Continuous Renal Replacement Therapy Technology

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16.1 Introduction to CRRT Thechnology

Continuous renal replacement therapies (CRRTs) are a group of continuous therapies used in the intensive care unit (ICU) setting. In the past, CRRTs were seen reductively as therapies directed to the replacement of renal function only. In recent years, thanks to improvements in hardware and software technology and the introduction of more specific filters, the role of CRRTs has expanded beyond the replacement of renal function in the setting of severe acute kidney injury (AKI). For example, CRRTs are now used in the setting of less severe AKI associated with liver failure, heart failure, or sepsis.

In order to achieve optimum results with CRRT, it is necessary to have close cooperation between nephrologists and intensivists, as described in "Vicenza Model" [1]. In this model, the critically ill patient is followed in partnership by the nephrologist and intensivist so that they can prescribe and deliver *in a timely fashion* the best type of CRRT for the single patient's clinical condition.

16.2 CRRT in Renal Replacement Therapies

Extracorporeal blood purification (EBP) is a treatment in which a patient's blood is passed through a device where solute, toxins, and fluid are removed. EBP is primarily used in patients with renal failure but more than 20 years ago, it was suggested that EBP could remove inflammatory mediators from the plasma of patients with sepsis and improve pulmonary function [2]. Subsequently, surrogate clinical improvements with hemofiltration have been reported in animal and human studies, and cytokine removal from the circulation of animals and humans with sepsis has been demonstrated [3]. Shortly after, a survival benefit associated with higher dosages of continuous hemofiltration was reported [4]. With these advances, CRRT as a treatment for human septic shock was born. Since that time, many technological advances have occurred along with substantial changes in our basic understanding of sepsis and the inflammatory response. Newer filter and machine technologies now allow removal of inflammatory mediators via convection, diffusion, or adsorption. Of course, these inflammatory mediators are removed only from the plasma; the effects of CRRT on local tissue concentrations are less well understood. There are other ways by which CRRT may improve outcomes in sepsis: better acid–base control, better fluid balance and temperature control, cardiac support, protective lung support, brain protection with preservation of cerebral perfusion, bone marrow protection, and blood detoxification and liver support. Cardiac support can be achieved by the optimization of fluid balance, the reduction of organ edema, and the restoration of desirable levels of preload and afterload. By optimizing the patient's volume state and offering the ability to remove interstitial fluid, CRRT may provide additional support to the failing lung [5]. Blood purification may improve the encephalopathy of sepsis by removing uremic toxins and amino acid derivatives and correcting acidemia. Continuous therapies also offer the advantages of minimizing both osmotic shifts and hemodynamic insults that threaten cerebral perfusion pressure [6]. Through the removal of uremic toxins, blood purification also reverses immunoparalysis [7] and may improve bone marrow function such as erythropoiesis [8]. Thus, CRRT is increasingly recognized to be a multiple organ support therapy (MOST) .

16.3 Definition and Settings of CRRT

CRRT uses three processes for blood purification: convection (hemofiltration), diffusion (dialysis), and adsorption (onto the blood surface of the fibers of the filter). All may be combined in the one treatment. Improvements in filter and

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Table 16.1 Definitions and characteristic of the different continuous renal replacement therapy (CRRT) types

Treatment	Abbreviation	Type of process	Molecules target	Note
Dialysis	CVVHD	Diffusion	Low molecular weight If high cutoff membrane is used this treatment can remove high molecular weight molecules; it is important to be aware of possible albumin loss	According to the filter, cutoff is possible to enhance the removal of middle and high molecular weight molecules
Hemofiltration	CVVH	Convection	Middle/high molecules	According to the exchange of plasma water and the type of filter is possible to extend the molecules removal to the high molecular weight molecules (e.g., cytokines)
Hemodiafiltration	CVVHDF	Diffusion and convection	Middle molecules	This treatment is the combination of CVVHD and CVVH (the reinfusion can be done in pre- or post-dilution or both according to the software and hardware available)
Highflux dialysis	CVVHFD	Diffusion and convection (back filtration)	Middle molecules	This treatment is a subtype of CVVHDF. The convection is due to the filter characteristic of high flux that determines an ultrafiltration of plasma water in the first part of the filter and back filtration of the dialysate (reinfusion) in the second part of the filter
Pulse high volume	pHVHF	24 h cycles of HVHF followed by CVVH	High molecular weight molecules	Sequential treatment (HVHF followed by CVVH, this treatment in 24 h provides high dialytic dose in convection)

CRRT machine technology now allow great flexibility in adjusting the convection/diffusion/adsorption prescription for a given patient. For example, high cutoff filters are now available which allow removal (by diffusion) of molecules with a molecular weight just below that of albumin. Other high-flow filters permit plasma water exchanges of about 6–9 L per hour. High-adsorption membranes can increase removal of high molecular weight inflammatory molecules not otherwise removed by convection or diffusion.

