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# Introductory Chapter: Principles and Methods of Acute Therapies

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<http://dx.doi.org/10.5772/intechopen.82503>

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## 1. Introduction

Continuous renal replacement therapy (CRRT) is a slow and smooth continuous extracorporeal blood purification. CRRT is usually implemented over 24 h to several days with an aim of gentle removal of fluid overload and excess uremic toxins, where the continuous filtration simulates the continuity of kidney functions. It is usually indicated in critically ill and hemodynamically unstable (adult and pediatric) patients with acute kidney injury (AKI) and/or multiorgan failure, sepsis/shock, acute brain injury, or other causes of increased intracranial pressure or generalized brain edema in intensive care unit (ICU), where such patients cannot tolerate the relatively fast removal of fluids (and solutes) by conventional hemodialysis (HD).

Continuous renal replacement therapy witnessed significant improvement since the technique was implemented by Peter Kramer of Göttingen (Germany) in 1977 [1]. The technique was established when Kramer was trying to introduce a catheter into the femoral vein for initiating HD. Accidentally, the catheter went into the femoral artery, when Kramer realized the value of the arterial-venous pressure difference (i.e., blood flow driven by mean arterial pressure) in providing ultrafiltration and convection/hemofiltration concept and the need of replacement solutions, which was known as “continuous arterio-venous hemofiltration (CAVH)”. Later, in 1987, Peter Robert Uldall (Toronto, Canada) [2] introduced the “continuous veno-venous hemofiltration (CVVH)” by providing a pump and replacing the need of the arterial pressure, a technique that avoided (a) the potential risks and complications of puncturing a major artery (e.g., infection, distal thrombosis, and disconnection/bleeding) and (b) the possible slow or altered blood flow rates due to frequent hypotension in critically ill or shocked patients.

Continuous renal replacement therapy is based on four main physiologic principles. These are (a) diffusion, (b) ultrafiltration, (c) convection, and (d) adsorption. In clinical practice, there is more than one principle implemented in achieving the goals of required treatment (e.g., diffusion, ultrafiltration, and convection). CRRT can be performed in one or more of the following four modalities: (1) slow continuous ultrafiltration (SCUF), (2) continuous veno-venous hemofiltration (CVVH), (3) continuous veno-venous hemodiafiltration (CVVHDF), and (4) continuous veno-venous hemodialysis (CVVHD). Other therapeutic modalities that can be used in conjunction with CRRT include therapeutic plasma exchange and hemoperfusion/adsorption.

The performance and delivery of CRRT depends on an efficient vascular access (e.g., internal jugular or femoral vein), specifically designed HD machines and high-flux membranes/dialyzers. Synthetic and biocompatible membranes/dialyzers are capable of efficiently removing excess fluids and clearing small and middle-larger-size uremic toxins [3], and some have high adsorptive affinity to proteins, endotoxins, and inflammatory mediators (e.g., cytokines) [4]. Following high convective volume of ultrafiltration, the replacement/substitution solutions, which can be infused before (predilution) or after the dialyzer (postdilution), are sterile physiological fluids [5] that consist of balanced electrolyte solutions of either lactate or bicarbonate base, which resembles the composition of the ultrafiltrate (but without the removed uremic wastes). The long duration of this extracorporeal blood purification technique, where the blood is in direct contact with blood tubes and dialyzer membrane for longer period than conventional HD, requires continuous anticoagulation to prevent clotting and extend the circuit life. Heparin has been widely used, but it has been associated with increased risk of bleeding. Regional citrate anticoagulation (RCA) is the more preferred and recommended method of anticoagulation, where it has been associated with significantly less bleeding [6], less blood transfusion [7], and extended life of the extracorporeal circuit [8].

Initiation of CRRT is indicated in patients with (a) hemodynamic instability/shock, (b) diuretic-resistant fluid overload, (c) severe metabolic acidosis ( $\text{pH} < 7.2$ ), and (d) refractory hyperkalemia ( $\text{K}^+ > 6.5$ ). CRRT has also been considered in drug toxicity and in prevention of radiocontrast-induced nephropathy [5]. The goals of CRRT include (i) clearance of uremic toxins, (ii) correction of electrolytes disturbance, (iii) acid-base balance, (iv) hemodynamic stabilization, (v) fluid balance, (vi) nutritional support, and (vii) removal and/or modulation of inflammatory mediators in septic patients. The success of CRRT depends on the prescribed and achieved dose of replacement/substitution fluids, treatment duration, type of dialyzer, and method and dose of anticoagulation, in addition to a well-established CRRT management protocol (e.g., type, size, length, placement and care of central lines, indications, when to start, and when to stop CRRT). Furthermore, the delivery and performance of CRRT requires well-trained medical and nursing staff.

Despite the general safety and valuable advantages, CRRT has some limitations. These include the requirement of a large-bore central vascular access (a risk source of infection), hypotension (decreased organ perfusion), continuous anticoagulation (inappropriate doses or inadequate control of anticoagulants may lead to bleeding, which is associated with a decrease in hemoglobin level and/or drop in blood pressure and possible need of blood transfusion, or clot formation that is associated with short circuit life, interruption of prescribed dose,

inadequate therapy, and increased cost), electrolyte imbalance (potassium, phosphorus, and magnesium), drug removal (e.g., antibiotics), and immobilization of the patient for prolonged periods [9].

However, most of these limitations can either be prevented or be controlled [10]. A drop-in blood pressure, though much less encountered than in intermittent HD, is usually compensated for by the patient or, in some cases, requires inotropic support to maintain effective mean arterial pressure. Furthermore, CRRT prescription can be modified at any time during treatment based on hemodynamic situation. A well-established protocol of RCA, for example, can help in maintaining the patency of the extracorporeal circuit for a longer period and in avoiding uncontrolled bleeding. Implementation of infection control policies and procedures, including aseptic techniques, can help in preventing or reducing the vascular access catheter-associated infection. Regular monitoring and assessment of electrolytes and blood gases and the selection of appropriate replacement solutions (e.g., bicarbonate-based buffer and required composition of electrolytes and supplements) not only can help in replacing plasma volume removed by ultrafiltration but can also ensure the correction of electrolyte and acid-base imbalances. Drug removal in CRRT depends on its molecular weight, the sieving coefficient, and the degree of protein binding. Drugs with significant protein binding are removed minimally. Some drugs may be removed by adsorption to the membrane. Most of the commonly used drugs, including antibiotics, require monitoring and dose adjustments [11]. Finally, CRRT patients are prone to hypothermia due to the significant volume of blood that is circulated outside the body, and the significant volumes of the substitution and dialysate fluid used. Although newer CRRT machines are equipped with blood warmers that can bring both dialysate and substitution fluids to 37°C (98.6°F), a close monitoring of body temperature of patients is recommended especially when larger volumes of substitution and dialysate solutions are used.

## 2. Conclusions

Severe acute kidney injury, especially when it is caused or associated with sepsis, carries increased risk of progression to chronic kidney disease and end-stage renal failure. In addition, it is associated with prolonged hospitalization, financial burden, and increased mortality rate. Critically ill patients with acute kidney injury and/or multiorgan failure in ICU require special modalities of therapies to ensure hemodynamic stability, euvolemic status, and acid-base and electrolytes balance with an aim of speeding up renal recovery and avoiding deleterious consequences. CRRT stands as a valuable supportive therapeutic modality for such patients. CRRT management includes specific indications, adequate prescription, timing of initiation and termination, proper anticoagulation, and removal of endotoxins and inflammatory mediators in different settings of associated sepsis.

## Disclosures

No funding sources and relevant disclosures to declare.

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