



Renal replacement therapy: a practical update

Traitement substitutif de l'insuffisance rénale : une mise à jour pratique

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Abstract *Acute kidney injury (AKI) is defined as an abrupt decrease in kidney function, with the most severe form requiring some method of renal replacement therapy (RRT). The use of RRT is required in 5-10% of critically ill patients who develop severe AKI. Renal replacement therapy can be provided as either intermittent hemodialysis or one of the various modes of continuous renal replacement therapy (CRRT), with CRRT potentially conferring an advantage with respect to renal recovery and dialysis independence. There is no difference in mortality when comparing low ($< 25 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$) vs high ($> 40 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$) RRT dosing. Continuous renal replacement therapy may be run in different modes of increasing complexity depending on a given patient's clinical needs. Regional citrate anticoagulation is recommended as the therapy of choice for the majority of critically ill patients requiring CRRT.*

Résumé *L'insuffisance rénale aiguë (IRA) se définit par une réduction subite de la fonction rénale, et sa forme la plus grave nécessite un type de traitement substitutif. Le recours à un traitement substitutif de l'insuffisance rénale est nécessaire chez 5-10 % des patients critiques qui souffrent d'une IRA grave. Le traitement substitutif de l'insuffisance rénale peut prendre la forme d'une hémodialyse intermittente ou de l'un des divers modes de traitement substitutif de l'insuffisance rénale en continu, ce second type de traitement conférant potentiellement un avantage en matière de récupération de la fonction rénale*

et d'indépendance de la dialyse. Aucune différence de mortalité n'a été observée en comparant un traitement substitutif de l'insuffisance rénale à faible dose d'ultrafiltration ($< 25 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) vs à dose élevée ($> 40 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$). Le traitement substitutif de l'insuffisance rénale en continu peut être réalisé selon différents modes de complexité croissante en fonction des besoins cliniques d'un patient donné. Une anticoagulation régionale au citrate est recommandée comme traitement de choix pour la majorité des patients critiques nécessitant un traitement substitutif de l'insuffisance rénale en continu.

This narrative review is intended for physicians involved in the care of critically ill patients who may require renal replacement therapy (RRT). It is intended for the clinician who may not have formal training in critical care or nephrology, nor advanced knowledge of modes of dialysis. Although the use of intermittent hemodialysis (IHD) is important for scenarios such as severe hyperkalemia and certain toxidromes (e.g., acetylsalicylic acid and lithium overdose), this paper will limit its discussion to continuous RRT (CRRT) modes. The main areas of focus will be: i) an epidemiologic review of acute kidney injury (AKI), ii) timing of RRT, iii) understanding the physical dialysis circuit, iv) modes of dialysis, v) effluent dosing, and vi) anticoagulation (and its complications).

Epidemiology

The treatment of critically ill patients is increasingly complex, particularly as the population ages and age-related co-morbidities become superimposed on critical illness. Furthermore, technologic and other pharmacologic

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advances have allowed these complex patients to be rescued. Indeed, advanced modes of life-support technology have enabled critical care physicians to manage diseases in ways unimaginable a generation ago.¹⁻³ One such mode, RRT, has gained wide acceptance in supporting patients with isolated AKI, or as part of multi-organ system failure. Importantly, AKI is not a disease *per se* but rather a heterogeneous syndrome with numerous, often overlapping etiologies. Depending on the definition used, AKI affects up to 25% of intensive care unit (ICU) patients and has an associated mortality ranging between 15% and 60%.⁴⁻⁹

The International Acute Dialysis Quality Initiative (ADQI) group¹⁰ defined AKI as an abrupt decrease in kidney function, but is not limited to oliguria nor anuria. The ADQI group emphasizes that AKI is best viewed as a continuum of renal injury, the most severe of which requires some form of RRT. Indeed, as a syndrome, it may include patients with traditionally “normal” renal indices but functional impairment relative to physiologic demand.¹¹ While there is broad consensus that more sensitive and specific biomarkers to diagnose AKI are needed, changes in serum creatinine and urine output still form the basis of all diagnostic criteria for AKI.^{9,10,12,13} The ADQI consensus document on AKI has been updated,¹⁴ and many large international series have provided a consistent picture—i.e., AKI is associated with decreased overall survival, and increasing severity of AKI leads to increased chances of death.¹⁵⁻²⁵ Even mild, reversible AKI can increase mortality and the need for long-term dialysis.^{18,21,23,26-28} Furthermore, AKI increases the long-term risk of cardiovascular disease and chronic kidney disease.²⁹⁻³⁴ Based on these facts, the interest in identifying and preventing AKI is understandable.³⁵⁻³⁹

