Renal Replacement Therapy

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KEYWORDS

• Continuous renal replacement therapy • Timing • Dose • Citrate • Heparin

KEY POINTS

- Early renal support therapy may be more effective than late renal replacement therapy (RRT) to improve the outcomes of patients with acute kidney injury (AKI).
- Continuous RRTs should be preferred to intermittent therapies, mainly for hemodynamically unstable patients with AKI.
- The prescribed dose should be carefully evaluated for each patient and the delivered dose continuously monitored during the treatment.
- Citrate anticoagulation may be used for all patients without contraindications, particularly in high-expertise centers: heparin as a first choice is still feasible in nonbleeding patients, especially for units using RRT less frequently.

INTRODUCTION

Acute kidney injury (AKI) is a clinical syndrome characterized by a sudden decrease in kidney function resulting in accumulation of fluids, creatinine, urea, and other waste products.[1] The incidence of AKI widely ranges depending on the studied population and on the definition used. Through integration of the previous risk, injury, failure, loss, and end stage classification (RIFLE) and acute kidney injury network (AKIN) classifications, in 2012 the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines defined AKI as an increase in the serum creatinine level of 0.3 mg/dL (26.5 μmol/L) or more within 48 hours, a serum creatinine level that has increased by at least 1.5 times the baseline value within the previous 7 days, or a urine volume of less than 0.5 mL/kg of body weight per hour for 6 hours.[2]

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Approximately 5% to 7% of hospitalized patients develop AKI during their hospital length of stay; this incidence is further increased to 25% among critically ill patients in the intensive care unit (ICU).[1,3] A mortality rate more than 50% has been reported for patients with AKI and multiorgan failure.[3] In the absence of any effective pharmacologic therapies, AKI is usually managed through supportive treatments focused on optimization of fluid balance, prevention or treatment of electrolyte and acid-base disturbances, adjustment of the dosing of medications that are excreted by the kidney, and avoidance of secondary hemodynamic and nephrotoxic renal injuries. Beyond these conservative therapies, renal replacement therapy (RRT) is essentially the only effective method for the management of the critically ill patients with severe AKI.[1,3]

Even if it is currently a matter of debate if RRT optimization may reduce the mortality of patients with AKI,[4] it is reasonable to remark that avoidance of renal support in an oligo-anuric critically ill patient is not acceptable. Furthermore, an accurate evaluation of the most important issues on RRT, such as timing, modality, and dose of treatment, may be quintessential to improve renal and nonrenal outcomes in these patients.

TIMING OF INITIATION

The adequate timing for the RRT initiation in patients with AKI has not been exactly defined, so far. In current practice, the decision to initiate an RRT is often based on clinical or biochemical features of fluid overload and/or solutes imbalances (azotemia, hyperkalemia, severe acidosis).[2] However, these emergency indications characterize a rescue therapy for renal substitution in which the initiation of the treatment forestalls an imminent death. More reasonably, current practice should be based on the preemptive initiation of RRT, well before the development of these advanced complications; the aim is to early support the renal function during early phases of organ dysfunction instead of completely replacing kidney function in the late phases of organ insufficiency (**Table 1**).

An early onset of RRT is usually considered to be associated with an improved outcome in patients with AKI, even if no significant evidence supports this notion in current literature; however, indications of RRT and timing of RRT initiation are currently 2 of the fundamental questions listed among the top priorities in research in this field.[4] The levels of evidence that guide current practice primarily derive from retrospective and observational cohort studies and small, underpowered prospective trials.[5] With not-graded recommendations, the KDIGO guidelines currently suggest to emergently initiate an RRT when life-threatening changes in fluid, electrolyte, and acid-base

Table 1
Examples of possible indications for a late RRT aimed to completely substitute the kidney function and for an early renal support therapy aimed to promptly maintain homeostasis, to reduce organs dysfunction, and the further renal insult

RRT	Renal Support Therapy
Absolute Indications (Life-Treating Conditions)	**Relative Indications**
Acid-base control	Volume removal in patients with fluid overload
Ions alterations	Immunomodulation in sepsis
Solutes control	Allowing to reach an adequate nutrition support
	Blood purification during cancer chemotherapy

balance exist and to further consider, in the broader clinical context, the presence of conditions that can be modified with RRT for clinical decision making to start RRT (Fig. 1).[2]