Adequate vascular access is very important in facilitating the blood flow (Q_B) needed to deliver an appropriate dose and filtration fraction (FF). Arterial access for CRRT is very rarely used today. Hence, we have used a "veno-venous" classification of current CRRT therapies, as below (see also Table 16.1):

- CVVHD: Continuous veno-venous hemodialysis (diffusion)
- CVVHFD: Continuous veno-venous high flux hemodialysis (diffusion and convection due to back filtration thanks to the high flux filter used)
- CVVHDF: Continuous veno-venous hemodiafiltration (diffusion and convection)
- CVVH: Continuous veno-venous hemofiltration (convection)
- pHVHF: Pulse high volume hemofiltration (a combination of HVHF followed by CVVH, convection)

In all of the above treatments, it is possible to enhance blood purification by increasing the adsorption characteristics of the filter used. For example, it is possible to use a filter with the ability to filter out endotoxin.

pHVHF is a subtype of CRRT. In this type of treatment, used to treat patients with severe sepsis or septic shock, it is possible to provide a high diffusive dose during the day by the HVHF (Q_R: 4–9 L/h)—this facilitates removal of inflammatory cytokines. The HVHF is followed by CVVH (Q_R: 3–4 L/h) to maintain the clinical results during the night.

All these types of CRRT can be used in critically ill patients according to the target of molecules to be removed—allowing optimal treatment of critically ill patient with multiple organs dysfunction syndrome/multiple organs failure syndrome (MODS/MOFS).

Typical CRRT prescriptions are summarized in Table 16.2. These prescriptions are only guidelines and they can vary according to the local policy, the available software and hardware, and the experience and availability of nurses. For example, pHVHF treatment is not feasible if adequate staff time is not available to change the large number of bags required. The important point is to prescribe *on a daily basis* the best locally available form of CRRT for an individual patient.

The main options for anticoagulation are heparin, citrate, or none. Anticoagulation is discussed in detail in Chap. 15, where clotting of the extracorporeal circuit is a concern (e.g., when no anticoagulation is used). A number of strategies

Table 16.2 Renal and septic dose suggested in continuous renal replacement therapy (CRRT)

Treatment	Abbreviation	Type of process	Renal dose $Q_{B\ ml/min}/Q_{D\ L/min}/Q_{R\ L/min}$ Provide at least 25–30 ml/kg/h[a]	Septic dose[b] $Q_{B\ ml/min}/Q_{D\ L/min}/Q_{R\ L/min}$ Provide at least 35–40 ml/kg/h More than 40 ml/kg/h in septic shock[a]
Dialysis	CVVHD	Diffusion	150–200/2–3/–	150–200/6/–
Hemofiltration	CVVH	Convection	150–200/0/2[c]	150–200/0/3–4[c]
Hemodiafiltration	CVVHDF	Diffusion and convection	150–200/2–3/1[d]	150–200/6/2[d]
Highflux dialysis	CVVHFD	Diffusion and convection (back filtration)	150–200/2–3/0	150–200/6/0
Pulse high volume	pHVHF	24 h cycles of HVHF followed by CVVH	–	HVHF: 150–200/–/4–6 CVVH: 1 50–200/–/3–4[c]

[a] The dose must to be corrected depending on the percentage of infusion in pre-dilution that decreases the efficiency of diffusion and convection (post-dilution) due to the blood dilution pre-filter

[b] During treatments in sepsis or septic shock, it is recommended to use high flux filters or high cutoff membrane in order to enhance the removal of high molecular weight molecules such as cytokines. According to the membrane cutoff, the treatment can be switched to CVVHD in order to avoid albumin losses that occur during convection

[c] It is suggested to use a percentage between 100 and 60 % in pre-dilution according to: Q_B (Filtration fraction must to be below 15–20 %), possibility to provide anticoagulation (decreasing FF), monitor type, clinical conditions

[d] Pre or post-dilution according to the filtration fraction (FF). Pre-dilution if FF is more than 20 %

can be used: increasing the blood flow to maintain the FF below 15–20 %, increasing the pre-dilution of replacement fluid in CVVH to 80–100 % and in CVVHD mode, using dialysis more than filtration.