Sepsis-associated AKI deserves special mention since sepsis is the most important risk factor in determining the need for RRT.⁴⁰ Bagshaw *et al.* reported an AKI incidence of 42% in their Australian cohort of septic patients.⁴¹ A ten-year retrospective study of AKI in septic patients found that the use of RRT was steadily increasing in all cohorts, but mortality was declining.⁴² Although outpatient dialysis is traditionally intermittent, ICU studies show that intermittent and continuous modes can be used effectively in the ICU population.^{43,44} Nevertheless, in North America, Europe, and Australia, continuous modes predominate.⁴⁵⁻⁴⁷ Despite there being no proven survival advantage when intermittent hemodialysis is compared with CRRT in critically ill patients, CRRT appears to confer an advantage with respect to hemodynamic stability and better control of fluid balance, renal recovery, and dialysis independence.^{43,44,48} A recent meta-analysis showed that among 26 identified studies,⁴⁹ CRRT was associated with higher rates of renal recovery compared

with IHD. Disadvantages of CRRT are limited mobility, the need for continuous anticoagulation, and significantly higher costs relative to IHD.⁵⁰

Timing of RRT

Although AKI is common in critically ill patients, only 5–10% of patients go on to require some form of RRT.^{46,51} That said, the use of RRT is rapidly increasing,^{33,52,53} likely because of the aging population and growing complexity of patients admitted to the ICU. Sparse evidence exists to direct the clinician as to when to initiate RRT.⁵⁴ Two recent trials have specifically tried to address the initiation time of RRT in critically ill patients: the ELAIN (Effect of early vs delayed initiation of renal replacement therapy) trial⁵⁵ and the AKIKI (Initiation strategies for renal replacement therapy in the intensive care unit) trial.⁵⁶ The ELAIN study was a single-centre randomized trial of 231 predominately post-surgical patients. Early RRT was defined as initialization within eight hours of diagnosis of KIDGO (Kidney disease: Improving Global Outcomes) stage 2; delayed RRT was defined as initiation of RRT within 12 hr of stage 3 AKI; the median difference in actual time was 21 hr. Early RRT resulted in an impressive decrease in mortality compared with delayed RRT (39.3% vs 53.6%, respectively; $P = 0.03$) and greater renal recovery (53.6% vs 38.7%, respectively; $P = 0.02$).

The AKIKI study was a multicentre trial with 620 mixed medical/surgical patients with a different definition of early (less than six hours of KDIGO [Kidney Disease: Improving Global Outcomes] stage 3) vs late AKI (traditional criteria to worsening AKI or complications). The median difference to RRT initiation was 57 hr. There was no difference in 60-day mortality in the early compared with late groups (48.5% vs 49.7%, respectively; $P = 0.79$). Perhaps more interesting is the actual RRT utilization, which was 98% for early RRT compared with 51% for delayed RRT. In other words, the delayed arm avoided unnecessary RRT. The resulting inference for a clinician is intriguing but speculative—i.e., were there many patients in the early cohort that could have also avoided RRT? Some authors^{57,58} have cautioned readers on the conclusions of these studies. Both studies had limitations that reduced the confidence in their conclusions, including implausible treatment effect (both trials were powered assuming a > 15% mortality reduction), low fragility index (small number of patients required to convert a trial from being statistically significant to not significant),⁵⁹ and ELAIN being a single-centre study. A recent study, with none of these short-comings, showed no difference in

mortality when comparing early initiation with delayed initiation of RRT in septic patients.⁶⁰

With these results, it is still difficult to provide a recommendation on when to initiate RRT. Nevertheless, the clinician can be reassured that starting RRT earlier does not increase mortality, but at the cost of an increased number of unnecessary treatments. The ongoing STAART-AKI (ClinicalTrials.gov identifier: NCT02568722) trial should help inform physicians when to initiate renal replacement therapy

The physical aspects of RRT

Dedicated vascular access is needed for RRT and can be obtained with a purpose-designed dual lumen catheter placed in a central vein using the Seldinger technique. The veins used in order of preference, as per KDIGO guidelines, are the internal jugular, femoral, or subclavian.⁹ The subclavian vein is the third choice due to a higher risk of thrombosis and stenosis.⁶¹ A non-tunneled catheter with its tip placed in the superior vena cava is favoured for immediate, short-term use. Chronic use favours tunneled catheters to decrease the risk of infection; the distal tip is usually placed in the right atrium. The catheter lumens are labelled and colour coded as the “arterial” (red) blood in-flow line, which is the proximal/intake port, and the “venous” (blue) blood out-flow line for the distal/discharge port.⁶²

