CHAPTER 174

Clinical Effects of Continuous Renal Replacement Therapies

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OBJECTIVES

This chapter will:

1. Describe different renal replacement strategies and their clinical effects on critically ill patients.
2. Review the benefits and side effects of continuous renal replacement therapies.
3. Compare the clinical effects of continuous therapies with those of intermittent and hybrid techniques.

Different renal replacement therapy (RRT) modalities and prescriptions will result in various clinical effects in individual critically ill patients. These effects can be acknowledged either as desirable clinical outcomes of the dialytic treatment or as undesirable side effects that should be avoided. With extracorporeal RRT, an obvious antagonism between (s)low-efficiency continuous therapies and high-efficiency intermittent treatments has been growing since Kramer et al. first introduced the idea of continuous hemofiltration 20 years ago.[1]

The kidneys remove water, various solutes, and non-volatile acids, thereby maintaining homeostasis; they also metabolize inflammatory mediators and excrete administered drugs or their metabolites. The first point to be addressed, then, in examining clinical effects of RRT and their impact on the altered homeostasis of critically ill patients is to evaluate whether the optimal treatment should closely mimic the 24 hours lasting functions of the kidneys or if renal support can be managed safely on an intermittent basis, as with other therapies administered as repeated boluses.

FLUID REMOVAL

Continuous RRT (CRRT) slowly and continuously removes fluid, approximating ongoing urinary output, whereas intermittent hemodialysis must extract up to 2 days' worth of administered fluid plus excess body water, which may be present in the anuric patient as a result of a pathologic process, in one relatively brief session. The intravascular volume depletion associated with intermittent hemodialysis (IHD) is due to the high rate of fluid removal required and the transcellular and interstitial fluid shifts caused by the rapid dialytic loss of solute.[2] The major consequence of rapid fluid removal is hemodynamic instability. Critically ill patients need continuous volume infusions: blood and fresh frozen plasma, vasopressors and other continuous infusions, and parenteral and enteral nutrition, which must be delivered

without restriction or interruption even in hypercatabolic patients. In the clinical setting of anuria, providing such infusions carries a constant risk for fluid overload and high daily ultrafiltration requirements. Examples of patients in whom sudden intravascular volume shifts may be catastrophic are the patient with acute respiratory distress syndrome (ARDS), the septic patient who is becoming refractory to vasopressors, and the patient with cerebral edema. Furthermore, all critically ill patients tolerate hypotension poorly, with a definite risk of cardiac arrest, particularly if they are already inotrope dependent. Indeed, the damaged kidneys, which have temporarily lost pressure-flow autoregulation, also may be threatened with fresh ischemic lesions occurring with each hemodialysis session,[3] leading to a delay in renal recovery. Patients should be assessed actively for the final target of fluid removal and must be reassessed carefully and frequently, whichever method is used to achieve this. Setting the rate of removal requires consideration of the severity of complications of fluid overload, anticipated fluid intake, expected rate of vascular refilling, and cardiovascular tolerance to transient reduction in intravascular volume resulting from ultrafiltration. Although many tools can be used to predict the response to fluid administration (such as pulse pressure variations or passive leg raising), there are no good indicators to predict tolerance to fluid removal. A fluid removal trial (reverse fluid challenge) is therefore often the only option while assessing cardiovascular tolerance with the available hemodynamic tools.

The importance of fluid balance management is enhanced in the specific category of patients with decompensated heart failure. In fact, it is just these patients who may well respond positively to continuous ultrafiltration with a rise in cardiac index, while avoiding a fall in arterial pressure, owing to a beneficial change in preload optimizing myocardial contractility on the Starling curve.[2] In many instances, congestive heart failure not responding to conventional therapy now can be treated successfully in this way.[4]

In critically ill children, the correction of water overload is considered a priority. It has been shown that restoring adequate water content in small children is the main independent variable for outcome prediction.[5,6] This concept is much more important in critically ill neonates, in whom a relatively larger volume of fluid must be administered to deliver an adequate amount of drug infusion, parenteral or enteral nutrition, and blood derivatives.[7] Several retrospective and observational studies also have confirmed the importance of fluid overload as an independent variable affecting adult critically ill patients' mortality.[8,9] It is possible that starting ultrafiltration when a lower degree of fluid accumulation has been reached and targeting a negative fluid balance in the first treatment hours may improve outcome. However, provided no prospective data, it is impossible to recommend a priori at what level of fluid gain RRT should be started or the net ultrafiltration rate that should be prescribed. These factors should be tailored according to individual patient requirements.