16.4 Indications to Start CRRT

Currently, the use of renal replacement therapy (RRT) in patients with AKI is extremely variable and is based primarily on experience, habits, and local resources. Indications to start CRRT in isolated AKI are "classical indications" and are summarized in Table 16.3. In practice, patients with AKI in the ICU setting often have MODS/MOFS—earlier initiation of CRRT may be beneficial in such patients. There is increasing evidence that fluid overload associated with AKI contributes significantly to morbidity and mortality and this concern may prompt "early" initiation of CVVH, especially in children or in patients after cardiac surgery. There is ongoing interest in developing biomarkers of early AKI (such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase associated lipocalin (NGAL))—such biomarkers might facilitate appropriate earlier initiation of CRRT in certain patients.

Initiation of CRRT results in a considerable escalation in both the complexity and cost of care. While CRRT is extensively used in clinical practice, there remains uncertainty about the ideal circumstances of when to initiate RRT and for what indications. The process of deciding when to initiate RRT in critically ill patients is complex and is influenced by numerous factors, including patient-specific and

Table 16.3 Classical indications to start continuous renal replacement therapy (CRRT) in isolated acute kidney injury (AKI)

Indications	Characteristics	Absolute (A)/relative (R)
Metabolic abnormality	BUN > 76 mg/dl	R
	BUN > 100 mg/dl	A
	K > 6 mEq/L	R
	K > 6 mEq/L with ECG abnormalities	A
	Dysnatremia	R
	Mg > 8 mEq/L	R
	Mg > 8 mEq/L with anuria and absent deep tendon reflexes	A
Acidosis	pH > 7.15	R
	pH < 7.15	A
	Lactic acidosis related to metformin use	A
Anuria/oliguria	RIFLE class R	R
	RIFLE class I	R
	RIFLE class F	R
Fluid overload	Diuretic sensitive	R
	Diuretic resistant	A

clinician-specific factors and those related to local organizational/logistical issues (Fig. 16.1). Studies have shown marked variation between clinicians, and across institutions and countries. As a consequence, analysis of ideal circumstances under which to initiate RRT is challenging [9]. Early initiation probably improves outcomes. Relative versus absolute indications to start CRRT are more important overall in patients with MODS or MOFS or sepsis. RIFLE (risk, injury, failure, loss, and end-stage kidney staging criteria) class can be used as a surrogate of timing and can be used to follow the clinical trend and trajectory of the patient.