Interdialytic lock solution is used to decrease the risk of catheter thrombosis and the risk of infection. Heparin ($1,000 \text{ U}\cdot\text{mL}^{-1}$ to $10,000 \text{ U}\cdot\text{mL}^{-1}$), citrate (4–47%), and tissue plasminogen activator have all been used. Heparin and citrate are equivalent in maintaining patency.⁶³ The effectiveness of citrate and antimicrobial lock solutions in decreasing the rate of catheter-related infections remains unclear and is the subject of ongoing investigation.⁶⁴ In addition to the risk of bleeding from an inadvertent bolus of the locking solution with catheter access, all catheters will leak locking solution for the first 30 min with some systemic effects occurring for up to four hours. Heparin carries a further risk of heparin-induced thrombocytopenia, and citrate risks a metallic taste and perioral and/or digital paresthesia.⁶⁵

Standard CRRT mechanical units have an extracorporeal circuit with a warmer hemofilter and dedicated pump for blood. They may also have additional pumps that are used for other fluids that vary depending on the therapy mode, such as pumps for replacement fluid and dialysate. Incorporated scales are used for gravimetric fluid balancing.⁶⁶

Filters are composed of approximately 10,000 hollow fibres with diameters of approximately 200 µm and a

membrane thickness of 20–50 µm.⁶⁷ The membrane material can be made from either cellulose-derived or synthetic polymers. Optimal biocompatibility is important so as to prevent damage to red blood cells and contact activation of neutrophils and platelets, either directly or through the activation of the coagulation cascade and the complement system.⁶⁸ For example, the AN-69 synthetic polyacrolonitrile membrane can cause an anaphylactoid reaction due to bradykinin accumulation in patients receiving angiotensin converting enzyme inhibitors.⁶⁹

Membranes vary by the number and size of pores, which influences permeability and the movement of water for a given transmembrane pressure, referred to as flux. They also vary in the degree to which larger solutes, such as inflammatory mediators, are adsorbed. Filters are available with different surface areas and volumes. A filter with an extracorporeal volume of > 200 mL becomes important in instances where the filter clots before the blood can be returned to the patient.

Renal replacement modalities

Water and solutes pass from the blood through the semipermeable membrane during dialysis mainly by ultrafiltration, convection, and diffusion.

Ultrafiltration and convection involve movement of water across the membrane due to a pressure gradient. Ultrafiltration refers to the movement of plasma water while convection is the movement of solutes within the plasma water. Convection is sometimes called “solvent drag” (Fig. 1). Diffusion is the movement of solute driven by the concentration gradient across a semipermeable membrane. In dialysis, it is the gradient between the patient’s blood on one side of the filter and the dialysate on the other.

Running the dialysate counter-current to the blood increases the removal of small solutes such as urea and creatinine.⁷⁰

Continuous RRT may be run in different modes of increasing complexity depending on a given patient’s clinical needs.⁶⁶ A schematic of the different modalities is shown in Figs 2, 3, 4, 5 and Table 1. The modes differ in whether the primary driver of solute removal is convection, diffusion, or both.

Slow continuous ultrafiltration

Slow continuous ultrafiltration (SCUF) is used to remove plasma water in patients without significant electrolyte or other acid-base abnormalities. Blood is pumped through the fibres of the dialysis filter at a pressure higher than that surrounding the fibres. The hydrostatic pressure gradient

between the blood compartment of the filter and the filtrate compartment is the **transmembrane pressure**, which determines the **rate of fluid removal**. Using **higher flux membranes** allows for **more fluid removal** at the **same transmembrane pressure**. While SCUF has the advantage of **decreased complexity** and nursing **workload** compared with other modes, it **cannot correct electrolyte** or acid-base abnormalities. While the major effect of SCUF is fluid removal, **some solute clearance** occurs because of **convection**, but at a much **lower efficiency** than other continuous modes described below.

