2000
160	1070	1340	1600	1870	2140
170	1140	1420	1700	1990	2270
180	1200	1500	1800	2100	2400
190	1270	1590	1900	2220	2540
200	1340	1670	2000	2340	2670
210	1400	1750	2100	2450	2800
220	1470	1840	2200	2570	2940
230	1540	1920	2300	2690	3070
240	1600	2000	2400	2800	3200
250	1670	2090	2500	2920	3340

CITRATE ACCUMULATION

- Citrate accumulation vs overload
  - Accumulation (usually equated to toxicity): Citrate-calcium complexes not metabolized, resulting in metabolic acidosis and reduced ionized calcium systemically
  - Overload: Excess citrate administration (relative to buffer requirements) in context of intact metabolism, resulting in metabolic alkalosis (*due to concomitant net load of sodium ions leading to plasma alkalinization through an increased SID*)

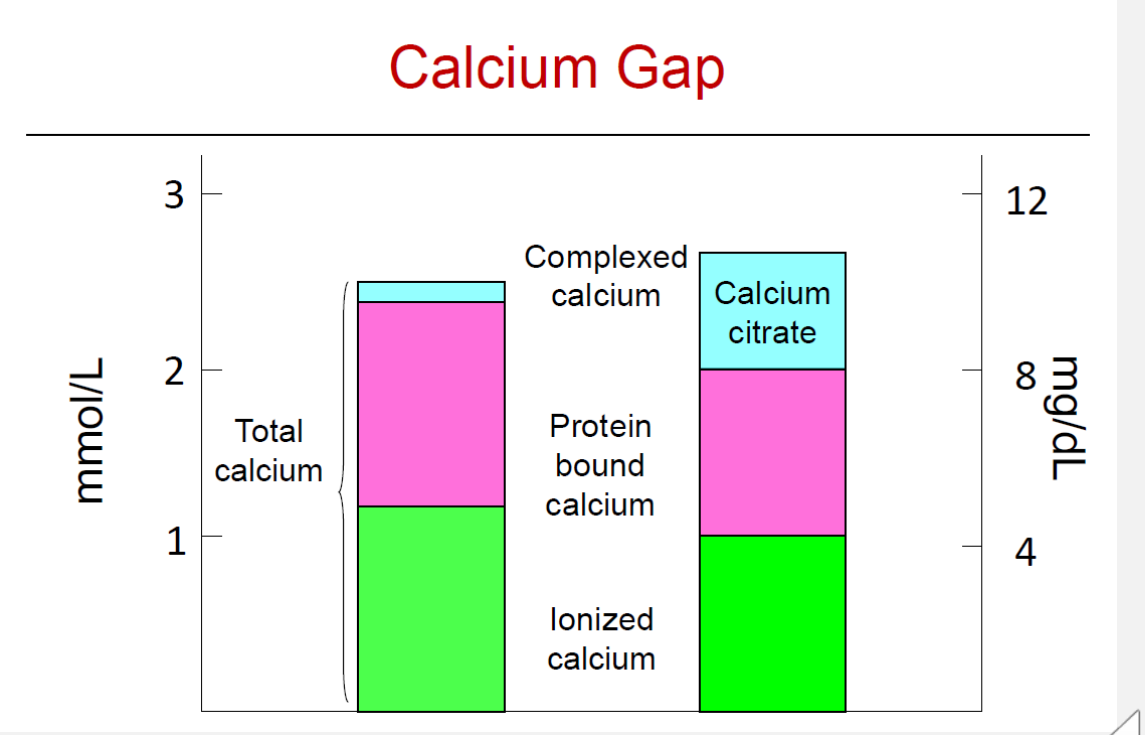


	Citrate accumulation	Citrate net overload
Mechanism	Incomplete citrate metabolism: persistence of circulating citrate–calcium complexes in the blood	Excess citrate administration relative to buffer requirements
Diagnosis		
Acid-base	Metabolic acidosis	Metabolic alkalosis
Ca_{tot}/Ca_i ratio	Increased (>2.5)	Normal (< 2.5)
Other	Increased need for calcium substitution Trend for a decreased ionized calcium level	None
Appreciation	Potentially lethal (via severe hypocalcemia)	Benign and easy to fix
Incidence	Rare	Common
Management	Decrease blood flow or increase dialysate flow rate (if mild) Consider alternative anticoagulation strategy	Decrease blood flow or increase dialysate flow rate

Schneider, A.G., Journois, D. & Rimmelé, T. Complications of regional citrate anticoagulation: accumulation or overload?. *Crit Care* **21**, 281 (2017). https://doi.org/10.1186/s13054-017-1880-1