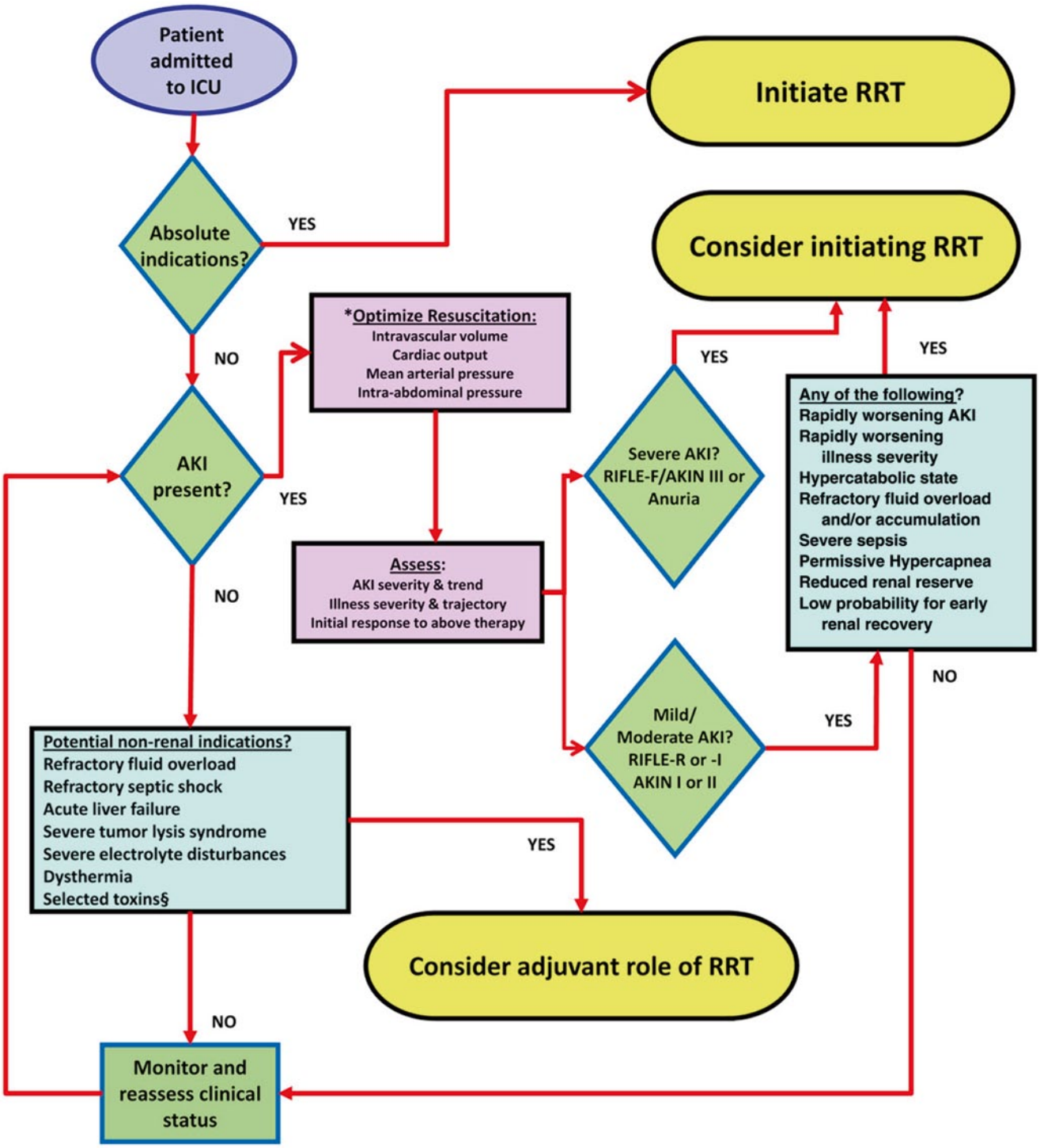

Fig. 16.1 Treatment algorithm. (From: Bagshaw et al. [9])

16.5 Dose of CRRT

It is important to know for every treatment the *real* dose delivered to the patient as opposed to the *prescribed* dose [10]. Often, due to downtime (alarms, problems with vascular access, patient being moved to radiology, etc.), the real dose is significantly lower. Another factor impacting on adequate prescribed and delivered dose of CRRT is underestimation of the patient's weight. This is likely to be a common problem as the majority of ICU patients are in a state of hyperhydration [11] but remain very difficult to weigh.

More CRRT seems to improve outcomes but only until up to a certain point [12]. Optimal dose seems to be between 25 and 35 ml/h/Kg in most patients. Higher doses are sometimes used in septic and hypercatabolic patients. In the case of septic patients, the idea is to remove noxious mediators of inflammation (the benefits of this approach have not yet been well validated in clinical trials). Thus, some have advocated two types of CRRT prescriptions: CRRT at "renal dose" and CRRT at "sepsis dose." Urea kinetics have not been well validated in the AKI setting but in practice measures such as K, Kt, and Kt/V are often used.

16.6 Conclusions

CRRTs are a group of continuous therapies that are now widely used in critical care. Today, thanks to improved hardware and software technology we have a wide spectrum of treatments that can be used during AKI in critically ill patients not only to support and substitute the renal function but also to protect, restore, and maintain the function of other organs. In this paradigm, CRRT has the role of MOST. The process of deciding when to initiate RRT in critically ill patients is complex and is influenced by numerous factors, including patient-specific and clinician-specific factors and those related to local organizational/logistical issues. Relative indications are more important to start CRRT when AKI is a part of a more complex clinical situation of MODS or MOFS. It is important to ensure that the prescribed and delivered (real) dose of CRRT is adequate for a given patient. In order to achieve optimal results with the various forms of CRRT, it is necessary to have close cooperation between nephrologists and intensivists, as described in the "Vicenza Model."

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