Continuous veno-venous hemofiltration

Continuous veno-venous hemofiltration (CVVH) uses **convection** to remove **solutes** through **large volume fluid ultrafiltration**. Convection **sweeps solutes** along with the fluid **independent** of their **concentration gradient**. The **porosity** of the **membrane** determines **which solutes** are removed. **Small solute** molecules, such as **urea**, and **middle-sized** molecules, such as inflammatory **cytokines**, are **cleared**. With the **large volume** of fluid removed, intravascular **volume** must be **maintained** using a **replacement fluid**. The **prescription** is **based** on the patient's serum **potassium** and **acid-base** balance. For example, **bicarbonate** containing fluids are used in the setting of a **metabolic acidosis** or normal **saline** when significant metabolic **alkalosis** develops. The **replacement fluid** can be infused **either before** the hemofilter (**pre-dilution**) or **after** the hemofilter (**post-dilution**). **Post-dilution** results in **more concentrated blood** in the **filter** and **higher solute clearance**. Nevertheless, **more concentrated blood** can lead to a **shorter filter lifespan**. While **pre-dilution** means **lower solute** concentrations and **clearance**, this is offset by a **higher ultrafiltration rate** and **longer filter life**. **Pre-dilution** does require a **larger volume** of **replacement fluid** than **post-dilution**.

Hemofiltration allows for **volume** removal as well as correction of **electrolyte** and **acid-based** abnormalities **based** on the selection of **replacement fluid**.

Continuous veno-venous hemodialysis

Continuous veno-venous hemodialysis (CVVHD) uses **counter-current dialysate** flow to remove **small solutes** by **diffusion** according to their concentration gradients. Solute **clearance** can be **increased** with **higher dialysate** or **blood flow** rates.

Dialysates contain **physiologic concentrations** of sodium, chloride, magnesium, and **glucose**. Serum **potassium** can **vary** significantly in critical illness depending on factors such as **pH**, **insulin** and **sympathomimetic** drugs, **gastrointestinal losses**, residual

or recovering renal function, and **high hemofiltration** rates. The **potassium** concentration of the dialysate is **prescribed separately** usually ranging from **0 to 5 mmol·L⁻¹**. It is not unusual for the **potassium prescription** to **change frequently**. **Dialysate** is **buffered** with either **bicarbonate** or a bicarbonate precursor such as **lactate**, **citrate**, or **acetate**. The use of **bicarbonate precursors** requires the patient to be able to **metabolize** them, which can be impaired in **liver** failure or **shock** states. Importantly, in **CVVHD**, there is **minimal ultrafiltration** and therefore **no significant fluid removal**.

Continuous veno-venous hemodiafiltration

Continuous veno-venous hemodiafiltration **combines** hemodialysis (**diffusive dialysis**) and hemofiltration (**convective dialysis**). The **ultrafiltrate** can be **replaced** by either **replacement fluid** as in hemofiltration and the counter-current/co-current dialysate flow.

The choice of **CRRT mode** is **determined** by the patient's **volume** status, serum **urea**, and **potassium**, as well as **acid-base** balance. **Slow continuous ultrafiltration** could be considered in conditions with isolated **volume overload**, such as **heart** or **liver failure**, malnutrition, capillary leak syndromes, or in patients who have become **resistant to diuretics**. Isolated **electrolyte** abnormalities can be managed with **hemodialysis (CVVHD)**. Nevertheless, **most critically ill** patients receive large amounts of intravenous **fluids** as part of their resuscitation and ongoing prescriptions and nutrition. This means that those with kidney injuries usually require ongoing management with fluids and electrolytes. This can be accomplished using either **hemofiltration (CVVH)** using **appropriate replacement fluid** or with **hemodiafiltration (CVVHDF)** depending on the medical centre's preference.

Effluent dosing

Similar to any drug, a physician **prescribes** the RRT "**dose**" based on a wide variety of pharmacokinetic and pharmacodynamic principles. Among many things, the clinician must take into account factors such as age, body weight, mode of elimination, and co-administered drugs. **Dosing** of RRT is traditionally defined as the **effluent flow** in **mL·kg⁻¹·hr⁻¹**. In particular, the dose intensity has been of great interest and studies have compared low (**< 25 mL·kg⁻¹·hr⁻¹**) vs high (**> 40 mL·kg⁻¹·hr⁻¹**)^{71,72} effluent rates. The **RENAL** (Intensity of continuous renal replacement therapy in critically ill patients) **study** provided the best evidence that there are **no differences** in patients treated with these two strategies.⁷³ In that study, at 90 days after randomization, death occurred in 44.7% of