CITRATE ACCUMULATION – DIAGNOSIS

- **Worsening HAGMA**
- **Total to ionized calcium ratio > 2.5 (high total calcium and low ionized calcium)**
- Low systemic iCa with increasing need to top up calcium replacement



CITRATE ACCUMULATION – RISK FACTORS

- Intact oxygen delivery and intact mitochondrial function of metabolic organs (liver, muscles) required to citrate metabolism
- Risk factors include
  - Hepatic dysfunction
  - Shock states
- Contraindications/Caution
  - Hypocalcemia – rhabdomyolysis, tumour lysis, secondary hyperparathyroidism
  - Liver failure
  - Significant lactic acidosis, severe shock states
  - Toxidromes impairing mitochondrial function
  - Coagulopathy

CITRATE ACCUMULATION – MANAGEMENT

- Reduce citrate dosing – But will have to weigh against suboptimal anticoagulation
- Reduce blood flow rate – Will require lower citrate flow rate to meet citrate dose; hence overall less citrate load
  - May have to switch to a predominant dialysis (if not filtration fraction will rise)
- Increase dialysis/filtration dose – Increase removal of calcium citrate complexes
- Consider no anticoagulation/alternative anticoagulation

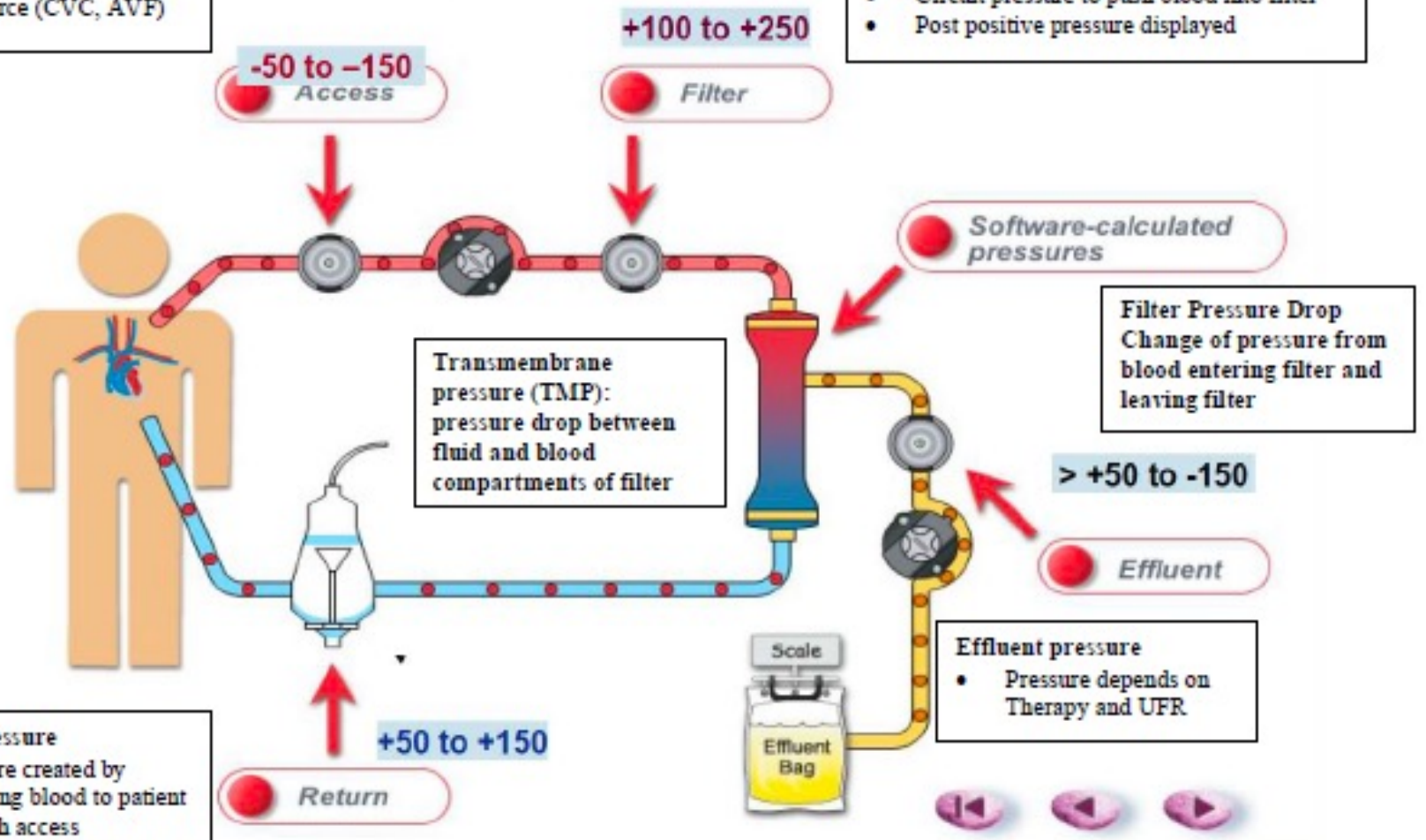
PRESSURE ALARMS

Pressure Monitoring

Access Pressure
- Pressure created by pulling blood through access
- Access pressure usually negative

