Chapter

Renal Replacement Therapies in the Intensive Care Unit

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Abstract

Renal replacement therapies (RRT) are commonly used in critically ill patients to achieve solute clearance, maintain acid-base status, and remove fluid excess. The last two decades have seen the emergence of large randomized control trials bringing new evidence regarding how RRT should now be managed in the ICU. RRT is considered a vital supportive care and needs to be adequately prescribed and delivered. This chapter first summarizes the basic principles and characteristics of the three major RTT modalities: intermittent hemodialysis (IHD), prolonged intermittent RRT (PIRRT), and continuous RRT (CRRT). Then, the large body of literature regarding indications for initiation (*early* vs *late*), choice of modality (*intermittent* vs *continuous* and *diffusion* vs *convection*), dosing (*intensive* vs *less-intensive*), and anticoagulation alternatives is reviewed to guide clinical decision-making. Recent evidence in the optimal timing of discontinuing RRT is reported. Finally, troubleshooting scenarios frequently seen in clinics and requiring an adapted RRT prescription are also discussed.

Keywords: renal replacement therapy, intermittent hemodialysis, hemofiltration, continuous renal replacement therapy, prolonged intermittent renal replacement therapy, intensive care unit

1. Introduction

Prevalence of acute kidney injury (AKI) was evaluated at 22% in hospital settings in a large meta-analysis of 3.5 million patients and raised up to 57% when admitted to intensive care units (ICUs) [1, 2]. The incidence of dialysis-requiring AKI has increased by 10% yearly from 2000 to 2009 in the United States [3]. Hence, renal replacement therapy (RRT) is widely used in modern acute care settings as a supportive management of severe acute kidney injury (AKI) and multiorgan failure (MOF). While RRT in chronic end-stage kidney disease (ESRD) is mostly reserved for nephrologists, its prescription in context of acute-care settings is shared between many medical specialties.

The first section reviews the basic principles and characteristics of the different modalities used in ICUs nowadays. Then, the main section is meant to guide clinicians in evidence-based RRT prescribing by examining the most relevant body of literature published in the last decade. Indications, timing of initiation, modality choice, dosing,

anticoagulation, and discontinuing RRT are discussed. Finally, some specific and more challenging scenarios are briefly covered as well as other pragmatic aspects.

2. Basics

2.1 Principles: diffusion, ultrafiltration, and convection

Despite major improvements in technologies from the first experimental hemodialysis (HD) in 1924 to the first continuous arteriovenous hemofiltration (CAVH) circuit in 1977, general principles guiding the removal of water and solutes for almost any type of extracorporeal renal replacement therapies initiated in the ICU remain the same: diffusion, convection, ultrafiltration and sometimes adsorption (see **Figure 1**) [4]. These three major concepts will be integrated according to the renal replacement therapy (RRT) modality chosen. The notable exception is peritoneal dialysis (PD), which, nowadays, is rarely initiated in acute setting such as AKI in ICU adult populations. However, PD for AKI is often used in children and has been shown useful in resource-limited settings (e.g., no reliable access to electricity or CRRT devices) as well as in extraordinary circumstances when usual CRRT capacities have been overflowed (e.g., recent COVID19 pandemic). Nevertheless, in most centers, PD as a modality of RRT is restricted to ESRD patients requiring maintenance dialysis and is rarely an option in ICUs. For these reasons, only blood-based extracorporeal renal replacement therapies will be reviewed in this Chapter.

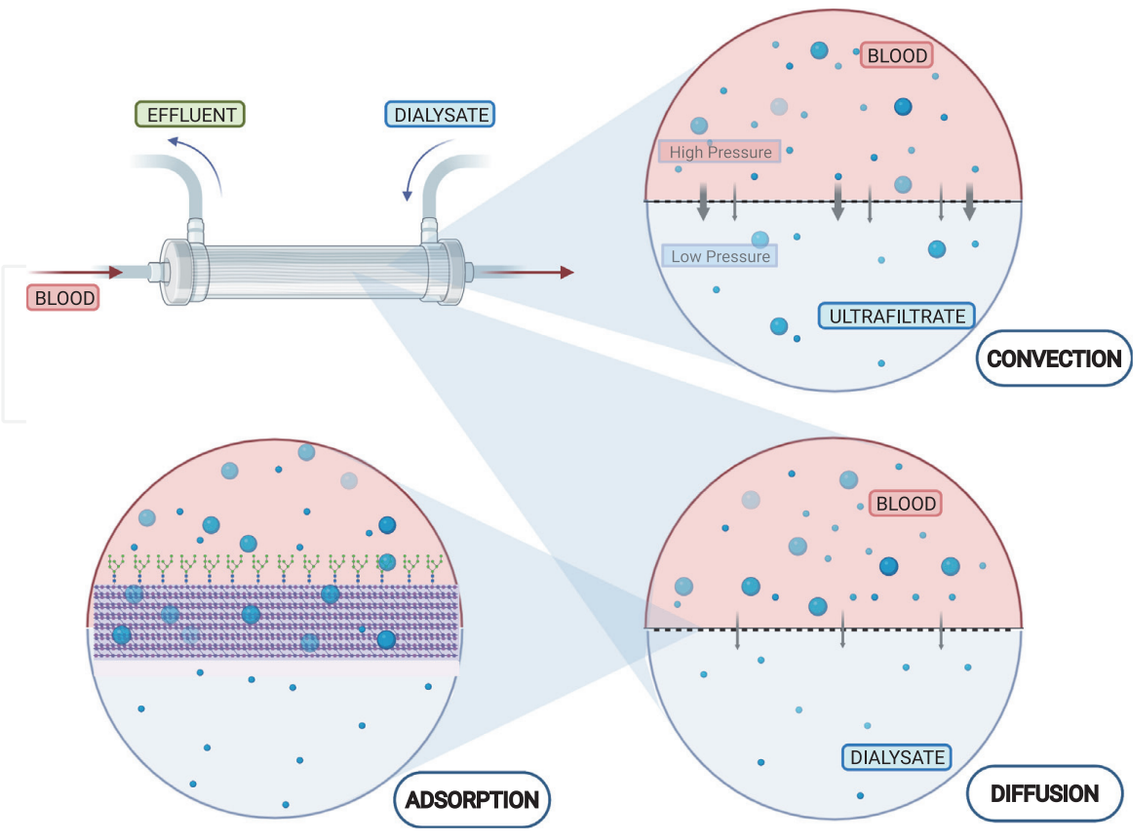

Figure 1.
Principles guiding blood-based extracorporeal RRT.

Diffusion, as used in HD, is the movement of solutes across a semipermeable membrane. The direction and intensity of that movement are driven by the concentration gradient (from higher to lower). Circulating blood and the dialysate in opposite direction on each side of the semipermeable membrane (countercurrent flow) maximizes concentration gradient and potentiates solute clearance. Another key aspect driving diffusion-based clearance is the size of the solute, where smaller solutes (<100 Daltons) cross the membrane faster than larger molecules. Other important properties are protein binding, distribution volume, and electrical charge [5].

Ultrafiltration (UF) is the movement of fluid across a semipermeable membrane using pressure differential (from higher to lower pressure) to generate the ultrafiltrate. In RRT, net UF represents the total amount of fluid removed to obtain the net fluid balance, which can be prescribed per hour (e.g., −50 mL/h) during CRRT or per session (e.g., −2 liters) during intermittent HD.

Convection, as used in hemofiltration, is the clearance of dissolved solutes along plasma crossing the semipermeable membrane (ultrafiltrate) (a mechanism sometimes called "solvent drag"). When used alone, convection requires to generate a large amount of ultrafiltrate (containing dissolved toxins/solutes) to achieve adequate clearance. Hence, a substantial amount of sterile solution needs to be reinjected to the patient to compensate for the volume removed by convection to maintain volume and solutes homeostasis. Convection can remove larger, middle-sized molecules at which diffusion is inefficient [5, 6].

Adsorption is the adherence of a molecule to the surface of a polymer, or a charged membrane exposed to the blood. As opposed to convection, where middle and small molecules completely cross the membrane and are therefore removed by the effluent fluid, the polymer/membrane will be progressively saturated by those molecules, leading to a progressive reduced adsorptive capacity for longer treatments. There is an increasing interest in the potential of adsorption to reduce the inflammatory response by adsorbing cytokines, endotoxins, or exotoxins mostly in septic shock. Mixed results on the true added benefit of this technology have been reported and dialyzer/cartridge generating adsorption is not widely used in the current practice [7].

2.2 Modalities characteristics: IHD, PIRRT/SLED, and CRRT

All extra-corporeal RRT technologies used in ICUs can be separated into three modalities: intermittent hemodialysis (IHD), prolonged intermittent RRT (PIRRT) (also called sustained low-efficiency dialysis [SLED]), and continuous RRT (CRRT). Their ability in fluid and solute removal is all based on one or on the combination of the basic principles described above (See **Figure 2**).

In HD (A) and CVVHD (B), blood and dialysate circulate on each side of the semipermeable membrane. Diffusion is the driving force that contributes to solute clearance. For all RRT devices, pressure differential between the two compartments, using dedicated pumps to generate transmembrane pressure (TMP), controls convection flow and ultrafiltration rate. The removed liquid containing waste is usually called effluent for all modalities.

In CVVH (C), convection is the main mechanism used to provide solute clearance. The generation of ultrafiltrate is continuously compensated by the reinjection of replacement fluid. That replacement can be injected before the filter, after the filter, or a combination of both (called pre- vs. post-filter reinjection ratio). Adding pre-filter replacement fluid dilutes blood and its components, notably its hematocrit reducing the overall thrombogenicity. Hence, increasing pre-filter/post-filter ratio reduces the risk of circuit clotting. On the opposite, a proportional increase in hematocrit at the end of the filter will occur when increasing the convection volume in a 100% post-filter CVVH configuration.