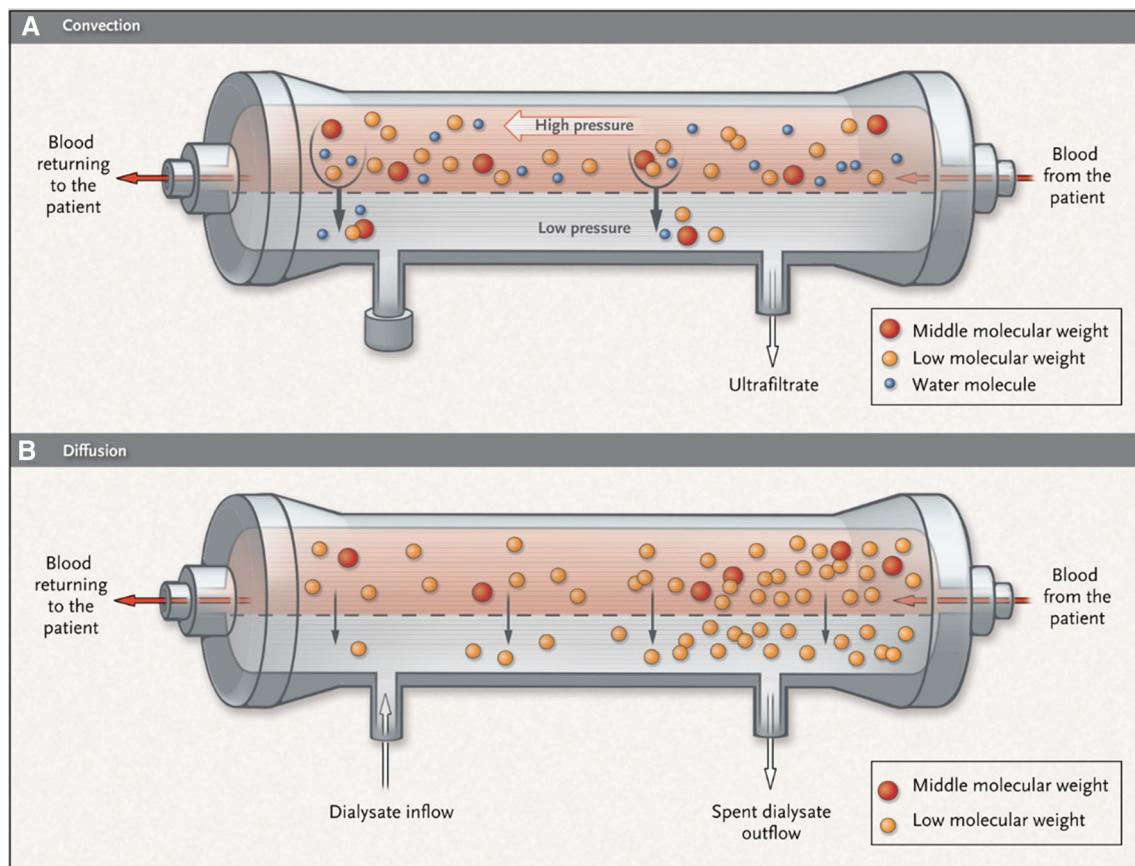
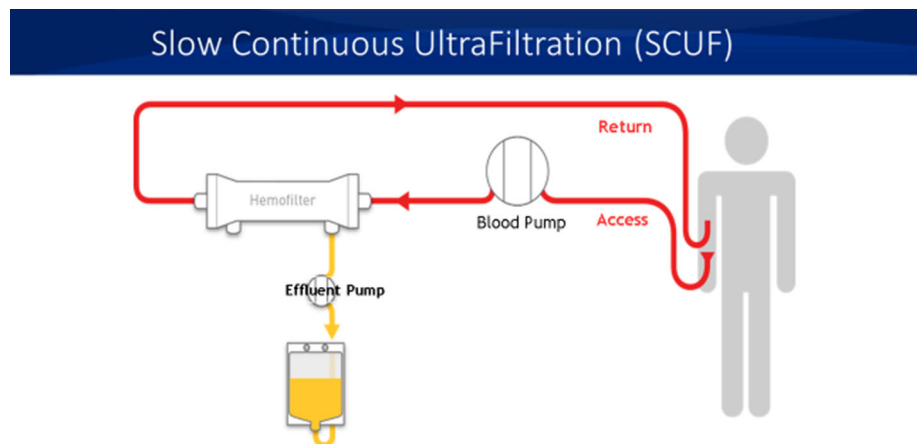


Fig. 1 A) Convection; B) Diffusion. Reproduced with permission from: Tolwani A. Continuous renal replacement therapy for acute kidney injury. *N Engl J Med* 2012; 367: 2505-14