Blood flow rate
Blood source (CVC, AVF)

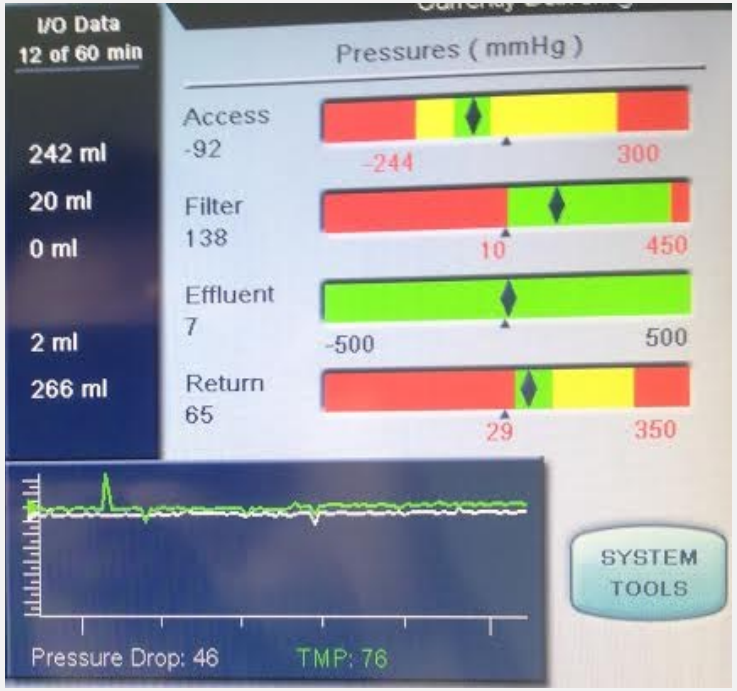
Filter Pressure
- Circuit pressure to push blood into filter
- Post positive pressure displayed



Return Pressure
- Pressure created by returning blood to patient through access
- pressure usually positive
- Uses internal pressure senor / deaeration chamber monitor line

NORMAL PRESSURES

- Access pressure: -50 to -150mmHg
- Filter pressure: 100 to 250mmHg
- Return pressure: 50 to 150mmHg
- Transmembrane pressure: maximum 450mmHg

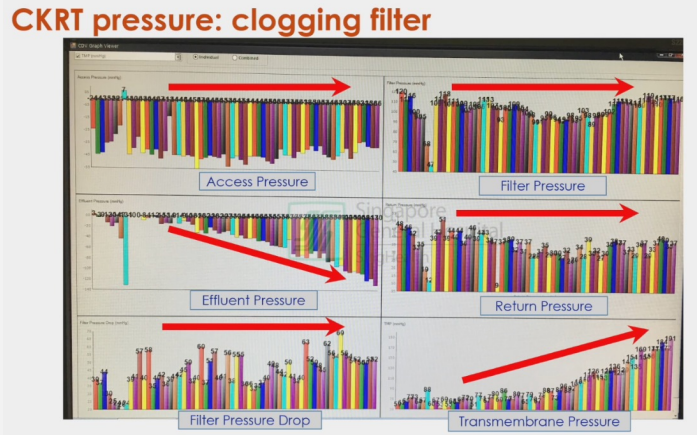


ABNORMAL PRESSURES

Access	Filter	Return
Extremely negative – poor blood flow to catheter -Sucking against vessel wall -Hypovolemia -Increased intraabominal or intrathoracic pressure impeding venous return -Deep breaths pulling blood in opp direction out of catheter -Catheter clotted/kinked/clamped -Positional	**Extremely positive** -Usually gradually rises as filter clogs (natural filter degradation) -Sudden rises – clot, line kinked/clamped, pre-dilution replacement flow rate too high Sometimes transmembrane pressure (TMP) is reported High TMP w normal return pressure suggests filter prob, high TMP with high return pressures suggest line and/or filter problem	**Extremely positive** -Line is kinked/dislodged -Line is trapped against vessel wall -Line is clotted -Line is inserted into artery
		Low return pressure (negative) -Low blood pump speed -Line disconnection -Pre-sensor, post-pump line is clamped