CVVHDf (D) results from the combination of (B) and (C) where both convection and diffusion achieve solute clearance. The replacement fluid may be mixed pre- and post-filter as well in addition to using a countercurrent dialysate flow. However, diluting blood pre-filter also decreases the concentration gradient, which is a major driving force in diffusion. The prescription should be adapted according.

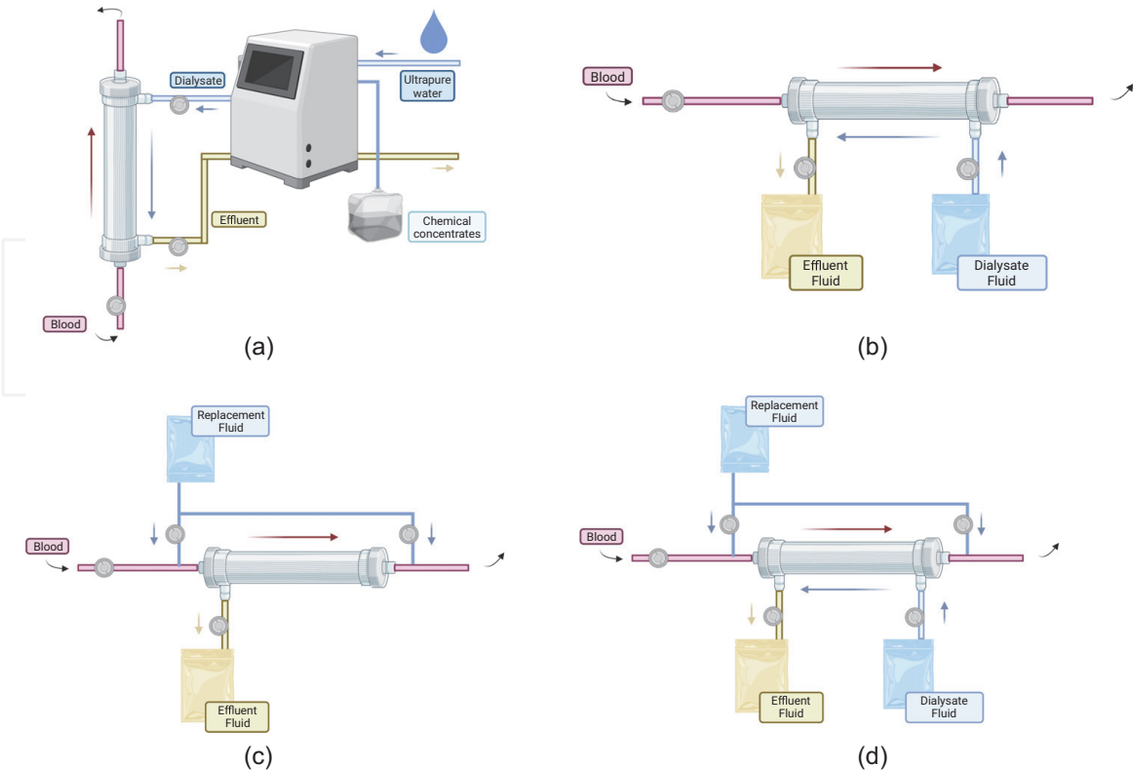

Figure 2.
Schematic representation of IHD and CRRT circuits' configuration. (A) HD: A dedicated intermittent HD device generates large volumes of physiological dialysate using sterile water and chemical concentrates. Up to 800 mL/min of new dialysate can be constantly generated for most HD devices. The composition/prescription of this dialysate can be individualized according to the patient's need. (B)(C)(D) a dedicated CRRT machine uses commercially available bags of physiological solution, using low effluent flow (20–35 mL/kg/h).

Net fluid balance (net UF) can be obtained in all modalities: in IHD and CVVHD, by generating a TMP, which leads to ultrafiltrate. In CVVH and CVVHDF, the volume of reinjection needs to be slightly lower than the ultrafiltrate generates, which leads to a negative fluid balance.

It should be noted that some centers can generate high volumes of convection when using intermittent RRT. This modality is named hemodiafiltration (HDF), requires an adapted dialysis machine, and is increasingly used in Europe and Asia for ESRD patients. However, its implementation in ICU settings remains limited, partly due to the need to maintain a water treatment system adapted to HDF [8]. As a result, when reporting intermittent RRT in the ICU, we generally consider only IHD.

From a clinical standpoint, each modality is associated with typical blood flow rates (Qb) and dialysate flow rates (Qd) which translates into conventional treatment durations and frequencies (see **Table 1**).

PIRRT represents the application of intermittent hemodialysis technology (machine, filter, dialysate) with a modification of the typical IHD prescription. The objective is to provide a better hemodynamic tolerability than IHD. Hence, in centers offering this modality, PIRRT is generally used in place of CRRT such as in patients with hemodynamic instability, especially if a substantial negative fluid balance (net UF rate) is desired. PIRRT is typically delivered 8 hours with slower blood and dialysate flows than IHD. However, this modality is not optimal for acute RRT indication such as severe hyperkalemia or intoxication with dialyzable substances (e.g., salicylates, methanol, and ethylene glycol) because of its lower flow rates. In some centers, a dedicated HD nursing staff is required to deliver a PIRRT treatment.

	Intermittent hemodialysis (IHD)	Prolonged intermittent renal replacement therapy (PIRRT)	Continuous renal replacement therapy (CRRT)
Type of clearance **D**=Diffusion **C**=Convection	IHD: D HD*f*: D + C	SLED: D SLED*f*: D + C	CVVH: C CVVHD: D CVVHD*f*: D + C
Type of machine	IHD machine	Usually, IHD machine	CRRT machine
Duration	3–4 hours	6–12 hours	Continuous
Frequency	3–4 days/week	3–7 days/week	Continuous
Qb range (mL/min)	350–400	150–250	100–250
Qd range (mL/min)	500–800	100–300	25–30
Usual UF rate	0–5000 mL/session	0–5000 mL/session	0–200 mL/hour

IHD: intermittent hemodialysis, HDf: intermittent hemodiafiltration; SLED: sustained low-efficiency dialysis, SLEDf; sustained low-efficiency hemodiafiltration.

Table 1.
Typical prescribing patterns of RRT modalities.

CRRT is characterized by small flow rates, notably reinjection, dialysis, and UF rates. It allows reducing the hemodynamic effects of fluid and solute changes. However, this continuous modality requires a permanent connection to the CRRT machine, supervision and is at high risk of clotting if no anticoagulation is prescribed. In most centers, an adequately trained ICU nurse can manage a CRRT treatment.

3. Prescribing RRT

Even though RRT is widely used, and most ICUs have elaborated standardized protocols to simplify IHD/CRRT prescription, many factors need to be considered before, during, and when stopping this therapy: patient's characteristics, local resources, physician's preferences as well as scientific evidence.

3.1 Initiating

3.1.1 Indications

Indications for initiating RRT in acute care are frequently classified as *absolute* vs. *relative* or as *emergent* vs. *semi-urgent*. Although the terms "absolute" or "emergent" might seem dichotomic as if a clear cut-off was defined, they are subject to interpretation in clinical practice [9]. It is generally accepted to begin RRT in a timely manner once any of these conditions occur if concordant with the goals of care (see **Table 2**).

On the other hand, whether to initiate and when to do so while not meeting any of these indications has received a lot of interest in the last few years in the attempt to prevent morbidity and mortality. Indeed, initial observational studies had supported the rationale that a proactive/early RRT will help to quickly normalize renal homeostasis while minimizing inflammation and uremic toxicity. On the other hand, this approach could lead to initiate RRT in patients who will never develop clear indications as some will spontaneously recover in addition to exposing them to unnecessary

1. Refractory to medical treatment:
   a. Hypervolemia with pulmonary edema
   b. Severe hyperkaliemia ($K^+ > 6.5$ mmol/L) or rapidly rising kaliemia
   c. Severe acidemia (pH <7.1–7.2) due to metabolic acidosis ($HCO3^- < 12$–15 mmol/L)
2. Uremic complications of renal failure (e.g., pericarditis and encephalopathy)
3. Dialyzable toxin exposure

Table 2.
Absolute indications of initiating RRT.

RRT complications. This has led to the constantly evolving *early* vs. *late* paradigm which has been investigated in five recent landmark randomized controlled trials (RCTs) (see **Table 3**). A careful reminder of the definitions used to classify severity of acute kidney injury (AKI) is mandatory before reviewing these trials (see **Table 4**).

In 2016, the results of the first large RCT trying to answer this complex question were published. The Early Versus Late Initiation of Replacement Therapy In Critically Ill Patients with AKI (**ELAIN**) trial was a single-center based in Germany with mostly surgical patients [12]. The RRT modality was CVVHDF at a dosing of 30 ml/kg/h and using regional citrate as anticoagulation. All participants in the early group (< 8 h of stage 2) vs. 91% in the delayed group (< 12 h of stage 3 or $K^+ > 6$ mmol/L, urea >100 mg/dL, $Mg^{2+} > 4$ mmol/L, UO < 200 ml/12 h or refractory edema) received RRT. An important characteristic is a relatively small difference in the time to begin RRT from initial randomization across groups (21 hours (IQR 18–24)) and in the overall use of RRT (9%) between both arms. A significant statistical mortality benefit was obtained favoring the early arm (HR 0.66 (0.37–0.97), p = 0.03). A few months later, the Artificial Kidney Initiation in Kidney Injury (**AKIKI**) trial was published; a multicenter and much larger study from 31 French ICUs totalizing 620 patients [13]. The modality was at the discretion of physicians (30% received CRRT as sole therapy) and 80% had sepsis-related conditions (sepsis, severe sepsis, or septic shock). Almost all participants in the early group (< 6 h of stage 3) compared to 51% in the delayed group ($K^+ > 6.0$ mmol/L, urea>112 mg/dL, pH < 7.15, pulmonary edema or oliguria/anuria >72 h) received RRT. The difference in the time to begin RRT between the two arms was 55 hours. No difference was seen in mortality (60 days), but more catheter-related bloodstream infections were reported in the early group (p = 0.03). In 2018, the Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit (**IDEAL-ICU**) trial, which took place in 29 ICUs in France was published [14]. This trial included 488 patients within the first 48 hours of their septic shock. The modality was also at the discretion of physicians. Almost all participants in the early group (< 12 h of Failure stage) compared to 62% in the delayed group ($K^+ > 6.5$ mmol/L, pH < 7.15, pulmonary edema or persistent AKI 48 h after inclusion) received RRT. No difference was seen in mortality (90 days). It is important to notice that this trial was stopped early for futility (initially designed for 864 patients).