SOLUTE REMOVAL, ACID-BASE CONTROL, AND ELECTROLYTE BALANCE

An attribute of IHD often quoted by proponents is that it is highly efficient at clearing small solutes such as urea and electrolytes. In fact, this is a false argument and a disadvantage. The primary rationale for using continuous therapy is to maintain a more physiologic, constant removal

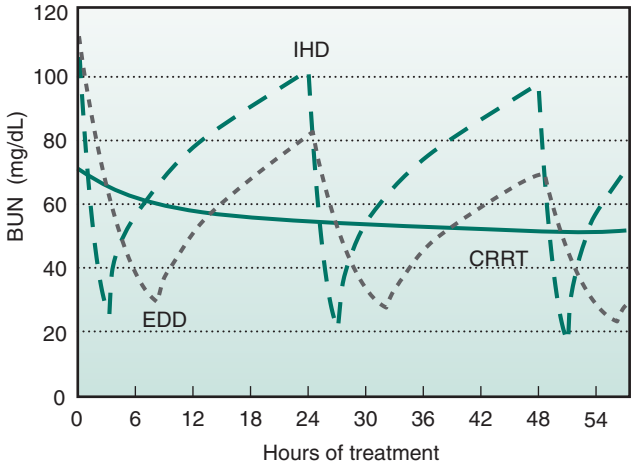

FIGURE 174.1 Example of changes in mean blood urea nitrogen (BUN) concentration during continuous renal replacement therapy (CRRT), intermittent hemodialysis (IHD), and extended daily dialysis (EDD) during 2 days of therapy.

of fluid and solute, electrolytes, and other molecules. In the process, the cumulative clearance of urea and creatinine by a continuous method is significantly superior to that achieved by intermittent hemodialysis applied up to four times per week, even in septic patients. Indeed, intermittent hemodialysis sessions six times per week would be required to achieve the same uremic control[10] (Fig. 174.1).

The clinical impact of these physiologic aspects of solute control have not been elucidated fully. Nevertheless, several facts have been established in patients with end-stage renal failure. In the National Cooperative Dialysis Study, rates for indices of morbidity, including cardiovascular events and hospitalization rate, were higher in the group of patients whose target average urea was 100 mg/dL (36 mmol/L) than in the patients whose target urea was 50 mg/dL (18 mmol/L).[11] An effect of uremia relevant to intensive care is immunosuppression, with impaired phagocytosis and defective lymphocyte and monocyte function. Uncertainty regarding the relative contributions of uremia, malnutrition, and bioincompatible membranes is evident from previous studies.[12] Work must be done specifically in patients with acute kidney injury (AKI). It is possible that dose prescription for solute control has to be tailored on a patient-to-patient basis. The trial by Ronco et al. showed an adequate dialytic dose (metabolic control) at a continuous venovenous postdilution hemofiltration of 35 mL/kg per hour compared with a hemofiltration rate of 20 mL/kg per hour in 425 critically ill patients with AKI.[13] However, recently, studies in the Japanese population have shown that CRRT dose even lower than recommended by the KDIGO default dose (20–25 mL/kg/hr)[14] can achieve adequate control of serum urea concentrations.[15]

Nonvolatile acids, normally excreted by the glomerulus and renal tubules, cross hemofilters by diffusion and convection. Once again, the main concern with IHD is the physiologic effects of rapid clearance, particularly in critically ill, catabolic patients with accelerated acid production. Acid accumulation may interfere with normal myocardial electrical conduction and contractility. Rapid delivery of bicarbonate during dialysis may exacerbate intracellular acidosis, although this point is still controversial. Bicarbonate is the standard buffer used with intermittent hemodialysis; a number of buffers have been used with CRRT—most commonly, lactate and sodium bicarbonate. Acetate, of

course, should not be used because of its vasodilating, hypoxia-inducing, and cytokine- and complement-activating properties.[16] No clinical difference has been observed in the relative merits of lactate versus bicarbonate buffering, apart from the need to avoid lactate buffering in patients with fulminant hepatic failure.[17] The essential point is that both can be delivered with continuous therapy.