The association between early RRT and survival was first suggested by case series with historical controls conducted in the 1960s and 1970s[6]; in these studies, levels of blood urea or blood urea nitrogen (BUN) were used to define the early and late start of dialysis. Similarly, a recent prospective multicenter observational cohort study performed by the Program to Improve Care in Acute Renal Disease (PICARD) analyzed the RRT initiation, defined according to the predialysis BUN concentrations. In this study, a late onset of RRT resulted statistically associated with an increased risk of death in a multivariate analysis.[7] Similar results were also obtained by other studies comparing early versus late onset of RRT when BUN or blood urea were considered to define them.[7]

Timing between the extracorporeal therapy initiation and the ICU admission is another issue that should be taken into account for classification purposes of early and late RRT. Data available from the Beginning and Ending Supportive Therapy (BEST) for the kidney registry[8] reveal that when timing was analyzed in relation to ICU admission, the late RRT was associated with greater crude mortality, covariate-adjusted mortality, RRT requirement, and hospital length of stay.[8]

As pointed out by Shiao and colleagues,[9] the staging of AKI at the RRT initiation, evaluated through clinical classifications, may be used to identify early and late treatments. In an observational study on surgical patients with AKI, these investigators have showed a statistical correlation between late RRT and worst renal and nonrenal outcomes.[9]

Although several studies have suggested a possible positive role of early RRT among patients with AKI, contrasting results are available in literature. In 2002 Bouman and colleagues[5] showed no differences for ICU or hospital mortalities and for renal recovery among patients treated with an early or late RRT. However, if cumulatively considered in systematic review or meta-analysis, independently by parameters used to define the onset, an early initiation of RRT seems to be associated with an improved outcome.[10] In a recent meta-analysis, including 15 unique studies published until 2010 on comparison between early and late initiation of renal

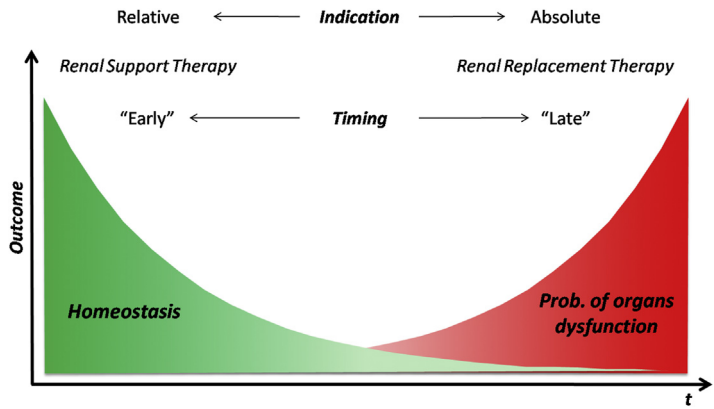

Fig. 1. If compared with a late RRT, an early renal support therapy seems to allow a prompt maintenance of systemic homeostasis, mainly if the treatment prescription fulfills the concept of *adequacy* and it is specifically oriented to patients' relative indications. As a consequence, the renal support therapy seems to be associated with a reduced probability of organ dysfunction and progression of kidney disease.

support, Karvellas and colleagues[10] have calculated an odds ratio for 28-day mortality of 0.45 associated with an early RRT. Similar results were obtained by Wang and Yuan[11] in 2012 in a meta-analysis encompassing data from 2955 patients; the results of this study have clearly demonstrated that an early initiation of both continuous and intermittent RRT may reduce the mortality of patients with AKI compared with late treatments.

Once identified, the conditions are potentially improvable through an early renal support therapy; once an early initiation of RRT has been decided, physicians must address the vascular access placement and the prescription phases in which the modality and the dose of the treatment should be decided.

VASCULAR ACCESS

A large-bore, double-lumen, noncuffed, nontunneled dialysis catheter is typically used for RRT in critically ill patients with AKI. The vein used for the catheter insertion should be chosen taking into account the patients' clinical characteristics (eg, the risk to evolve forward chronic kidney disease) and the instrumental features (eg, vein thrombosis or ratio between vein and catheter diameter). Ceteris paribus, the international KDIGO guidelines suggest a specific order for catheter placement (**Table 2**).[2]

The rationale is mainly based on the evaluation of the incidence of catheter-related complications (eg, infection or thrombosis) related to each site as well as taking into account the relative high frequency of chronic renal disease in patients with AKI, the long-term RRT requirements, and the need of a vascular access for chronic dialysis such us an artero-venous fistula.

The catheter should be inserted with the use of ultrasonographic guidance and with adherence to infection-control policies.[1] No evidences exist in literature about the most effective lumen dispositions within a dialytic catheter to reduce recirculation and improve clearance of the treatment.