In an attempt to definitively clarify the question of *Timing*, the Standard versus Accelerated Initiation of RRT in AKI (**STARRT-AKI**) trial was later published in 2020. It included 3019 patients from 168 ICUs in 15 countries [15]. Patients mostly received CRRT (70%) and had both medical (65%) and surgical (35%) conditions. Almost all participants in the early group (*accelerated strategy*) (<12 h of stage ≥2) compared to 62% in the delayed group (*standard strategy*) ($K^+ > 6$ mmol/L, pH < 7.2, $HCO3^- < 12$, pulmonary edema or persistent AKI 72 h after inclusion) received RRT. Once again, no difference was seen in mortality (90 days), including in the subgroup

Studies (year)	Settings	Population	Early-group criteria	Delayed-group criteria	Primary outcome	Secondary outcomes or safety endpoints
ELAIN (2016)	Germany single center CVVHDF (30 ml/kg/h)	n = 231 93.5% surgical (46.8%-cardiac) SOFA 15.6 vs. 16.0	< 8 h of stage 2 RRT: 100%	< 12 h of stage 3 or K^+ > 6 mmol/L, *urea >100 mg/dL, Mg^{2+} > 4 mmol/L, UO < 200 ml/12 h, refractory edema RRT: 91%	90-day mortality: E: 39.3% D: 54.7% HR 0.66 (0.37–0.97, **p = 0.03**)	Median RRT duration (days): E: 9 vs. D: 25 HR:0.69 (0.48–1.00) 90-day RRT requirement: OR 0.87 (0.31–2.44)
AKIKI (2016)	France 31 ICUs 30% CRRT-only >50% intermittent	n = 620 80% sepsis-related SOFA 10.9 vs. 10.8	< 6 h of stage 3 RRT: 98%	K^+ > 6.0 mmol/L, urea>112 mg/dL, pH < 7.15, pulmonary edema or oliguria/anuria >72 h RRT: 51%	60-day mortality: E: 48.5% D: 49.7% (p = 0.79)	60-day RRT dependence: E: 2% vs. D: 5% (p = 0.12) CRBI: E: 10% vs. D:5% (**p = 0.03**)
IDEAL-ICU (2018)	France 29 ICUs stopped early (futility) CRRT and IHD	n = 488 <48 h of septic shock SOFA 12.2 vs. 12.4	< 12 h of Failure stage (RIFLE) RRT: 97%	K+ > 6.5 mmol/L, pH < 7.15, pulmonary edema or persistent AKI after 48 h RRT: 62%	90-day mortality: E: 58% D: 54% (p = 0.38)	Median RRT duration (days): E: 4 vs. D: 2 90-day RRT dependence: E: 2% vs. D: 3% (p = 1.00)
STARRT-AKI (2020)	15 countries 168 ICUs 70% CRRT 30% intermittent	n = 3019 65% medical 35% surgical SOFA 11.6 vs. 11.8	<12 h of stage ≥2 RRT: 97%	K^+ > 6 mmol/L, pH < 7.2, $HCO3^-$ < 12, pulmonary edema or persistent AKI 72 h after inclusion RRT: 62%	90-day mortality E: 43.9% D: 43.7% (p = 0.92)	Median RRT duration (days): E: 4 vs. D: 5 RR = −0.48 (−0.82–(−)0.14) 90-day RRT dependence: E: 10% vs. D: 6% RR = **1.74** (95% CI 1.24–2.43) Any adverse event: E:23% vs. D:16.5% (**p < 0.001**)
AKIKI-2 (2021)	France 39 ICUs 40% CRRT 60% intermittent	n = 278 55% septic shock For inclusion (3/3): 1)MV or vasopressor 2)AKI stage 3 3)Oligo-anuria >72 h or urea 112 to 140 mg/dL	<12 h of fulfilling inclusion criteria RRT: 98%	K^+ > 6 mmol/L, pH < 7.15, *urea>140 mg/dL, pulmonary edema (No time criteria) RRT: 79%	RRT free days (day 28) E:12 D: 10 (p = 0.93)	60-day mortality: E:44% vs. D:55% (p = 0.07) RRT duration (days) E:5 vs. D: 5 (p = 0.75) 60-day RRT dependence: E:4% vs. D: 1% (p = 0.62)

**Urea conversion to SI units: 100 mg/dL = 35.7 mmol/L, 112 mg/dL = 40 mmol/L, 140 mg/dL = 50 mmol/L.*
E: Early-group, D: Delayed-group, UO: urine output, CRBI: Catheter-related bloodstream infection, MV: mechanical ventilation.

Table 3.
Landmark RCTs on timing of RRT initiation.

KDIGO (2012) [10]			RIFLE (2007) [11]		
Stage	**Creatinine**	**Urine output**	**Stage**	**Creatinine**	**Urine output**
1	1.5–1.9 x baseline Or ≥ ↑ 0.3 mg/dL	<0.5 ml/kg/h x 6–12 h	**Risk (R)**	1.5 x baseline Or ↓ GFR > 25%	<0.5 ml/kg/h x 6 h
2	2.0–2.9 x baseline	<0.5 ml/kg/h x ≥ 12 h	**Injury (I)**	2 x baseline Or ↓ GFR > 50%	<0.5 ml/kg/h x 12 h
3	≥ 3.0 x baseline Or ≥ 4.0 mg/dL Or Initiation of RRT	<0.3 ml/kg/h x ≥ 24 h Or Anuria ≥12 h	**Failure (F)**	3 x baseline Or ↓ GFR > 75% Or ≥ 4.0 mg/dL	<0.3 ml/kg/h x ≥ 24 h Or Anuria ≥12 h
			Loss (L)	Persistent acute renal failure >4 weeks	
			ESKD (E)	ESKD >3 months	

↑: increase of serum creatinine, ↓: decrease of GFR, ESKD: end-stage kidney disease.
Creatinine conversion to SI units: 0.3 mg/dL = 26.8 μmol/L; 4.0 mg/dL = 353.6 μmol/L).

Table 4.
KDIGO and RIFLE classifications of AKI.

analysis (including medical vs. surgical). Notably, a difference was obtained in RRT dependence at 90 days which was higher in the accelerated group (RR = 1.74 [95% CI 1.24–2.43]). Significantly more adverse events (23% vs. 16.5% $p < 0.001$) occurred when exposed to the accelerated strategy, mainly driven by hypotension ($p < 0.001$), and mild hypophosphatemia ($p < 0.001$), with the trend toward more bloodstream infections ($p = 0.07$). Compared to previous studies, distinctive pragmatic characteristics should be noted. First, if the clinician did not have absolute equipoise regarding initiation of RRT (e.g., expected impending renal recovery), the patient was not included. Also, the delayed strategy did not mandate RRT initiation once the criteria were fulfilled but was based on clinical judgment. Results from this study have substantially affected how and when RRT is now initiated in ICUs worldwide.

STARRT-AKI has confirmed evidence against the preemptive use of RRT prior to developing standard RRT initiation criteria. However, a question remained unanswered: how far can we delay RRT initiation without negative outcomes? The Artificial Kidney Initiation in Kidney Injury-2 (**AKIKI-2**) trial, published in 2021, was developed to answer that question, assessing the potential benefits of a more-delayed strategy in terms of RRT-free days. That trial took place in 39 ICUs in France and included 278 patients. To be eligible for randomization, three criteria had to be achieved: (1) mechanical ventilation or vasopressor + (2) AKI stage 3 + (3) Oligo-anuria >72 h or urea 112 to 140 mg/dL[1]. Almost all participants in the "early group" (similar to the *delayed group* from STARRT-AKI) (<12 h of fulfilling inclusion criteria) compared to 79% in the delayed group (*more-delayed strategy*) ($K^+ > 6$ mmol/L, pH < 7.15, urea>140 mg/dL[2], pulmonary edema) received RRT. Median time between randomization and initiation of RRT was 3 hours versus 33 hours. Noteworthy, the difference in RRT use of 19% between the two groups is about half of what

[1] Urea criteria led to inclusion of 61% in the *delayed* and 55% in the *more-delayed* strategy.

[2] Urea criteria led to initiation of RRT in 59%.

has been obtained in the three previous studies. No difference was reported in RRT-free days on day 28 even though no time criteria were applied in the delayed group, contrasting to previous studies. The primary outcome of 60-day mortality was not significantly higher in the more-delayed group compared to delayed (55% vs. 44%, p = 0.07). Though, in the preplanned multivariate analysis, the more-delayed strategy was associated with increased 60-day mortality (HR 1.65 p = 0.018). Overall, the more-delayed strategy did not demonstrate decreased use of RRT, but worrisome findings suggesting potential harms.

3.1.2 Predicting the need of RRT

As shown in those studies where a substantial number of patients randomized to a delayed strategy never required RRT initiation, correctly predicting who will progress to an AKI stage where RRT is required is complex in a real-life setting. Since the last decade, a growing number of tools and biomarkers have been developed, and reported useful, to inform about the likelihood a patient with AKI will worsen, and progress to receive RRT [16]. Various urine and blood biomarkers have been studied, such as the urine neutrophil gelatinase-associated lipocalin (uNGAL), interleukin-18 (IL18), or the NephroCheck (TIMP2*IGFBP7), with a pooled AUC or 0.720, 0.668 and 0.857 respectively. More functional biomarkers, such as a diuretic response of less than 200 mL to a loading dose of 1.0 to 1.5 mg/kg of intravenous furosemide (FST – Furosemide stress test) have also been shown useful in predicting the risk of progression to RRT with a pooled sensitivity and specificity of respectively 0.84 (95% CI 0.72–0.91) and 0.77 (95% CI 0.64–0.87) [17]. The growing interest in such complementary tools is associated with the publication of multiple confirmation studies in recent years, leading to recent consensus in favor of their use in standard clinical practice [18]. However, their implementations in real-life ICU settings are still in the beginning.