One specific comment concerns the difference between continuous venovenous hemofiltration (CVVH) and all other techniques, including dialysis and the use of diuretics. In all pharmacologic and dialytic techniques, the removal of sodium and water cannot be dissociated, and the mechanisms are correlated strictly. In particular, the diuretic effect is based on a remarkable natriuresis, whereas ultrafiltration during dialysis may result in hypo- or hypertonia, depending on the interference with diffusion and removal of other molecules such as urea and other electrolytes. In such circumstances, water removal is linked to other solutes in proportions that are dependent on the technique used. In CVVH, the mechanism of ultrafiltration produces a fluid that is very similar to plasma water except for a minimal interference resulting from Donnan effects. In such a technique, ultrafiltration is basically iso-osmotic and isonatremic, and water and sodium removal cannot be dissociated, with sodium elimination linked to the sodium plasma water concentration. During hemofiltration in general, the ultrafiltrate composition is definitely similar to plasma water, but the sodium balance can be affected significantly by the sodium concentration in the replacement solution. Hence, sodium removal can be dissociated from water removal in CVVH, thereby allowing definitive manipulation of the sodium pool in the body. This effect cannot be achieved with any other technique. The advantage is that not only plasma concentrations but also the electrolyte content in the extracellular and possibly intracellular volume can be normalized.[18]

The increased solute clearance achieved by CRRT may cause unwanted losses of amino acids, vitamins, catecholamines, antibiotics, and other compounds.[19] Severe hypophosphatemia (<1.0 mg/dL; <0.32 mmol/L) occurs in about half of ICU patients, and CRRT can contribute to this deficiency, especially when high intensity treatment is prescribed.[19] Hypophosphatemia is associated with respiratory and cardiac depression, immune dysfunction. This condition should be prevented or adequately treated with supplementation, especially in CRRT patients.[19] Phosphate-containing CRRT replacement fluids are now available that protect against hypophosphatemia. Hypomagnesemia also can occur during CRRT, because the replacement fluid also lacks magnesium.

One of the most active areas of research in intensive care in recent years has involved the modulation of the septic response with the aim of reducing the persistently high mortality in this group of patients. One avenue has been to investigate the potential benefit of CRRT in the sepsis syndrome. Although skepticism counters the idea that any improvement is due to nonspecific changes such as fluid removal or lowering the core temperature in febrile patients, some evidence suggests that cytokines and complement, among other mediators, are cleared from the blood by convection or adsorption, or both, onto high-flux synthetic hemofilter membranes. Whether this removal translates to significant reversal of end-organ damage by inflammatory mediators and results in a reproducible reduction in mortality or morbidity is still being elucidated. However, there is little doubt that use of biocompatible membranes is important and that mediator removal, to be beneficial, must be continuous and convective, not intermittent and diffusive.[20] However, recent data definitely showed that an "average" extracorporeal blood purification, conducted with high dialytic dose, is not beneficial in the septic patient.[21] Whether this lack of effect is due to inadequate mediators control or to a wrong pathophysiologic concept (septic patients do not change their clinical course by simply modulating circulating mediators) is currently unknown. Some research is being conducted to better discriminate patients who may be responding to high-dose CRRT from those who do not.[22]

SIDE EFFECTS OF CONTINUOUS RENAL REPLACEMENT THERAPY

Although considerable attention has focused on the perceived benefits of CRRT, less emphasis has been placed on the possibility that this modality may carry increased risk. As a continuous extracorporeal therapy, CRRT often requires continuous anticoagulation, which can increase bleeding risk. Conversely, clotting of the extracorporeal circuit also occurs frequently with CRRT, which potentially may contribute to blood loss, thereby exacerbating anemia in critically ill patients. The increased solute transfer associated with the use of CRRT may enhance removal of amino acids, vitamins, catecholamines, and other solutes with a beneficial function in critically ill patients.