Fig. 2 Slow continuous ultrafiltration



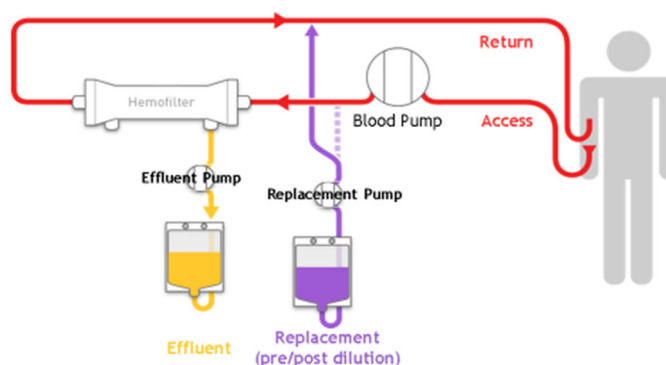
patients for both higher and lower intensity groups (odds ratio, 1.00; 95% confidence interval, 0.81 to 1.23; $P = 0.99$). Furthermore, there were no significant differences between the groups in any of the secondary or tertiary outcomes. Fig. 1 outlines the expert consensus opinion to guide the clinician for best practice when dosing RRT.⁷⁴ To ensure outcomes similar to those seen in the ATN and

RENAL trials, this figure shows the recommendation that the clinician provide an average daily effluent dosing between 20 and 25 mL·kg⁻¹·hr⁻¹. No evidence to date suggests incremental benefit to higher effluent dosing.

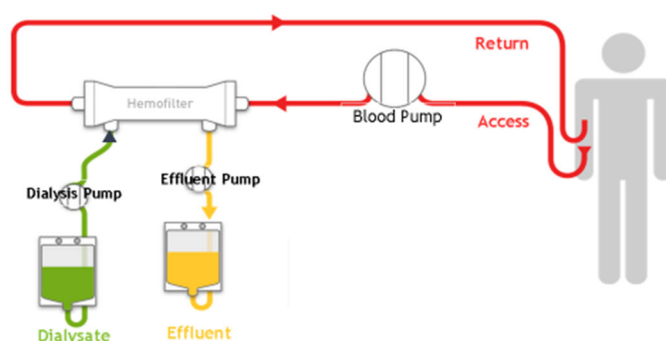
A common problem in dosing studies is that the actual intended delivery dose often falls short of the prescribed dose.^{73,75} Claude-Del Granado *et al.* addressed this problem

Fig. 3 Continuous veno-venous hemofiltration

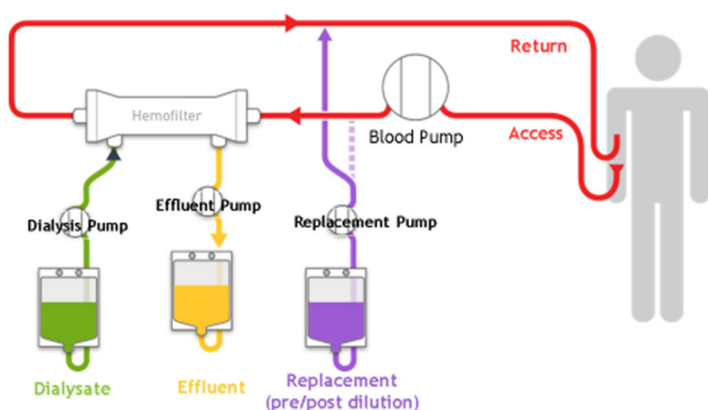
Continuous Venovenous Hemofiltration (CVVH)

**Fig. 4** Continuous veno-venous hemodialysis

Continuous VenoVenous HemoDialysis (CVVHD)

**Fig. 5** Continuous veno-venous hemodiafiltration

Continuous VenoVenous HemoDiaFiltration (CVVHDF)



by physically measuring the urea clearance adjusting for machine down-time and pre-dilution.⁷⁶ As mentioned earlier, pre-dilution is when the replacement fluid is mixed with the blood (thus lowering hematocrit) prior to the blood entering the filter. Although this increases filter

life, less efficient clearance occurs vs post-filter replacement. These authors observed that the actual dose significantly underestimated the prescribed dose by nearly 25%. Interestingly, the authors observed that the major factors affecting the treatment time had little to do with

Table 1 Summary comparison of modalities

	SCUF	CVVH	CVVHD	CVVHDF
Primary mechanism	Ultrafiltration	Convection	Diffusion	Diffusion and convection
Treatment time	Continuous	Continuous	Continuous	Continuous
Blood flow rate	100 mL·min ⁻²	50-300 mL·min ⁻¹	50-300 mL·min ⁻¹	50-300 mL·min ⁻¹
Dialysate	No	No	500-4000 mL·hr ⁻¹	500-4000 mL·hr ⁻¹
Replacement fluid	No	500-4000 mL·hr ⁻¹	No	500-4000 mL·hr ⁻¹
Anticoagulation	Heparin, citrate, none	Heparin, citrate, none	Heparin, citrate, none	Heparin, citrate, none