3.1.3 Conclusion

In summary, only the first smallest single-center RCT of almost entirely surgical patients has shown a mortality benefit of early initiation of RRT compared to a delayed strategy. The three subsequent trials consisting of more than four thousand patients with a variety of modalities and populations (including surgical subgroup analysis) concluded the absence of such advantages of early initiation. Also, the added resources required to initiate 35–45% more RRT must not be neglected. Furthermore, significant harms have been reported in the early-initiation approach: catheter-related bloodstream infections (AKIKI), 90-day RRT dependence, and any adverse event (STARRT-AKI). On the other hand, the latest trial might help in determining the upper limit of postponing RRT. Therefore, a conservative approach consisting of watchful waiting, unless a life-threatening indication emerges, seems recommended for most cases with the caveats that the risk-benefits ratio is uncertain once criteria used for inclusion in the latest trial are reached.

3.2 Modality choice

3.2.1 Intermittent vs. continuous

Although there are substantial variations in practice, hemodynamic instability is the most common reason to choose slow intermittent (PIRRT) or continuous (CRRT)

Study (year)	Design	# of Pts	CRRT	IHD	Survival	Renal Recovery
Mehta et al. (2001) *ARF ICU*	RCT	166	CVVHDF or CAVHDF	Qb 200–300	CRRT 34.5% IHD 52.4% **(p < 0.02)**	CRRT 34.9% IHD 33.3% (p = NS)*
Guerin et al. (2002)	Prospective observational (unadjusted)	587	variable	variable	CRRT 20.6% IHD 41.2% **(p < 0.001)**	Not mentioned
Gasparovic et al. (2003)	RCT	104	CVVH	Qb 200–250	CRRT 28.8% IHD 40.4% (p = NS)	Not mentioned
Augustine et al. (2004)	RCT	80	CVVHD	Qb 300	CRRT 32.5% IHD 30.0% (P=NS)	CRRT 12.5% IHD 10.0% (p = NS)*
Vinsonneau et al. (2006) *HEMODIAFE*	RCT	259	CVVHDF	Qb 278	CRRT 32.6% IHD 31.5% (p = 0.98)	CRRT 93.3% IHD 90.2% (p = NS)**
Lins et al. (2009) *SHARF Trial*	RCT	316	CVVH	Qb 100–300	CRRT 41.9% IHD 37.5% (p = 0.430)	CRRT 74.5% IHD 83.1% (p = 0.474)**
Schefold et al. (2014) *CONVINT Trial*	RCT	252	CVVH	Qb 200–250	CRRT 45.4% IHD 39.7% (p = 0.72)	CRRT 77.2% IHD 73.6% (p = 0.90)**
Truche et al. (2016)	Prospective observational (adjusted)	1360	CVVH or CVVHD	variable	CRRT 53.5% IHD 65% (p = NS)	CRRT 64.7% IHD 42.9% (p = 0.29)**

**In all patients randomized.*
***In patients who survived at ICU discharge.*
CAVHDF: Continuous arteriovenous hemodiafiltration, p: p-value, NS: Non-significant.

Table 5.
Major studies comparing CRRT to IHD.

therapy. The 2012 KDIGO AKI guidelines suggest using CRRT rather than intermittent RRT for these patients (grade B – moderate quality of evidence) [19]. However, empirical data has not proven what might seems obvious at first to clinicians. In fact, the use of PIRRT or CRRT compared to IHD in randomized trials has failed to demonstrate differences in hard outcomes such as mortality or recovery of renal function [20–26] (see **Table 5**). Still, it is important to note that heterogeneity is found in dosing, CRRT subtypes, delivered blood flow, and that the most unstable patients were excluded for most of them.

As mentioned earlier, in patients with hemodynamic instability, the choice between PIRRT and CRRT mostly depends on local availability. The level of evidence regarding PIRRT is still limited, but advantages compared to CRRT may include: reduced costs and flexible treatment schedule allowing the patient to be more easily mobilized during daytime. As opposed to fixed CRRT solutions, the dialysate composition can be more easily adapted to the patient's needs even during the dialysis session. However, no clear antimicrobial dose adjustments are recommended with that modality. In patients who regain stability, the RRT prescription can be rapidly adapted, from PIRRT to a conventional IHD prescription, using the same technology.

3.2.2 Diffusion vs. convection

Given that both clearance methods are efficient at clearing small solutes, the question is mainly about the added benefit (or harm) of removing medium-sized pro-inflammatory molecules such as cytokines, endotoxins, or exotoxins. In ESRD patients, for those treated with HDF compared to IHD, some benefits were demonstrated in large RCTs on reducing intradialytic hypotension and use of erythropoietin-stimulating agents, but more importantly, an all-cause mortality benefit (HR 0.78, 95%CI 0.62–0.98) and cardiovascular mortality (HR0.69, 95%CI 0.47–1.0) were obtained when optimal convective volumes were delivered [27]. However, in AKI no such benefits have been demonstrated with certainty. A 2012 meta-analysis of 19 RCTs, comparing hemofiltration (CVVH) to hemodialysis (mostly CVVHD) found no effect on mortality (RR 0.96, 95%CI 0.71–1.15), or other clinical outcomes (RRT dependence in survivors, vasopressor use, organ dysfunction) despite increased clearance of medium to larger molecules, including inflammatory cytokines [28]. Despite fewer studies, similar results have been shown when comparing intermittent modalities offering diffusion only (IHD) to convection (HDF) in ICUs [8].

3.2.3 Conclusion

Since neither the modality mode (*intermittent* vs. *continuous*) nor the clearance method (*convection* vs. *diffusion* vs. both) has shown its superiority, local expertise remains a core element when choosing the modality. Pragmatical aspects such as required staff, costs, and immobilization consequences on the ability to perform rehabilitation and anticoagulation are also important considerations, all summarized in **Table 6**.

3.3 Dosing

Like any treatment, RRT intensity or delivered dose must be tailored to the patient's need. While underdosing may result in insufficient clearance of uremic toxins, uncontrolled electrolytes, or acid–base status, overdosing leads to electrolytes disorders, hydrophilic micronutrients depletion, hazardous therapeutics dosing (e.g., antibiotics), and unnecessary expenses [29]. Ultrafiltration is a critical component of RRT prescribing but is not part of *dosing* which refers to the clearance capability. Another key point is that the actual delivered dose is often lower than the prescribed dose for multiple reasons: vascular access limiting Qb, interruptions for radiologic studies or surgery, circuit change or clotting, etc.

3.3.1 Intermittent modalities

For all intermittent modalities, as seen in **Table 7**, the blood flow rate is the limiting factor highlighting the value of maximizing the potency of vascular access. A subsequent option to optimize clearance is increasing the *frequency* or *duration* of treatments. Then, to lesser levels, increasing filter surface and dialysate flow rate[3]. For dosing assessment (or *clearance adequacy*), guidelines recommend using the clearance

[3] A Qd/Qb ratio higher than 1.5 has minimal to no impact on small solute clearance while using high-flux filter

Modality			Anticoagulation*
IHD	Flow	High (Qb < Qd)	Without ± saline flush ± heparin-coated filters Systemic: UFH (continuous) LMWH (bolus)
	+	Short sessions – Allow exams and mobilization Lowest cost Lowest immobilization	
	—	Hypotension with rapid fluid removal Higher complexity (dedicated dialysis staff)	
	HDF -Removal of medium-sized molecules (added benefit uncertain in AKI) -Large amount of replacement fluid requiring ultra-pure water (Dedicated water treatment complicating ICU implementation)		
CRRT	Flow	Low Qd and convection, Moderate Qb	Without Systemic: UFH Regional: citrate
	+	Hemodynamic stability No treatment-induced increase intracranial pressure Fine fluid control Lower complexity to operate (ICU staff only)	
	—	Hypothermia – Negative energetic balance Immobilization Higher costs (commercial bag for replacement fluids)	
PIRRT	Flow	moderate (Qb ≥ Qd)	Without ± saline flush ± heparin-coated filters Systemic: UFH, LMWH
	+	Online production of dialysate and IHD tubing (lower cost than CRRT) Reduced immobilization (low rehabilitation impact if done overnight)	
	—	Higher complexity (dedicated dialysis staff in some centers)	

Qb: blood flow rate, Qd: dialysis flow rate, UFH: unfractionated heparin, LMWH: Low-molecular-weight heparin.
**See anticoagulation section for more details.*

Table 6.
Pragmatical considerations with RRT modalities.

of urea over the treatment session. It can be estimated with the urea reduction ratio (URR)[4] and the Kt/V_{urea}[5] for small molecules clearance, while the appreciation of medium-sized molecules removal is inferred by the quantification of beta-2-microglobulin (not done in acute care RRT) [19, 30–32]. However, variations of urea generation and difficulty defining the distribution volume (V_{urea}) in metabolically unstable patients are serious limitations in acute care settings. While KDIGO-AKI 2012 guideline still recommends an overall Kt/V_{urea} of 3.9 per week (1A – high-quality), the European Renal Best Practice (ERBP) 2013 position statement recommends against the use of Kt/V_{urea} as a measure of dialysis (1A – high-quality) but

[4] URR = 100 × (1 - [C_t/C_o]), in which C_t = BUN at the end of dialysis and C_o = predialysis BUN

[5] Kt/V_{urea}, in which K = clearance, t = time, V = distribution volume estimated as body water volume. For example, Qb 300 ml/min x 180 min = 54,000 ml = 54 L and 70 kg x 0.6 L/kg (60% body weight) = 42 L. Estimated non-adjusted Kt/V_{urea} = 54/42 = 1.3
More refined equation using pre/post-dialysis BUN is now used to account for UF and physiological BUN generation, known as the Daugirdas equation.