Continuous therapies must be continuous to work. How many treatments really last more than 18 to 20 hours per day? Down time because of filter-circuit-catheter clotting, circuit change, frequent replacement, or substitution of solution bags, and patient mobility (surgery, diagnostics) should be monitored carefully; any of these factors may have significant impact on dialysis dose.[23] Also of concern are recent reports that technical problems with the delivery of CRRT, including machine malfunction, medication errors, and compounding errors, may contribute to increased patient morbidity and mortality. Detection of safety problems and adverse events is particularly difficult when the rates of expected morbidity and mortality are already high in the population undergoing a procedure, as is the case with CRRT in critically ill patients with AKI.

Currently, few available studies in the nephrology literature provide substantive information on the safety or adverse effects of CRRT or intermittent hemodialysis in the critically ill population. After the introduction of new technology and devices into medical practice, a natural tendency is to assume that the novel therapeutic approach is providing benefit. This is especially the case when a therapy is applied to a critically ill patient 24 hours a day and becomes part of the typical equipment of an intensive care unit (ICU) bed. The level of attention from ICU caregivers probably is superior when a dedicated dialysis nurse administers conventional hemodialysis for few hours during a day shift. Nonetheless, a new generation of dedicated CRRT machines has been released recently with strict safety features and the possibility of a broad range of prescriptions. In any case, the ideal therapy still does not exist, and specific ICU staff training is mandatory before the routine use of such modern monitors. There will never be a solution to the unwise use of a perfect system.[24]

A specific subchapter of side effects should be related to renal recovery. Recent reports have suggested a benefit for CRRT with respect to recovery of renal function.[25,26] Compared with CRRT, initiation of IHD in critically ill adults with AKI is associated with a higher likelihood of chronic dialysis. Other studies already have presented such information[27,28]: chronic renal insufficiency at either death or

hospital discharge was diagnosed in 17% of patients whose initial therapy was conventional hemodialysis versus only 4% of patients whose initial therapy was CRRT ($p = .01$). Patients receiving a minimum exposure of 25 hours of CRRT and two treatments of 3 hours or more each of conventional hemodialysis, 92% of the patients undergoing CRRT had complete recovery of renal function, versus 59% of those receiving conventional hemodialysis ($p < .01$). Finally, a significantly higher percentage of patients crossing over from conventional hemodialysis to CRRT had complete recovery of renal function compared with those crossing over in the opposite direction (45% vs. 7%; $p < .01$). This evidence has not been confirmed prospectively nor retrospectively,[29] but clinicians should be aware of this additive risk occurring with intermittent prescriptions.

Another important (potential) CRRT side effect is relative to the application of citrate anticoagulation (better detailed elsewhere).

Sodium citrate forms a complex with ionized calcium, removing this central component from coagulation pathways. Citrate is infused before the patient's blood enters the CRRT circuit. Extracorporeal calcium concentrations below 0.35 mmol/L are usually sufficient for regional anticoagulation, requiring citrate doses of approximately 4 to 6 mmol/L blood. A substantial amount of calcium citrate complexes quickly passes the filter membrane and is lost in the effluent volume. The remaining calcium citrate enters the systemic circulation and is metabolized in the liver, muscle, and kidney, producing three molecules of bicarbonate for each molecule of citrate. Additional calcium infusions compensate for extracorporeal losses in the circuit, maintaining the patient's normal calcium levels. Caution with RCA should be exercised in patients with severe liver failure.[19] To monitor magnesium is very important because citrate chelates magnesium. First, it is mandatory to know and understand clearly the Stewart approach for acid-base balance because it is the only possibility to understand acid-base citrate management.[19] Indeed, citrate anticoagulation implies a large delivery of sodium with trisodium citrate, and the risk is to face metabolic alkalosis if patient is not able to remove sodium or if acid-base balance is not equilibrated with sodium removal or chloride intake.[19] Also, citrate is metabolized by the liver, it is transformed at the end in H_2O and CO_2, and the patient must be able to remove it, which may be difficult for chronic obstructive pulmonary disease (COPD) patients in spontaneous breathing or ARDS patients.[19] On the other hand, if the patient suffers some type of liver failure, he or she may face metabolic acidosis because of citrate accumulation that is monitored easily by the total Ca to ionized Ca ratio (if ratio increases above 2.5, the patient has a high risk of citrate accumulation syndrome and treatment should be stopped immediately).[19] For calcium supplementation at the end of the circuit, chloride calcium carries more chloride, and calcium gluconate is two to three time less concentrated than chloride calcium. Furthermore, chloride calcium causes a high risk of necrosis when infused peripherally.[19] Finally, blood products transfusions (fresh frozen plasma or red cell packed) deliver a citrate load. In such cases it may be preferable to use extra shots of calcium instead of manipulating regional anticoagulation.[19]