CVVH = continuous veno-venous hemofiltration; CVVHD = continuous veno-venous hemodialysis; CVVHDF = continuous veno-venous hemodiafiltration; SCUF = slow continuous ultrafiltration

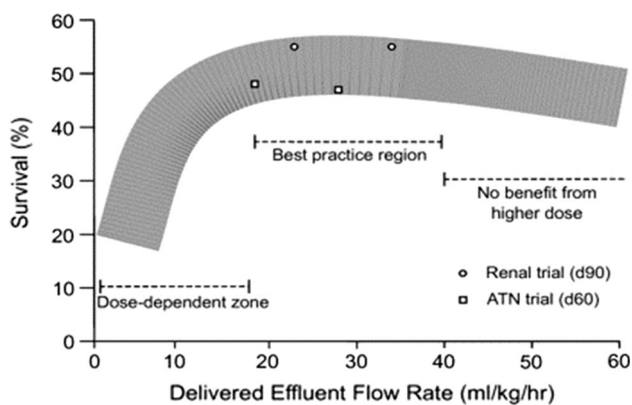


Fig. 6 Possible relationship between delivered dose of continuous renal replacement therapy and survival, with results from the ATN and RENAL trials illustrated

filter clotting, as one might predict with an extracorporeal circuit that requires anticoagulation. Common interruptions to delivering RRT were surgical procedures, the decision when to transition to IHD, and line or machine malfunction. The authors concluded that to achieve a prescribed dialysis dose, effluent based dosing should be increased by 20-25% to account for decreases in treatment time and reduced filter efficacy during CRRT. The KDIGO guidelines endorse the recommendation to increase effluent dosing by 25% to achieve best practice as shown in Fig. 6.⁹

Anticoagulation

Extracorporeal membrane clotting is a major concern during RRT. Clot-related membrane dysfunction is associated with decreased solute clearance, particularly for middle molecular weight molecules (500 D to 60 kD) such as B2-microglobulin and light chain proteins.^{69,75,77,78} Therefore, effective anticoagulation is paramount to prevent clotting of the circuit and to optimize filter efficiency. There are two major anticoagulation strategies: systemic and regional (Table 2).

Systemic anticoagulation

Systemic anticoagulation with unfractionated heparin (UFH) is low cost, the activated partial thromboplastin time is easy to monitor, and uses protamine as a reversal agent; therefore, it is the most widely method used worldwide.⁷⁸

The UFH is usually delivered to the patient by a separate intravenous line. Nevertheless, UFH use is associated with increased risk of bleeding (particularly in critically ill patients),⁷⁹ heparin-induced thrombocytopenia (HIT),⁸⁰ and potentially deleterious pro-inflammatory effects because it binds to the lysyl-residue of antithrombin and accelerates the interaction between thrombin and antithrombin, thereby inhibiting the anti-inflammatory action of antithrombin,⁸¹ and triggering the release of inflammatory mediators from endothelial cells.⁸²

Direct thrombin inhibitors such as argatroban are commonly used as alternative anticoagulants for patients with HIT. Its use is associated with shorter filter patency time but fewer bleeding complications.⁸³ Of note, regional RRT anticoagulation does not provide sufficient anticoagulation in the presence of HIT, and a combination of regional and systemic anticoagulation with a direct thrombin inhibitor is recommended.¹⁴

Finally, low molecular weight heparins act by binding predominantly to factor Xa; this effect is associated with fewer adverse events than UFH.⁸⁴ Low molecular weight heparins are eliminated through the kidneys, which limits their use in patients requiring RRT. Furthermore, monitoring the anticoagulant effect requires a close range of anti-Xa activity. This is an expensive test that is not widely available and may take up to 24 hr to give results,⁸⁵ which negatively impacts therapeutic decision making. There is insufficient evidence to support the use of low molecular weight heparins during CRRT and as such, it is not a recommended anticoagulation strategy.⁹

Table 2 Modes of anticoagulation during renal replacement therapy

Mode	Characteristics
No anticoagulation	No bleeding risk, but increased risk of circuit clotting
UFH	Widely available, easy to use, but increased risk of bleeding
LMWH	Limited use in patients with acute kidney injury
Thrombin antagonist	Indicated for patients with HIT
RCA	Highest filter patency rates, lower risk of bleeding, but requires rigorous protocols and is associated with potential citrate toxicity

HIT = heparin-induced thrombocytopenia; LMWH = low molecular weight heparin; RCA = regional extracorporeal citrate anticoagulation; UFH = unfractionated heparin