Studies (year)	Settings	Strategy	Dose delivered (Kt/V or total effluent rate ± SD)	Mortality	Secondary outcomes or safety endpoints
ATN (2008)	USA 27 ICUs n = 1124 AKI due to ATN	**Less-intensive**		60-day mortality: L: 51.5% I: 53.6% (p = 0.47)	Hypotension requiring vasopressor L: 10% vs. I: 14% (p = 0.02) Electrolyte disturbance L:20.7% vs. I:25.6% (p = 0.05)
		IHD/SLED 3x/week	1.31 ± 0.33		
		CVVHDF 20 mL/kg/h	22.0 ± 6.1		
		Intensive			
		IHD/SLED 6x/week	1.32 ± 0.36		
		CVVHDF 35 ml/kg/h	35.8 ± 6.4		
RENAL (2009)	Australia & New Zealand 35 ICUs n = 1508 AKI	**Less-intensive**		90-day mortality: L: 44.7% I: 44.7% (p = 0.99)	Hypophosphatemia L: 54% vs. I: 65%
		CVVHDF 25 mL/kg/h	22.7 ± 17.8		
		Intensive			
		CVVHDF 40 mL/kg/h	33.4 ± 12.8		

AKI: acute kidney injury; ATN: acute tubular necrosis; L: Less-intensive group, I: Intensive group.

Table 7.
Landmark RCTs on RRT dosing strategy.

rather to ensure that intermittent therapy is adapted to maintain volume balance and metabolic homeostasis [19, 33].

One RCT includes intermittent modalities compared to dosing-based strategies. The Acute Renal Failure Trial Network **(ATN)** study included 1124 patients in 27 centers in the United States and compared intensive-therapy (IHD or SLED 6 days/week if stable and CVVHDF 35 mL/kg/h if unstable) to less-intensive therapy (IHD or SLED 3 days/week if stable and CVVHDF 20 ml/kg/h if unstable) [34]. Targeted Kt/V_{urea} was 1.2 to 1.4 for intermittent therapy and additional UF-only session could be done in the less-intensive strategy. No difference was obtained in 60-day mortality, RRT duration, or recovery of kidney function. More hypotension and electrolyte disturbance were seen in the intensive strategy.

3.3.2 Continuous modalities

For CRRT, as the trans-membrane equilibrium is almost achieved at the end of the filter for small solutes, the limiting factor for clearance is therefore the effluent flow rate. Hence, the total delivered effluent rate, normalized to actual weight, is used to quantify clearance. According to the circuit configuration, that total effluent rate corresponds to the sum of the reinjection flow (pre- and post-filter) (if CVVH or CVVHDF) + the rate of dialysate flow (CVVHD or CVVHDF) + UF (see **Figure 3**). Even if the UF rate is included in the equation of the delivered dose, in clinical practice it is added once the targeted dose has been prescribed. First, it usually

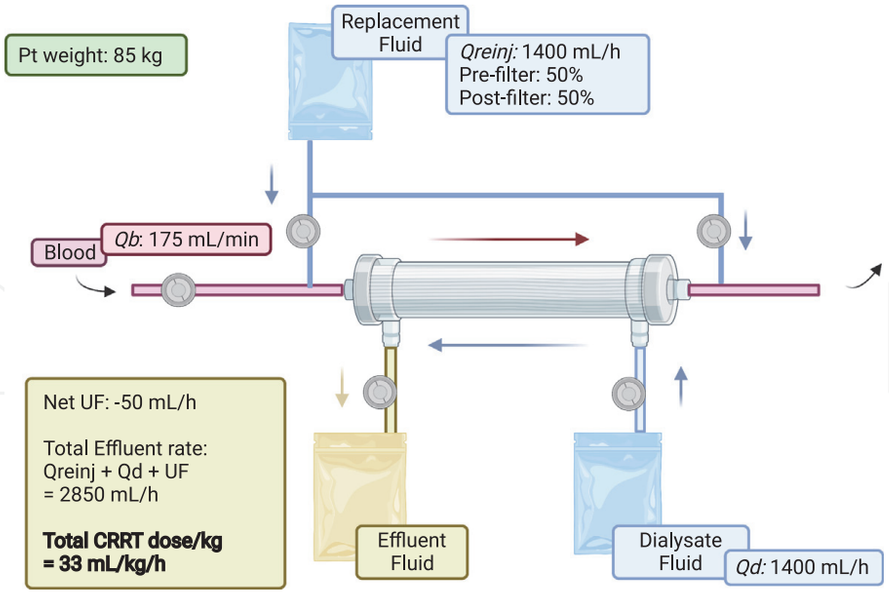

Figure 3.
Example of CRRT dosing using a CVVHDF circuit.

represents a fraction of total effluent in an average size patient.[6] Also, since this rate is regularly modified, its exclusion always allows minimally sufficient delivered dose. Other options to optimize CRRT clearance such as increasing blood flow rate or filter surface have a reduced effect on optimizing clearance efficiency.

Between 2000 and 2008, four major RCTs evaluated the impact of different CRRT doses in critically ill patients. In 2000, using CVVH in 425 patients, three groups were compared [20 vs. 35 vs. 45 (mL/kg/h)] and mortality was significantly higher in the lowest UF rate group at 15 days after stopping RRT [35]. No difference was reported between the two higher rates. In 2002, using CVVH in 106 patients, three groups were compared [early high-volume (48.2 mL/kg/h) vs. early low-volume (20.1 mL/kg/h) vs. late low-volume (19.0 mL/kg/h)] and no mortality benefits was seen at 28 days [36]. In 2006, a study of 206 patients compared two groups [CVVH (25 mL/kg/h) vs. CVVHDF (reinjection rate 25 mL/kg/h + dialysis rate 18 mL/kg/h)] and mortality was significantly higher in the CVVH-only (at 28-day and three months) [37]. In 2008, using CVVHDF in 254 patients [20 vs. 35 (mL/kg/h)] and no mortality benefit was detected [38].

To confirm these previous findings from single-center trials, two multicenter RCTs (USA and AUSNZ) focused on this topic (see **Table 7**). In 2008, the **ATN** study reported no advantage in regards to mortality, duration of RRT, or recovery of kidney function. In 2009, the Randomized Evaluation of Normal Versus Augmented Level Replacement Therapy (**RENAL**) study, with more than 1508 patients from 35 ICUs in Australia and New Zealand and using CVVHDF with post-filter reinjection randomized participants between higher (40 mL/kg/h) vs. lower (25 mL/kg/h) intensity group [39]. As in the ATN study, no difference in mortality was observed. Based on these results, the KDIGO-AKI guideline recommends a delivered effluent volume of at least 20–25 mL/kg/h for AKI patients requiring RRT (1A – high-quality). As previously mentioned, a slightly higher dose should be prescribed in order to achieve that

[6] In an 80 kg patient, an UF of 100 mL/h on a total dose of 25 ml/kg/h (2000 mL/h) represents 5%.

target regarding the dose truly delivered [19]. Some situations may require greater rates such as extreme metabolic imbalances or acute liver failure (see *Clinical Pearls* section).

3.3.3 Conclusion

In summary, for both modalities, current evidence does not support using intensive therapy for all patients. For intermittent modalities, it seems appropriate to prescribe IHD at least 3 times a week to maintain volume and metabolic balance as long as there is no sign of underdosing (either a $Kt/V_{urea} < 1.2$ per session or URR < 67%). The weekly Kt/v_{urea} does not apply in patients requiring additional IHD sessions to achieve a volume balance, as well as in patients with significant renal function. For continuous therapies, a prescribed effluent volume of 25–30 mL/kg/h is adequate in most scenarios to ensure a delivered dose of at least 20–25 mL/kg/h.

3.4 Anticoagulation

Sustained circuit patency is crucial to optimize delivered RRT and contact of blood with extracorporeal circuit activates platelets and pathways of coagulation [40]. KDIGO-AKI guidelines suggest a flow chart to guide anticoagulation decision [19]. At first, it integrates the risk–benefit ratio of anticoagulation and whether another condition requiring systemic anticoagulation is present. RRT can be performed without or with systemic or regional anticoagulation.

3.4.1 No anticoagulation

Although KDIGO-AKI guideline recommends using anticoagulation when bleeding risk is low, it is still common practice in many centers to deliver RRT without anticoagulation in this scenario unless filter patency is an issue. For example, in the STARRT-AKI trial, 24% of the 3019 included patients had no anticoagulation at the initiation. A key concept in preventing circuit clotting is maintaining a low filtration fraction (FF). Filtration fraction indicates relative fluid removed from blood across the dialysis membrane. Higher percentage means higher concentration of blood constituents. Fractions above >20% are associated with increased clotting [41]. The equation for CRRT (blood flow rate being converted from mL/min to mL/h to standardize units) is:

$$\begin{aligned} FF &= \frac{\text{Total UF rate}}{(\text{Plasma flow} + \text{Pre} - \text{filter})\ \text{rates}} \\ &= \frac{(\text{pre} - \text{filter} + \mathbf{\text{total UF}} + \mathbf{\text{post}} - \mathbf{\text{filter}})\ \text{rates}}{((1 - \mathbf{\text{hematocrit}})\text{x}\ \mathbf{\text{blood flow}}\ \text{ml/h x 60 min/h}) + \text{Pre} - \text{filter})\ \text{rates}} \end{aligned}$$

*where **total UF** usually integrates all intravenous volumes received by the patient (e.g., IV medications, IV fluids, parenteral nutrition) in addition to the net UF (negative volume balance targeted) converted to mL per hour.*

Modifying elements only found to either the numerator or the denominator (marked in bold) have higher impact on the FF. Hence, from a clinical perspective, reducing FF is achievable by modifying flow rates: reduce net UF, increase pre-filter/post-filter ratio, increase blood flow, reduce hematocrit. Additionally, since hematocrit might be

reduced by pre-filter reinjection, it is obvious that administering blood transfusion directly pre-filter should be avoided when possible. Also, the catheter patency is essential by allowing prescribed flow rates, by avoiding stasis induced by alarms (e.g., kinked) and by maintaining a laminar flow (right jugular or femoral access).