TREATMENTS AND MODALITIES

The most adequate treatment of RRT for patients with AKI was not defined in literature for several years; the initial setting for RRT was usually chosen according to treatment availability in the center, technical skills of the operators, and patients' hemodynamic status.

Intermittent hemodialysis (IHD) was proposed as the treatment of choice for the management of critically ill patients with AKI. During IHD, solute and fluid control are mainly achieved by diffusion and ultrafiltration over a limited period of time (usually hours); consequently, major repercussions on patients' volemic status as well as a rapid change of fluid and solute components among different body compartments may all be expected during the treatment. Systemic hypotension occurs in approximately 20% to 30% of IHD treatments[12] as well as disequilibrium syndrome.[13] On the other

Table 2
In accordance with KDIGO guidelines, a specific order for catheter placement should be adopted if clinically acceptable and technically feasible

Options for Dialysis Catheter Placement	
First choice	Right jugular vein
Second choice	Femoral vein
Third choice	Left jugular vein
Last choice	Subclavian vein with preference for the dominant side

hand, continuous RRT (CRRT) includes a spectrum of treatments developed in the 1980s specifically for the management of critically ill patients with AKI who could not undergo traditional IHD because of hemodynamic instability or in whom IHD could not control the volume or metabolic derangements.[14] During CRRT, the lesser solute clearance and the slower removal of fluid per unit of time than IHD is thought to allow for better hemodynamic tolerance (**Table 3**).[1] Finally, experience with peritoneal dialysis (PD) in AKI is limited, except in the pediatric setting and in regions with limited resources.[2]

Although several randomized clinical trials have compared CRRT with IHD in patients with AKI, most of them have excluded hemodynamically unstable patients for the analysis. As a consequence, meta-analyses currently available on this topic have failed to demonstrate a clear superiority of continuous treatments over intermittent ones among critically ill patients with AKI.[15,16] Differently, in large observational studies including all patients receiving RRT, CRRT resulted an independent predictor of renal recovery among patients who survived to the acute illness.[2,17] Currently, CRRT is strongly suggested for hemodynamically unstable patients with AKI and for patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema in which large fluctuations of solute concentration and fluid shifts should be avoided.[2]

One last aspect may be relevant: if short-term hard outcomes are not impacted by RRT modality, it may not be the case for long-term ones. As a matter of fact, IHD has been suspected to cause long-term chronic kidney disease in patients with AKI. Two recent studies (a meta-analysis and a retrospective analysis) remarked that[18,19] compared with CRRT, IHD prescription for AKI treatment is significantly and strongly associated with a lower possibility of recovery of renal function. If these data were further confirmed, IHD should be abandoned for the treatment of AKI.

There are currently insufficient data to recommend a specific extracorporeal modality over another. In continuous veno-venous hemodialysis, solute removal is mainly achieved by diffusion; ceteris paribus, it is negatively related to the solute

Table 3
Advantages and disadvantages for IHD, prolonged, and CRRT

Treatments	Advantages	Disadvantages
IHD	• Rapid removal of toxins circulating solutes • Reduced downtime for diagnostic and therapeutic procedures • Reduced exposure to anticoagulation • Lower cost than CRRT	• Rapid fluid removal and frequent hypotension • Dialysis disequilibrium and risk of cerebral edema • Technically complex
Prolonged (e.g. sustained low-efficiency daily dialysis)	• Slower volume and solute removal than IHD • Faster solutes clearance than CRRT • Reduced downtime than CRRT • Reduced exposure to anticoagulation than CRRT	• Faster volume and solute removal than CRRT (increased risk for hypotension and disequilibrium syndrome in prone patients) • Technically complex
CRRT	• Continuous removal of toxin and solutes (avoid concentration rebound) • Hemodynamic tolerability • Easy control of fluid balance • Avoid disequilibrium syndrome • User-friendly machines	• Slower solutes clearance than IHD • Need for prolonged anticoagulation • Reduced possibility of patients' mobilization • Hypothermia • Increased costs than IHD

molecular weight. On the other hand, in continuous veno-venous hemofiltration (CVVH), solute removal is achieved by convection and strongly influenced by intrinsic properties of membrane as the ultrafiltration coefficient. The extracorporeal removal of small molecular weight molecules, as urea and creatinine, are of scarce interest during the early renal support therapy in the ICU; for this reason, many clinicians prefer to use CVVH for critically ill patients with AKI in the belief that convection can more effectively reduce the effects of the systemic inflammatory response syndrome by removing cytokines, most of which are middle molecular weight molecules. However, most controlled studies have not shown a clinically significant and sustained effect on cytokine plasma concentrations or an improvement in outcome. Therefore, the selection of a specific method is primarily based on institutional experience and preference.