TRIALS ON THE FINAL CLINICAL EFFECT: MORTALITY

Five recently published randomized clinical trials and one multicenter observational study have claimed that outcomes with CRRT are superior to those with intermittent hemodialysis.[27,30–33] None of these studies showed a superior outcome for CRRT compared with intermittent hemodialysis, and they do not support the belief that CRRT provides better outcomes than those obtained with intermittent hemodialysis.

A common key point that can be derived from these recent trials is that intermittent hemodialysis has become safer and more efficacious with contemporary dialytic techniques. Furthermore, liberal and extended use of CRRT may be less safe or efficacious than was considered or expected previously. The presumed ability of CRRT to provide more hemodynamic stability, more effective volume homeostasis, and better blood pressure support than intermittent hemodialysis has been the basis for the assumption that CRRT is a superior therapy. Over the past two decades, however, technical advances in the delivery of conventional hemodialysis have decreased dramatically the propensity of intermittent hemodialysis to cause intradialytic hypotension. These advances include the introduction of volume-controlled dialysis machines, the routine use of biocompatible synthetic dialysis membranes, the use of bicarbonate-based dialysate, and the delivery of higher doses of dialysis. Finally, a common issue arising from randomized trials comparing intermittent and continuous therapies is the possibility of switching one randomized treatment to the other. The change of modality is made in up to 20% of intermittent hemodialysis (IHD) patients because of hemodynamic instability and/or to significant fluid overload.[34] For different reasons the CRRT group may require switching of modality in a similar proportion: repeated filter clotting, metabolic reasons, bleeding, or issues related to the use of anticoagulation, thrombocytopenia, or because of clinical improvement of study patients. This apparent violation of study randomization suggests that the two techniques may be seen as complementary rather than alternative. In other words, expert clinicians in routine clinical practice may combine the benefits of both modalities, tailoring RRT from patient to patient and from session to session.

POTENTIAL COMPROMISE: HYBRID TECHNIQUES

Hybrid techniques have been given a variety of names, such as slow-efficiency daily dialysis (SLEDD), prolonged intermittent daily RRT, extended daily dialysis (EDD), or simply extended dialysis,[35–38] depending on variations in schedule and type of solute removal (convective or diffusive). Theoretically, the purpose of such therapies would be consolidation of the advantages offered by either CRRT or intermittent hemodialysis, including efficient solute removal with minimum solute dysequilibrium, reduced ultrafiltration rate with hemodynamic stability, optimized delivered-to-prescribed ratio, low anticoagulant needs, diminished cost of therapy delivery, efficiency of resource use, and improved patient mobility. Initial case series have shown the feasibility and high clearance rates that potentially are associated with such approaches. A single short-term, single-center trial comparing hybrid therapies with CRRT has shown satisfying results in terms of dose delivery and hemodynamic stability. The arrival of technology that can be used by nurses in the ICU to deliver SLEDD with convective components offers further options from a therapeutic point of view. It is now possible, using user-friendly ICU technology, to generate ultrapure replacement fluid and administer it as in

CRRT but at lower cost, in greater amounts, and for shorter periods of time, or to combine such hemofiltration with diffusion, or to use pure diffusion at any chosen clearance for a period that can encompass a given nursing shift, the "9 to 5" maximum staff availability period, or the nighttime period.