For intermittent therapies, major assets helping prevent clotting are shorter sessions and higher blood flows, but clotting may be seen even if using heparin-coated filters, especially when substantial UF volume is removed. If convection is used (HDF or SLEDf), pre-filter reinjection can be used as well.

3.4.2 Systemic

Most used agents are unfractionated heparin (UFH) and low-molecular-weight heparins (LMWH). Mostly reserved for patients with heparin-induced thrombocytopenia (HIT), direct thrombin inhibitors (e.g., argatroban and bivalirudin) or Xa inhibitors (e.g., fondaparinux and danaparoid) have been used in intermittent and continuous therapies, but will not be discussed further [42, 43].

UFH has some advantages (e.g., short half-life, antagonist readily available, low costs, and a large experience), but has substantial drawbacks (e.g., narrow therapeutic, unpredictable kinetics and heparin resistance, HIT) [19]. Thrombocytopenia is frequently encountered in ICU occurring in up to 44% of patients. However, HIT remains relatively uncommon in critically ill patients, with a reported incidence from 0.2–5% [44], and has been reported with intermittent and continuous RRT. When used solely for circuit anticoagulation, both the loading and infusion UFH doses need to be adapted to the patient's bleeding/clotting risk as well as continuously monitored with aPTT.

LMWH has replaced UFH in most dialysis units (intermittent therapies) mainly because of convenience of a single dose at start of session associated with the same efficacy (at preventing circuit thrombosis) and security (bleeding) [45]. In addition, a more reliable response is obtained (no monitoring required) along with a reduced risk of HIT. LMWH has been used for CRRT with monitoring of anti-Xa levels [46], but longer half-life and risk of accumulation combined with incomplete reversal by protamine may limit widespread use.

3.4.3 Regional

When systemic anticoagulation is not warranted by another indication than maintaining RRT circuit, regional anticoagulation is the recommended strategy. Regional heparinization has been described in CRRT (combining pre-filter UFH, and post-filter protamine), but KDIGO recommends against its use, notably in patients with increased bleeding risk [19]. Likewise, use of regional citrate anticoagulation (RCA) has been evaluated in intermittent therapies [47] but is not common practice. Hence, emphasis will be placed on RCA in CRRT.

As demonstrated in **Figure 4**, RCA may be perceived as complex [48] but has undeniable advantages: no risk of HIT, lower risk of bleeding compared to UFH along with longer filter lifespan. It is therefore recommended as first line for anticoagulation in CRRT in KDIGO-AKI guideline if no contraindication [19]. A 2015 meta-analysis demonstrated reduced circuit loss compared to UFH [HR 0.76 (95%CI 0.50–0.98) for systemic and HR 0.52 (95%CI 0.35–0.77) for regional] and reduced bleeding [RR 0.36 (95%CI 0.21–0.60)] [49]. A 2020 German RCT of 638 patients in 26 centers demonstrated longer filter lifespan (47 vs. 26 hours, $p < 0.001$), no mortality difference

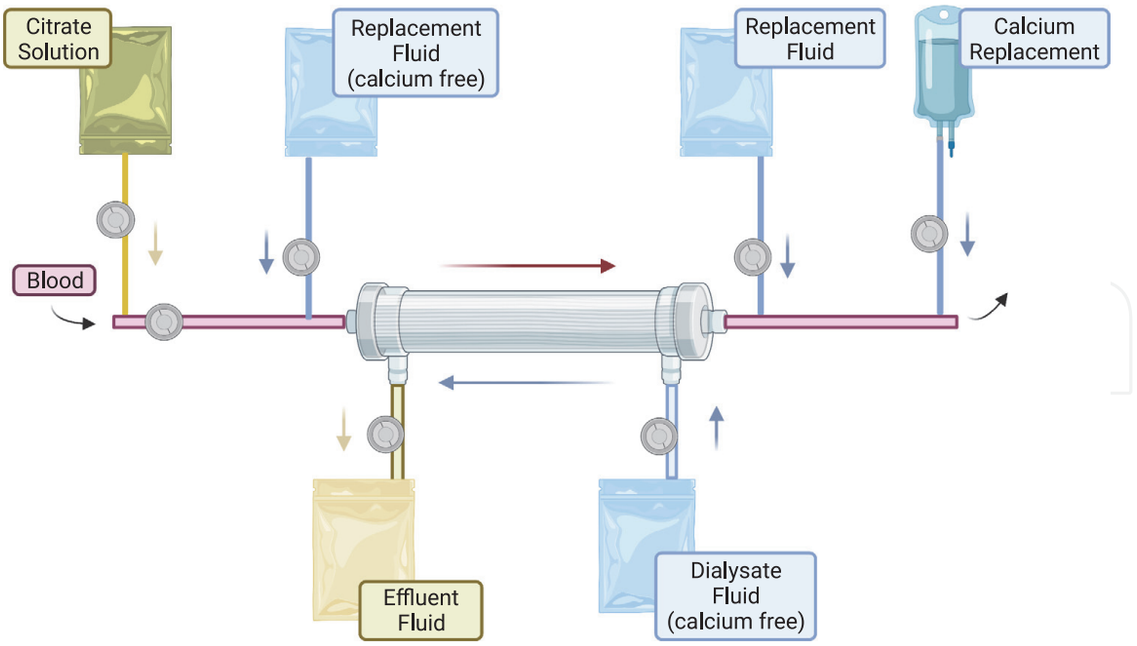

Figure 4.
CVVHDF with regional citrate anticoagulation (RCA). 1) blood, citrate solution, and optional calcium-free replacement fluid mix pre-filter. 2) citrate chelates circulating calcium (required for intrinsic and common pathways of coagulation). 3) calcium-free dialysate (avoiding calcium diffusion from dialysate to blood compartment) circulates countercurrent. 4) replacement fluid and calcium infusion to normalize calcemia are reinjected post-filter.

(51.2% vs. 53.6%, $p = 0.38$), fewer bleeding complications (5.1% vs. 16.9%, $p < 0.001$), but more infections (68% vs. 55.4%, $p = 0.002$) in RCA compared to systemic heparin [50].

Thorough protocols and expertise in preventing/monitoring complications are required during RCA. The most immediate risk being unreplaced calcium since most complex (Ca-Citrate) is removed by the filter and may lead to severe hypocalcemia. So, one must be extremely careful if the calcium replacement IV line is assembled independently (e.g., CRRT machine continues, but calcium IV line is no longer potent). Citrate metabolism is the next consideration. The liver metabolizes one citrate into three bicarbonates. Even though low bicarbonate replacement and/or dialysate fluids are usually used, RCA is associated with more metabolic alkalosis than heparin [50]. If the liver cannot metabolize citrate, accumulation can be seen and translate in an anion gap metabolic acidosis associated with rise in total calcium levels, but decline ionized calcium. Thus, monitoring total calcium/ionized calcium ratio is helpful and a ratio > 2.5 is a sign of citrate accumulation which is also associated with hypernatremia and hypomagnesemia. Of note, once believed an absolute contraindication of RCA, it has been used safely in patients with liver diseases. A 2019 meta-analysis of 10 observational studies (1241 patients with liver dysfunction) showed no difference in pH, bicarbonate, metabolic alkalosis, lactate levels and total/ionized calcium ratios compared to patients without liver disease [51]. However, a more careful approach than in usual patients should be taken (e.g., tighter biochemical monitoring, lower citrate dose or lower total calcium/ionized calcium threshold) to regularly reassess its safety.

In summary, sustained circuit patency is required to optimize RRT. Understanding filtration fraction is of great help, mainly if anticoagulation is contraindicated. Otherwise, if no other indication mandates systemic anticoagulation, LMWH is the usual first choice for intermittent therapies and RCA for CRRT.

3.5 Stopping RRT

Literature is lacking to guide discontinuation of RRT initiated in context of AKI as revealed by the KDIGO-AKI recommendation that simply states "when it is no longer required, because kidney function has recovered to meet patient need or because RRT is no longer consistent with goals of care" [19]. Assessment of recovering kidney function in particularly difficult during RRT. While on intermittent therapy, steady state is not attained therefore excluding use of routine clearance measurements. Interdialytic evaluation of urine volume and creatinine, absolute rise of serum biomarkers (creatinine and BUN), but most probably the rising kinetic over time are frequently used. In a prospective observational study, spontaneous urine output was the best predictor of weaning RRT [52]. A recent systematic review found that urine output prior to RRT discontinuation was the most studied variable, but no threshold value could be determined due to heterogeneity of studies [53]. Pooled analysis found a sensitivity of 66% and specificity of 74% to predict RRT discontinuation, but cut-off values varied from 100 mL increase/day to >1720 mL/24 h. Of note, in one RCT, diuretic-induced diuresis had no benefit on repeated need for RRT or renal recovery [54]. In a retrospective study, a 24-hr urine creatinine clearance >15 ml/min was associated with absence of CRRT need at 14 days [55]. In another study, a 24 h urine creatinine of ≥5.2 mmol on day 2 post-RRT had a 86% sensitivity and 81% specificity of not requiring additional RRT treatment [56]. On the other hand, longer duration of RRT, more severe disease (SOFA score) and older age were associated with restarting RRT which correlated with higher mortality [57].

In summary, clear guidance in stopping RRT is lacking and implies at first a minimal diuresis to avoid marked net fluid accumulation. Then, careful monitoring of clinical (weight, volume balance, diuresis) and paraclinical (serum biomarkers, urine creatinine clearance) data are valuable tools.

4. Miscellaneous pearls

Most of the content discussed in previous sections refers to general considerations for understanding and prescribing competently RRT in ICU. However, some challenging situations encountered in clinical practice and pragmatic concerns will be briefly reviewed.