DOSE

Because initial studies demonstrated a direct relationship between dose and survival, both for intermittent and continuous RRT,[20,21] great attention has been paid to identify the optimal dose of RRT in the last 10 years.

Dose may be represented by the efficiency (or clearance) of the treatment, which identifies the amount of blood cleared of waste products and toxins by the extracorporeal circuit over a given period of time.[22] The concept of clearance needs to be referred to a particular solute; urea, usually considered a uremic toxin marker, is most commonly used to quantify dose. Considering that CRRT is usually performed over several days or weeks, it is important to provide information about the total time during which the treatment clearance is delivered. The intensity of treatment is, thus, expressed as the product between the clearance and the effective time of treatment.[22] Including the downtime (the amount of time in which the treatment is interrupted), a significant difference could be found between the prescribed and the actual delivered doses. Finally, considering the whole pool of solute that needs to be cleared, it is possible to express the efficacy of the treatment as the ratio between the intensity and the volume of distribution of the marker solute.[22] All these concepts should be taken into consideration during the prescription phase of the treatment.

The demonstration of a direct correlation between dose and patients' outcomes prompted clinicians to carefully evaluate the initial RRT prescription. The *target prescribed dose* is the amount of clearance required for the specific patient in his or her specific clinical condition, and it represents the amount of clearance that the practitioner desires to actually deliver to the patient. During the treatment, considering the instantaneous flows in the extracorporeal circuit, a *current dose* may be identified. During downtime, when the machine treatment is stopped, the current dose is zero; the total amount of downtime during the treatment strongly influences the *delivered dose*.

In patients with AKI who are treated with CRRT in the ICU, the dose may be grossly estimated considering the effluent flow rate set in the CRRT machine[23] and then by indexing it over the patient body weight (ie, if a 60-Kg patient is treated with 1200 mL/h of isovolumic postdilution hemofiltration, the dose of its treatment may be indicated as 20 mL/kg/h). As for every simplification, with this method a relatively broad level of error should be accepted, especially when continuous predilution hemofiltration or continuous hemodialysis are delivered. Furthermore, it cannot obviously take into consideration the progressive decrease of membrane performance observed in the prolonged session (especially after the first 24 hours). As a matter of fact, the ease of this calculation may be very useful on the practical side.[24]

Several efforts have been made in the literature in order to define the most adequate dose; the idea is that CRRT delivery may imply a dose-dependent range, whereby the treatment efficiency does correlate with outcomes and a dose-independent range in which further improvements will not result in further benefits for these patients. Consequently, during the last decade, several attempts have been made in order to confirm the first dosage proposal (35 mL/k/h) that showed a direct correlation between CRRT efficiency and patients' outcomes.[21] However, the randomized evaluation of normal vs. augmented level (RENAL)[20] and the acute renal failure trial network (ATN)[25] studies seemed to definitely confute this evidence. These 2 large multicenter, randomized controlled trials did not show an improved outcome with a "more intensive dose" (40 and 35 mL/kg/h respectively) with respect to a "less intensive dose" (25 and 20 mL/kg/h respectively).[26] Based on these findings, the current KDIGO guidelines recommend delivering an effluent volume of 20 to 25 mL/kg/h for CRRT in patients with AKI.[2]

In addition, by comparing 2 multicenter CRRT databases, Uchino and colleagues[27] found that patients with AKI treated with low-dose CRRT were not associated with worse short-term outcomes compared with patients treated with the currently considered standard dose. In particular, comparing patients from The BEST study[3] and from The Japanese Society for Physician and Trainees Intensive Care (JSEPTIC) Clinical Trial Group,[28] the investigators observed no differences between groups of patient treated with a dosages of 14.3 mL/kg/h and 20.4 mL/kg/h.

Finally, considering that high-dose CRRT could lead to electrolyte disorders, removal of nutrients and drugs (eg, antibiotics), and high costs[29] and low-dose CRRT may expose patients to undertreatment resulting in worsening outcomes, seeking the range of an adequate treatment dose is currently a crucial issue. Nowadays, a delivered dosage (without downtime) between 20 and 35 mL/kg/h may be considered clinically acceptable.[27] In particular, a CRRT dosage prescription less than 20 mL/kg/h and more than 35 mL/kg/h may be definitely identified as the *dose-dependent range*, whereby the dialytic intensity is likely known to negatively affect outcomes (both caused by underdialysis and overdialysis). On the other hand, the prescriptions laying between these 2 limits can be considered as *practice-dependent*; variables such as timing, patient characteristics, comorbidities, or concomitant supportive pharmacologic therapies may have a significant role for patients' outcomes and should trigger a careful prescription and a closest monitoring of dose delivery (**Fig. 2**).