TRANSMEMBRANE PRESSURE AND PRESSURE FILTER DROP

- Transmembrane Pressure – High > 250mmHg
  - Difference in pressure between blood side of the membrane and dialysate/ultrafiltrate side of membrane
  - Represents what happens across the pores of the membrane - **clogging**
  - Management: Consider more diffusive (rather than convective approach)
- Pressure Filter Drop – High > 26mmHg
  - High levels suggest **clotting**
  - Management**:** Increase anticoagulation, assess access



DISCONTINUATION OF RENAL REPLACEMENT THERAPY

DISCONTINUATION OF RENAL REPLACEMENT THERAPY

- Limited clinical evidence to guide RRT discontinuations – mainly based on associative variables from retrospective studies
- Based on clinical discretion – Resolution of acute insult, urine output, urea/creatinine, solute stability, fluid balance, biomarkers (ongoing research)

Discontinuation of CRRT, as defined by the KDIGO AKI guideline, is "*when RRT is no longer required either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care*". These guidelines also state that "*using diuretics is not recommended to enhance kidney function recovery, or to reduce the duration or frequency of RRT*" [7]. Recent studies

Table 1. Some studies related to successful discontinuation of RRT in ICU

Study	Success	Modality	Time restart	Study type	Predictive variables
Wu et al. [9], 2008	Cessation of dialysis	IRRT: 51 (54.3%) CVVH: 43 (45.8%)	30 days	Retrospective multicenter observational	Urine output Dialysis duration SOFA Oliguria Age <65 years
Uchino et al. [10], 2009	Free from RRT	CRRT 100% CAVHD CVVH CVVHD CVVHDF	7 days	Prospective multicenter observational study	Urine output Serum creatinine
Katayama et al. [11], 2016,	Free from RRT	CRRT 100% CVVDH CVVH CVVHDF	7 days	Retrospective multicenter observational study	Urine output Serum creatinine CRRT duration
Fröhlich et al. [12], 2012	Free from RRT	CRRT 100% CVVH	7 days	Retrospective single-center observational study	Age Creatinine Urine output 2 h-CrCl

Romero-González G, Lorenzin A, Neri M, Ferrari F, Molano-Triviño A, Brendolan A, Ronco C. Discontinuation of Continuous Renal Replacement Therapy and Dialysis Dependence. Contrib Nephrol. 2018;194:118-125. doi: 10.1159/000485609. Epub 2018 Mar 29. PMID: 29597223.