4.1 Severe dysnatremias

Mild to moderate dysnatremias are frequent in critically ill patients, especially at initial presentation. Maximum correction rate and approach to treatment differ between guidelines [58]. Though, consensus exists that inadequate correction of chronic severe hyponatremias (<125 mmol/L for >48 hours) should be avoided due to risk of developing osmotic demyelination syndrome (ODS) [59]. Concurrent urgent need for RRT and this condition can be particularly challenging. Since most IHD machines have a minimum sodium of 130 mmol/L, even by prescribing short duration, low blood and dialysate flow rates, overcorrection is a possibility. In the opposite, CRRT has been used effectively at correcting hyponatremias in a predictable manner either by adding a 5% dextrose pre-filter infusion or via customized hypoosmolar dialysate fluids [60].

Limited evidence exists about hypernatremia. Most IHD machines have maximum sodium of 160 mmol/L and CRRT correction protocol has also been published.

Published protocols for **hyponatremias**:

- Rosner and Connor [61] – PMID: 29463598, DOI: 10.2215/CJN.13281117
- Yessayan, Yee [62] – PMID: 2479235, DOI: 10.1053/j.ajkd.2014.01.451

Published protocols for **hypernatremias**:

- Paquette, Goupil [63] – PMID: 27478592, DOI: 10.1093/ckj/sfw036

4.2 Acute hepatic failure or acute severe neurologic injury

Patients suffering from acute liver failure (ALF) and acute severe neurologic injury are associated with cerebral edema and increased intracranial pressure. Rapid clearance of plasma solutes/toxins, as in intermittent therapy, can also lead to intracranial pressure (probably by water shift from sudden plasma hypoosmolality) [64].

In ALF, both the KDIGO-AKI and European Associated for Study of Liver (EASL) guidelines recommend CRRT instead of IHD in patients with ALF [19, 65]. Furthermore, RRT may be initiated before usual thresholds since it has been associated with increased transplantation-free survival, probably by clearance of ammonia as hyperammonemia is associated with increased intracranial pressure [66, 67]. Some published protocols used very high doses of CVVHDF (effluent 90 mL/kg/h) [68]. Also, targeting mild hypernatremias (145–150 mmol/L) is recommended in high-risk patients (acute renal failure, ammonia >150 μmol/L, grade IV encephalopathy and use of vasopressor) [65]. Options are customized reinjection and dialysis fluids as discussed above or by adding hypertonic saline perfusion.

4.3 Vascular access

Vascular access should deliver stable and sufficient blood flow. In acute care setting, temporary dual-lumen central venous access is used for most patients. Ultrasound-guided catheter insertion is associated with higher successful placement, reduced attempts and time of procedure with less complications [69]. Choosing the site might have short-, mid- and long-term consequences.

Higher rates of catheter dysfunction are observed with femoral and left jugular site compared to right jugular, but no significant difference of urea reduction ratio or RRT downtime was observed [70]. More pneumothoraxes are observed with subclavian access [71].

Risks of catheter-related bloodstream infections and symptomatic deep-vein thrombosis are higher in femoral than subclavian and similar between jugular and femoral [71].

In patient with considerable risk of RRT dependence (mainly with pre-existing advanced CKD), large-bore venous subclavian catheter should be avoided since it can compromise future ipsilateral vascular access due to stenosis.

4.4 Disequilibrium syndrome

Dialysis disequilibrium syndrome is a rare, potentially fatal but usually preventable complication of RRT. The pathophysiology is still debated but commonly reports an

intracranial osmotic gradient due the rapid removal of urea and osmotic solute by RRT, leading to cerebral edema [72]. The large variation of symptoms and severity, from mild nausea to fatal cerebral herniation makes the diagnosis challenging. The syndrome is mostly reported in ESRD patients with advanced uremia who are initially started on high efficiency/ standard IHD prescription. Patients with ESRD (or with unknown kidney failure duration) should be treated with an adapted low-efficiency IHD prescription, for the first treatments, in order to minimize osmotic shift and risk of disequilibrium syndrome. A progressive increase in dialysate and blood flows and duration can therefore be implemented for the following treatments. Occurrence of this syndrome has also been reported in frail patients with septic shock and AKI even after repeated IHD sessions [73]. In patients who develop symptoms compatible to a disequilibrium syndrome during or quickly after an IHD session, management should include rapid treatment cessation and the administration of osmotic agents (mannitol, hypertonic saline) to quickly raise osmolality, despite the paucity of evidence. However, prevention should still be privileged. The overall risk of dialysis disequilibrium syndrome is lower with PIRRT, and notably reduced in patients treated with CRRT with standard dosing.

4.5 Managing IHD hypotension

Intradialytic hypotension is a common complication and can cause further ischemic injury to the recovering kidneys, thereby reducing the probability of renal recovery. Obligate intake in critically ill patients can be high due to nutritional needs and intravenous fluids, which leads to large net UF especially if IHD is performed thrice weekly [74].

Minimizing UF	• Avoidance of excessive inter-dialytic weight gain
	  ◦ Concentrated format of IV drugs
	  ◦ Reduce enteral free water
	  ◦ Reduce IV fluid
	  ◦ Optimize residual urine output with diuretics

Dialysis prescription	• Increase the session duration (to reduce the net UF per hour)
	• Increase the frequency to 4 or 5 IHD sessions per week
	• Optimize cardioactive electrolytes
	  ◦ Increase calcium dialysate concentration
	  ◦ Increase magnesium dialysate concentration
	• Minimize osmolarity shift during IHD:
	  ◦ Sodium modeling (gradual increase in sodium dialysate during treatment—may be associated with net sodium gain)
	• UF modeling (e.g., 50% of total UF during the first third of treatment time, then 50% over the last two-third)
	• Continuously adapt the UF rate to the residual blood volume
	• Cooling dialysate (may generate peripherical vasoconstriction and increase the MAP)

Pharmacologic interventions	• IV bolus of mannitol (rarely used) • IV bolus of hypertonic albumin • IV vasopressor (preemptive) • Oral midodrine (before or during treatment) • Adjust the timing of antihypertensive and/or antiarrhythmic medications and IHD treatment

Table 8.
Interventions to minimize intradialytic hypotension.

While patients in shock or with significant instability should be treated with PIRRT or CRRT (according to local availability), various interventions are associated with reduced risk of intradialytic hypotension during IHD (see **Table 8**). For most of them, despite being widely used in clinical practice, there is still a low level of evidence in context of AKI, as most evidence come from the ESRD population.

5. Conclusions

Renal replacement therapies delivered in ICUs are based on one or a combination of the same three basic principles of all extracorporeal blood-based treatments: diffusion, ultrafiltration and convection. Extensive literature has been published to guide clinicians for timing initiation, modality choice and dosing that could be summarized as:

- Timing: For most cases, a conservative approach of watchful waiting is recommended. Accelerated strategies have been associated with added resources, higher infections and RRT dependence without substantial benefits.

- Modality: Neither intermittent vs. continuous nor diffusion vs. convection have shown clear superiority. Hence, pragmatical considerations and mostly local expertise guide selection.

- Dosing: For intermittent therapy, ensuring volume balance, metabolic homeostasis and a delivered Kt/V $\geq$ 1.2/session or URR $\geq$ 67% seems adequate. For CRRT, prescribing an effluent volume of 25–30 mL/kg/h to ensure a 20-25 mL/kg/h delivered is recommended in most scenarios.

Significant differences are observed between guidelines and clinical practice regarding anticoagulation and timing of initiation. Forthcoming guidelines updates will further help to standardize approach in RRT prescription. However, data are scarce to guide termination of RRT; large prospective trials are needed before strong recommendations could be made. Finally, usual prescriptions could not be adequate for some patients with challenging scenarios, where an individualized strategies need to be applied.

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Conflict of interest

The authors declare no conflict of interest.

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References

[1] Mehta RL et al.. Spectrum of acute renal failure in the intensive care unit: The PICARD experience. Kidney International. 2004;**66**(4):1613-1621

[2] Hoste EA et al.. Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. Intensive Care Medicine. 2015; **41**(8):1411-1423

[3] Hsu RK et al.. Temporal changes in incidence of dialysis-requiring AKI. J Am Soc Nephrol. 2013;**24**(1):37-42

[4] Featherstone PJ, Ball CM. A brief history of haemodialysis and continuous renal replacement therapy. Anaesthesia and Intensive Care. 2019;**47**(3):220-222

[5] Claure-Del Granado R, Clark WR. Continuous renal replacement therapy principles. Seminars in Dialysis. 2021; **34**(6):398-405

[6] Basile C, Davenport A, Blankestijn PJ. Why choose high volume online post-dilution hemodiafiltration? Journal of Nephrology. 2017;**30**(2):181-186

[7] Hellman T, Uusalo P, Jarvisalo MJ. Renal replacement techniques in septic shock. International Journal of Molecular Sciences. 2021;**22**(19)

[8] Cote JM et al.. Intermittent convective therapies in patients with acute kidney injury: A systematic review with meta-analysis. Blood Purification. 2022;**51**(1):75-86

[9] Tandukar S, Palevsky PM. Continuous renal replacement therapy: Who, when, why, and how. Chest. 2019; **155**(3):626-638

[10] Section 2: AKI definition. Kidney Int Suppl (2011). 2012;**2**(1):19-36

[11] Venkataraman R, Kellum JA. Defining acute renal failure: The RIFLE criteria. Journal of Intensive Care Medicine. 2007;**22**(4):187-193

[12] Zarbock A et al.. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN randomized clinical trial. JAMA. 2016;**315**(20):2190-2199

[13] Gaudry S et al. Initiation strategies for renal-replacement therapy in the intensive care unit. The New England Journal of Medicine. 2016;**375**(2):122-133

[14] Barbar SD et al. Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. The New England Journal of Medicine. 2018; **379**(15):1431-1442