An interesting randomized trial assessed CVVH and EDD with filtration (EDDf) differences in achieving correction of several electrolyte abnormalities present before intervention.[39] Potential risk of hypophosphatemia in patients undergoing CVVH suggests the need for vigilance and frequent serum phosphate monitoring. In all patients, hypo- or hyperkalemia and magnesemia were avoided with the prescriptions used. Although the serum sodium was maintained within the normal range and levels were similar in both groups, significant differences in the chloride concentration were noted. The relative hyperchloremia in the EDDf patients almost certainly was due to the greater concentration of chloride in the fluids used for EDDf (111.8 mmol/L) than in the fluids used for CVVH (100.75 mmol/L). The investigators found that the two therapies affected metabolic acid-base variables differently. First, the concentration of lactate was lower with EDDf throughout the study period. This difference probably was explained by the use of lactate as buffer during CVVH versus bicarbonate during EDDf. Second, despite the increase in lactate with CVVH, median pH, bicarbonate, and base excess values were less acidotic with continuous treatment. These findings are consistent with the lower amount of buffer in EDDf fluids (26 mEq/L) than in CVVH fluids (45 mEq/L) and the relative hyperchloremia of these fluids. The effect of hyperchloremia also is likely to explain the difference in mean apparent strong ion difference (SID) between the two groups. A decrease in CO_2 in response to this metabolic acidosis accounted for the lower effective SID values observed during EDDf. Conversely, the strong ion gap was similar for both treatments, in keeping with probably equivalent clearance of unmeasured acids. Although the clinical significance of these differences is uncertain, a higher bicarbonate concentration in EDDf fluids may be desirable.

As a matter of fact, 17 studies comparing CRRT and hybrid therapies were conducted from 2000 to 2014:[40] 7 RCTs and 10 observational studies involving 533 and 675 patients, respectively. A recent meta-analysis showed no difference in mortality rates between EDD and CRRT. However, EDD apparently was burdened by a lower mortality risk in observational studies, but it is possible that such survival benefit is dependent on allocation or selection bias. In RCTs and observational studies, there were no significant differences in recovery of kidney function, fluid removal, or days in the intensive care unit, and EDD showed similar biochemical efficacy to CRRT during treatment (serum urea, serum creatinine, and serum phosphate).

CONCLUSION

Comparing intermittent and continuous therapies can be misleading. Besides the difficulty of conducting a well-designed, adequately powered, randomized trial (requiring at least 1200 patients), continuous and intermittent therapies represent a continuum in the management of AKI. Sicker patients, for example, potentially may derive greater benefit from CRRT, whereas less severely ill patients may do well with daily extended or intermittent treatments.

Should the therapy be 3 or 4 hours of intermittent hemodialysis with standard settings? Should it be CRRT at 25 mL/kg per hour effluent flow rate? Should it be SLEDD at blood and dialysate flow rates of 150 mL/minute for 8 hours during the day? Should SLEDD be applied for 12 hours overnight? Should a convective component be added to SLEDD to make it SLEDDf? Should CRRT and SLEDD be combined for the first 2 or 3 days when the patient is in the hyperacute phase, with SLEDD alone thereafter as recovery takes place? Indeed, from the point of view of the intensivist, the modes of RRT are beginning to resemble the modes of mechanical ventilation, with ventilator settings seamlessly being changed to fit the therapeutic goals and patient needs and phases of illness. Just as stereotypical approaches to ventilation are anachronistic, often resulting in an attempt to fit the patient into an inappropriate, fixed therapy, rather than tailoring the therapy to the patient, so should RRT be adjusted to fill the needs of the individual patient and his or her illness. Also, just as the possibility of showing that one mode of ventilation is better than another is apparently a lost cause, the same seems to hold true for RRT.

To summarize how to choose the most appropriate RRT modality at the start of treatment, *the optimal RRT is the safest, the simplest, and the most efficient.* Usually, this ideal treatment is the one the clinician knows best.

Key Points

1. Different renal replacement therapy prescriptions, modalities, and schedules can be administered to critically ill patients with acute kidney injury.
2. Clinical effects in critically ill patients depend on the selected renal replacement therapy protocol and on the severity and complexity of the clinical picture.
3. Modern, versatile machines and flexible prescriptions allow the clinician to choose from among various renal replacement therapies ranging from highly intermittent high-efficiency therapies to slow continuous hemofiltration, depending on the patient's hemodynamic stability, fluid balance needs, and acid-base and electrolyte status.

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