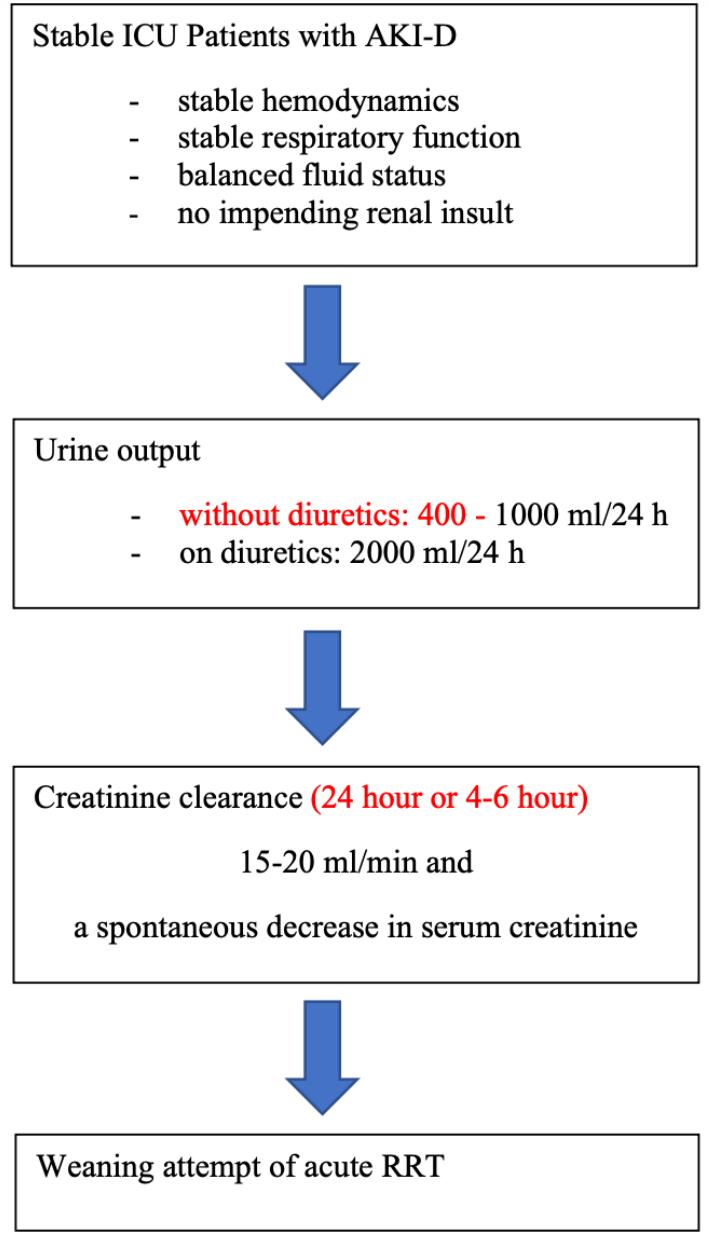


Fig. 1 Discontinuation of RRT in ICU patients wit[illegible]I-D: re[illegible]di-ness testing, predictors of renal recovery and weaning

Schiffl H. Discontinuation of renal replacement therapy in critically ill patients with severe acute kidney injury: predictive factors of renal function recovery. Int Urol Nephrol. 2018 Oct;50(10):1845-1851. doi: 10.1007/s11255-018-1947-1. Epub 2018 Aug 2. PMID: 30073616.

SPECIAL POPULATIONS

ACUTE BRAIN INJURY

- Considerations
  - Decrease in blood pressure may decrease cerebral blood flow
  - Dysequilibrium syndrome – Decrease in osmolality worsening cerebral edema
  - Bleeding risk in context of ICH
- Management
  - CRRT favoured over IHD in critically ill patients, if IHD used, slow blood/dialysate flows, shortened session times, use small surface dialysers, reduce temperature
  - Caution with excessive fluid and osmotic shifts
  - Caution with anticoagulation (esp systemic)

Davenport A. Practical guidance for dialyzing a hemodialysis patient following acute brain injury. Hemodial Int. 2008 Jul;12(3):307-12. doi: 10.1111/j.1542-4758.2008.00271.x. PMID: 18638083.

HYPONATREMIA

- In chronic hyponatremia, usually target 6-8mmol rise in sodium over 24 hours
- In principle, this can be achieved with CRRT by:
  - Either adjusting sodium concentration of replacement/dialysate fluid bags with D5 injections
  - Or administering a separate D5 infusion

LIVER FAILURE

- Considerations
  - Encephalopathy and cerebral edema
  - Hyponatremia
  - Coagulopathy
- Management
  - Cerebro-protective precautions
  - Citrate anticoagulation can still be considered with caution

Safety and efficacy of regional citrate anticoagulation for continuous renal replacement therapy in liver failure patients: a systematic review and meta-analysis

Wei Zhang[1,2†], Ming Bai[1*†], Yan Yu[1†], Lu Li[1], Lijuan Zhao[1], Shiren Sun[1*] and Xiangmei Chen[1,2*]

2019 Publication in Critical Care
-Systematic review and meta-analysis of observational studies
-Pooled citrate accumulation rate 12% and bleeding rate 5%
-No significant diff compared to non-liver patients in pH, lactate levels, totCa/ionCa ratio

SUMMARY

When to initiate RRT?	Solute or fluid imbalances. In severe AKI, consider initiation within 72 hours. Consider trajectory.
Intermittent vs Continuous?	Consider continuous if haemodynamically unstable or have significant acute brain injury. Otherwise generally both are acceptable options with pros and cons.
Dosing of CRRT?	Generally, 20-25ml/kg/hr, but prescribe slightly higher at 25-30ml/kg/hr because of inefficiencies. Higher dosing may be considered in severe solute derangements, toxins.
Pre vs post filter fluid replacement?	Pre-filter is beneficial for filter preservation but compromises solute clearance and vice-versa. Practically speaking, pre-filter fluid is used for citrate anticoagulation.
Vascular access?	Good vascular access is key. R IJ > Femoral > L IJ
RCA vs Heparin?	RCA has superior filter life preservation, possibly less bleeding
Citrate Toxicity?	Differentiate citrate accumulation from citrate overload. Diagnosis of accumulation based on HAGMA, total to ionized Ca ratio >2.5 Management: Reduce blood flow, increase dialysis dose, reduce citrate dose, alternative/withhold anticoagulation
Discontinuation of RRT?	Clinically guided – Based on resolution of indication, improvement in urine output, solute and volume stability