[15] Investigators S-A et al. Timing of initiation of renal-replacement therapy in acute kidney injury. The New England Journal of Medicine. 2020;**383**(3): 240-251

[16] Klein SJ et al. Biomarkers for prediction of renal replacement therapy in acute kidney injury: A systematic review and meta-analysis. Intensive Care Medicine. 2018;**44**(3):323-336

[17] Chen JJ et al. Furosemide stress test as a predictive marker of acute kidney injury progression or renal replacement therapy: A systemic review and meta-analysis. Critical Care. 2020; **24**(1):202

[18] Ostermann M et al. Recommendations on acute kidney injury biomarkers from the acute disease quality initiative consensus conference: A consensus statement. JAMA Network Open. 2020;**3**(10):e2019209

[19] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron. Clinical Practice. 2012;**120**(4): c179-c184

[20] Mehta RL et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. Kidney International. 2001; **60**(3):1154-1163

[21] Guerin C et al. Intermittent versus continuous renal replacement therapy for acute renal failure in intensive care units: Results from a multicenter prospective epidemiological survey. Intensive Care Medicine. 2002;**28**(10): 1411-1418

[22] Gasparovic V et al. Continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD)–what is the procedure of choice in critically ill patients? Renal Failure. 2003;**25**(5): 855-862

[23] Augustine JJ et al. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. American Journal of Kidney Diseases. 2004;**44**(6):1000-1007

[24] Vinsonneau C et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: A multicentre randomised trial. Lancet. 2006;**368**(9533):379-385

[25] Lins RL et al. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: Results of a randomized clinical trial. Nephrology, Dialysis, Transplantation. 2009;**24**(2): 512-518

[26] Schefold JC et al. The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): A prospective randomized controlled trial. Critical Care. 2014;**18**(1):R11

[27] Peters SA et al. Haemodiafiltration and mortality in end-stage kidney disease patients: A pooled individual participant data analysis from four randomized controlled trials. Nephrology, Dialysis, Transplantation. 2016;**31**(6):978-984

[28] Friedrich JO et al. Hemofiltration compared to hemodialysis for acute kidney injury: Systematic review and meta-analysis. Critical Care. 2012;**16**(4):R146

[29] Sigwalt F et al. Clinical complications of continuous renal replacement therapy. Contributions to Nephrology. 2018;**194**:109-117

[30] Palevsky PM et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. American Journal of Kidney Diseases. 2013;**61**(5):649-672

[31] Lowrie E, Lew N. The urea reduction ratio (URR). A simple method for evaluating hemodialysis treatment. 1992

[32] Daugirdas JT, Depner TA. A nomogram approach to hemodialysis urea modeling. American Journal of Kidney Diseases. 1994;**23**(1):33-40

[33] Jorres A et al. A European renal best practice (ERBP) position statement on the kidney disease improving global outcomes (KDIGO) clinical practice guidelines on acute kidney injury: Part 2: Renal replacement therapy. Nephrology, Dialysis, Transplantation. 2013;**28**(12): 2940-2945

[34] Network VNARFT et al. Intensity of renal support in critically ill patients

with acute kidney injury. The New England Journal of Medicine. 2008; **359**(1):7-20

[35] Ronco C et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. Lancet. 2000;**356**(9223):26-30

[36] Bouman CSC et al. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: A prospective, randomized trial. Critical Care Medicine. 2002;**30**(10):2205-2211

[37] Saudan P et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney International. 2006; **70**(7):1312-1317

[38] Tolwani AJ et al. Standard versus high-dose CVVHDF for ICU-related acute renal failure. J Am Soc Nephrol. 2008;**19**(6):1233-1238

[39] Investigators RRTS et al. Intensity of continuous renal-replacement therapy in critically ill patients. The New England Journal of Medicine. 2009;**361**(17): 1627-1638

[40] Schetz M. Anticoagulation in continuous renal replacement therapy. Contributions to Nephrology. 2001;**132**: 283-303

[41] Joannidis M, Oudemans-van Straaten HM. Clinical review: Patency of the circuit in continuous renal replacement therapy. Critical Care. 2007;**11**(4):218

[42] Fischer KG. Essentials of anticoagulation in hemodialysis. Hemodialysis International. 2007;**11**(2): 178-189

[43] O'Shea SI, Ortel TL, Kovalik EC. Alternative methods of anticoagulation for dialysis-dependent patients with heparin-induced thrombocytopenia. Seminars in Dialysis. 2003;**16**(1):61-67

[44] Kalpatthi R, Kiss JE. Thrombotic thrombocytopenic purpura, heparin-induced thrombocytopenia, and disseminated intravascular coagulation. Critical Care Clinics. 2020;**36**(2):357-377

[45] Lim W, Cook DJ, Crowther MA. Safety and efficacy of low molecular weight heparins for hemodialysis in patients with end-stage renal failure: A meta-analysis of randomized trials. J Am Soc Nephrol. 2004;**15**(12):3192-3206

[46] Joannidis M et al. Enoxaparin vs. unfractionated heparin for anticoagulation during continuous veno-venous hemofiltration: A randomized controlled crossover study. Intensive Care Medicine. 2007;**33**(9):1571-1579

[47] Goet E, Wentz B, Frank RD. Regional citrate anticoagulation protocol suitable for intermittent hemodialysis and post-dilution hemodiafiltration. Clinical Nephrology. 2021;**96**(2):90-95

[48] Kindgen-Milles D, Brandenburger T, Dimski T. Regional citrate anticoagulation for continuous renal replacement therapy. Current Opinion in Critical Care. 2018;**24**(6):450-454

[49] Bai M et al. Citrate versus heparin anticoagulation for continuous renal replacement therapy: An updated meta-analysis of RCTs. Intensive Care Medicine. 2015;**41**(12):2098-2110

[50] Zarbock A 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

[51] Zhang W et al. Safety and efficacy of regional citrate anticoagulation for continuous renal replacement therapy in liver failure patients: A systematic review and meta-analysis. Critical Care. 2019;**23**(1):22

[52] Uchino S et al. Discontinuation of continuous renal replacement therapy: A post hoc analysis of a prospective multicenter observational study. Critical Care Medicine. 2009;**37**(9):2576-2582

[53] Katulka RJ et al. Determining the optimal time for liberation from renal replacement therapy in critically ill patients: A systematic review and meta-analysis (DOnE RRT). Critical Care. 2020;**24**(1):50

[54] van der Voort PH et al. Furosemide does not improve renal recovery after hemofiltration for acute renal failure in critically ill patients: A double blind randomized controlled trial. Critical Care Medicine. 2009;**37**(2):533-538

[55] Shealy C, Campbell R, Hey J. 24-hr creatinine clearance as a guide for CRRT withdrawal: A retrospective study (abstr). Blood Purification. 2003; **21**:192

[56] Viallet N et al. Daily urinary creatinine predicts the weaning of renal replacement therapy in ICU acute kidney injury patients. Annals of Intensive Care. 2016;**6**(1):71

[57] Wu VC et al. Risk factors of early redialysis after weaning from postoperative acute renal replacement therapy. Intensive Care Medicine. 2008; **34**(1):101-108

[58] Hoorn EJ, Zietse R. Diagnosis and treatment of hyponatremia: Compilation of the guidelines. J Am Soc Nephrol. 2017;**28**(5):1340-1349

[59] Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. The New England Journal of Medicine. 1986;**314**(24):1535-1542

[60] Tandukar S et al. Severe hyponatremia and continuous renal replacement therapy: Safety and effectiveness of low-sodium dialysate. Kidney Med. 2020;**2**(4): 437-449

[61] Rosner MH, Connor MJ Jr. Management of Severe Hyponatremia with continuous renal replacement therapies. Clinical Journal of the American Society of Nephrology. 2018; **13**(5):787-789

[62] Yessayan L et al. Treatment of severe hyponatremia in patients with kidney failure: Role of continuous venovenous hemofiltration with low-sodium replacement fluid. American Journal of Kidney Diseases. 2014;**64**(2):305-310

[63] Paquette F et al. Continuous venovenous hemofiltration using customized replacement fluid for acute kidney injury with severe hypernatremia. Clinical Kidney Journal. 2016;**9**(4):540-542

[64] Lin CM et al. Intracranial pressure fluctuation during hemodialysis in renal failure patients with intracranial hemorrhage. Acta Neurochirurgica. Supplement. 2008;**101**:141-144

[65] European Association for the Study of the Liver. Electronic address, e.e.e et al. EASL clinical practical guidelines on the management of acute (fulminant) liver failure. Journal of Hepatology. 2017;**66**(5): 1047-1081

[66] Warrillow S et al. Continuous renal replacement therapy and its impact on hyperammonaemia in acute liver failure. Critical Care and Resuscitation. 2020; **22**(2):158-165

[67] Cardoso FS et al. Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure. Hepatology. 2018;**67**(2):711-720

[68] Slack AJ et al. Ammonia clearance with haemofiltration in adults with liver disease. Liver International. 2014;**34**(1): 42-48

[69] Rabindranath KS et al. Use of real-time ultrasound guidance for the placement of hemodialysis catheters: A systematic review and meta-analysis of randomized controlled trials. American Journal of Kidney Diseases. 2011;**58**(6): 964-970

[70] 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. Critical Care Medicine. 2010;**38**(4): 1118-1125

[71] Parienti JJ et al. Intravascular complications of central venous catheterization by insertion site. The New England Journal of Medicine. 2015; **373**(13):1220-1229

[72] Arieff AI. Dialysis disequilibrium syndrome: Current concepts on pathogenesis and prevention. Kidney International. 1994;**45**(3): 629-635

[73] Shaikh N, Louon A, Hanssens Y. Fatal dialysis disequilibrium syndrome: A tale of two patients. Journal of Emergencies, Trauma, and Shock. 2010; **3**(3):300

[74] Sharma S, Waikar SS. Intradialytic hypotension in acute kidney injury requiring renal replacement therapy. Seminars in Dialysis. 2017;**30**(6):553-558