Regional anticoagulation

A practical alternative to systemic anticoagulation is regional extracorporeal citrate anticoagulation (RCA). Sodium citrate is infused into the proximal limb of the CRRT circuit where it chelates ionized calcium. The resulting complex is partially filtered across the CRRT membrane, which prevents clotting in the CRRT circuit. Hypocalcemia is prevented through an infusion of calcium with the blood returning to the patient.⁸⁶

Demonstrable advantages of RCA include citrate's short half-life, longer CRRT filter life spans, and a reduced occurrence of bleeding.^{80,87-89} Disadvantages of RCA are the patient's inability to metabolize citrate (e.g., liver failure) within the systemic circulation, the complexity of citrate protocols, and citrate toxicity.^{9,90} Relative contraindications include patients with acute liver dysfunction or severe cirrhosis.^{90,91} When administered through the pre-filter line, citrate chelates calcium ions producing a soluble complex that is unavailable for calcium-dependent reactions in the intrinsic and extrinsic coagulation pathways.⁹² The target post-filter ionized calcium (iCa^{2+}) concentration is between 0.26 and 0.35 mmol·L⁻¹.⁹³ It is preferable to use calcium-free dialysate or replacement fluids to minimize citrate requirements.⁹⁴ The citrate infusion rate required depends on the concentration of the citrate solution and the blood flow in the circuit. Citrate that is not removed by the CRRT circuit enters the patient's circulation and is normally metabolized in the liver, kidney, or skeletal muscle with no anticoagulant effect on the patient.

Several studies have reported the safety and efficacy of RCA compared with systemic anticoagulation during the different modalities of RRT.^{80,95-97} It is clear that RCA is associated with longer circuit survival time and reduced risk of bleeding.^{98,99} RCA can be recommended as the therapy of choice for the majority of critically ill patients requiring CRRT.⁹

Given that citrate is predominantly metabolized by the liver, there is a reduced mitochondrial citrate metabolism in patients with liver failure that results in citrate accumulation and consequently, secondary hypocalcemia and metabolic alkalosis.

Measurement of blood or plasma citrate is not readily available or timely.^{97,100,101} Thus, the total to ionized calcium ratio is a practical and specific marker of citrate accumulation (goal ratio < 2.3) and should be calculated at least every 12 hr.^{102,103} Clinical signs of citrate toxicity relative to ionized hypocalcemia include coagulopathy and cardiac toxicity such as prolonged QTc interval, decreased contractility, hypotension and cardiac arrest.¹⁰⁰ Additionally, secondary to its nature as an ion and acting as a weak acid in solutions, citrate accumulation may produce a degree of anion gap metabolic acidosis; nevertheless, after citrate is metabolized by the liver, an excess of cations ensues and the result is metabolic alkalosis. Citrate anticoagulation has metabolic abnormalities unrelated to its impaired metabolism.^{87,91,100} The citrate chelates magnesium and crosses the CRRT filter, leading to hypomagnesemia. Tri-sodium citrate solutions are hypertonic due to their high sodium content. Low sodium replacement and dialysate solutions are used to prevent a patient developing hyponatremia.

There are several strategies to avoid citrate accumulation. These include ensuring that no added citrate is being used (e.g., with blood products administration). In addition, the citrate infusion rate can be decreased by 75% of the dose being used to that point. This is accompanied by an increase in the blood flow rate and replacement fluid and dialysate rate by at least 25%. A third option is to continue titrating the calcium chloride infusion rate, and lastly, if the ratio increases, the citrate infusion can be stopped and a non-anticoagulation RRT modality can be initiated.⁹⁴ Safe implementation of citrate requires a well-designed and flexible protocol with adjustable dosing and monitoring; strict adherence to the

protocol and its algorithm can prevent metabolic complications. It is feasible and **safe** to use RCA **even** in patients with **liver** failure.¹⁰⁰

Conclusions

Acute kidney injury is a complex and frequent complication among critically ill patients. When AKI occurs, RRT is required in about one out of ten patients. Although there is no mortality difference between IHD and CRRT, the latter seems to provide better renal recovery and dialysis independence, and is the therapy of choice in hemodynamically unstable patients. CRRT can be provided in different modes of increasing complexity depending on a given patient's clinical needs. Systemic anticoagulation with **UFH is the most common strategy worldwide** but RCA is currently the recommended therapy of choice in patients requiring CRRT.

Conflict of interest George Alvarez, Carla Chrusch, Terry Hulme, and Juan G. Posadas-Calleja have no conflicts of interest or disclosures.

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