ANTICOAGULATION

Anticoagulation (and filter patency) is a fundamental issue strictly related to dialysis delivery and to the personalized prescription of an adequate CRRT treatment. Systemic and regional anticoagulation, as well as heparin grafting membranes, are potentially able to reduce the filter clotting and consequently the membrane fouling. Analyzing data from the PICARD study, Claure-del Granado and colleagues[30] evaluated the association of an anticoagulation strategy used on solute clearance efficacy and circuit longevity. In particular, the investigators showed that, if compared with heparin or no anticoagulation, the use of regional citrate for anticoagulation in CRRT significantly prolonged the filter life and increased its efficacy in terms of delivered dose.[30] De Vriese and colleagues[31] clearly demonstrated membrane dysfunction affected solute clearance during CRRT treatment. Unfortunately, this predictable mechanism is not simply quantifiable in clinical practice. When the membrane fouling occurs and clearance of urea (a 60-Da non–protein-bound molecule) decreases by 20%, the clearance of larger solutes may have already been impaired in the CRRT circuit life span.[32] In this context, if middle molecular weight molecules are the solute target to be removed, an accurate

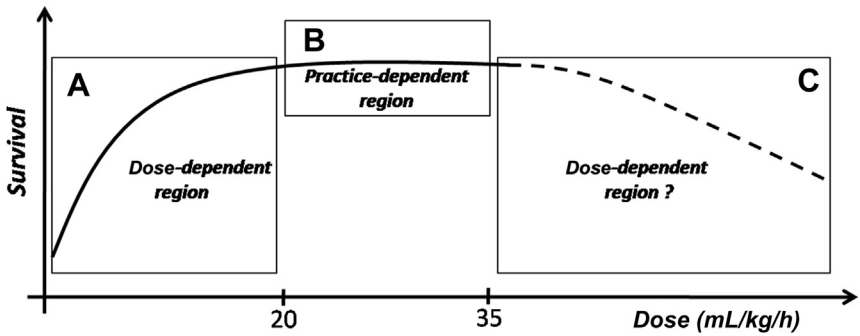

Fig. 2. Relationship between delivered dosage and patients' survival. Increasing the dosage to 20 mL/kg/h (*A*), the higher the dosage obtained during RRT, the higher the patient survival observed (dosage-dependent region). Further increase in dosage prescription to 35 mL/kg/h (*B*) may not influence patients' survival. On the other hand, other variables, such as the time of treatment, the optimization of blood perfusion, or drug adjustments, may influence the outcome (practice-dependent region). With further increase of prescribed dosage (more than 35 mL/kg/h) (*C*), patients may be prone to electrolyte disorders and removal of nutrients and drugs (eg, antibiotics), potentially reducing the survival.

anticoagulation should be performed also to ensure that an adequate sieving coefficient for these molecules is maintained for a long period of time.

Despite the most recent guidelines suggest using regional citrate anticoagulation in all patients without contraindications and with either high or low risk of bleeding, the administration of unfractionated heparin into the CRRT circuit remains the most used anticoagulation during CRRT. On the other hand, unfractionated or low-molecular-weight heparin, rather than other anticoagulants, are suggested for patients with a low risk of bleeding who present an absolute contraindication to citrate administration. Other anticoagulants are finally recommended in patients with heparin-induced thrombocytopenia; in particular, in these patients, all heparin must be stopped and direct thrombin inhibitors (such as argatroban) or factor Xa inhibitors (such as danaparoid or fondaparinux) rather than other anticoagulants or no anticoagulation should be adopted during RRT.[2]

SUMMARY

An early RRT aimed to support the residual kidney function during the early phases of organ dysfunction may improve the renal and nonrenal outcomes of patients with AKI with respect to late treatments. For critically ill patients in the ICU, and mainly for patients who require a slower fluid removal and a more gentle solute control, continuous treatments should be preferred. Vascular access placement as well as the treatment modalities should be carefully evaluated for each patient. The adequacy of the treatment should finally take into consideration the amount of clearance required for the treatment. The prescribed dose should be continuously evaluated for each patient, and the delivered dose should be monitored during the treatment. Mainly reducing downtime and membrane fouling, anticoagulation is able to reduce discrepancies between the prescribed and the actual delivered dose.

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