SECTION 25

Continuous Renal Replacement Therapies (CRRT)

CHAPTER 163

Indications for Continuous Renal Replacement Therapy: Renal Replacement Versus Renal Support

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OBJECTIVES

This chapter will:

1. Explain and describe the main clinical indications for starting continuous renal replacement therapy (CRRT).
2. Consider renal and nonrenal indications of CRRT.
3. Provide theoretical support for the early application of CRRT to control fluid overload, remove solutes, and improve patient survival.
4. Illustrate some nonrenal indications for the use of CRRT and to review recent literature about the new CRRT applications in treatment of patients with such conditions as sepsis, acute brain injury, and acute respiratory distress syndrome.

Continuous renal replacement therapy (CRRT) is a key component of management of critically ill patients with acute kidney injury (AKI). In current practice, the decision to dialyze is based most often on clinical features of volume overload and biochemical features of solute imbalance. Nevertheless, in the context of AKI, appropriate timing has not been defined, and what constitutes "early" versus "late" initiation has not been established.[1] The timing of RRT initiation is a potentially modifiable factor that may affect patient survival.

The question of when to select CRRT over other types of renal replacement therapy (RRT) in critically ill patients with AKI is still a matter of passionate debate among nephrologists. In current clinical practice, modality selection is driven by the availability of treatment, local expertise, and patient characteristics (mainly hemodynamic status and fluid overload).

Although there is usually no hesitation in offering RRT in the presence of life-threatening situations, there is also a tendency to avoid RRT as long as possible. This thought process reflects the decisions made for patients with end-stage renal disease (ESRD), in whom the initiation of RRT is associated with dialysis dependency. In AKI, classic or renal indications for RRT include severe acidemia, fluid overload with oliguria that does not respond to the use of diuretics, hyperkalemia, and signs of uremia, which in turn also could be related to the concept of "late" dialysis. The approach of waiting for AKI complications may delay dialysis initiation. Nonrenal indications focus on removing various dialyzable substances from the blood, such as cytokines in a patient with sepsis. Some of these "nonrenal" indications could be related to the concept of "early" dialysis.

We favor a strategy to avoid uremic, acid-base, electrolytes, and volume overload complications, considering RRT as renal support instead of renal replacement, and aiming to maintain normal acid-base, electrolyte, and fluid status.

In this chapter we discuss the traditional or classic indications for RRT, the concept of renal support, and if it potentially could modify outcomes.

TRADITIONAL INDICATIONS FOR CONTINUOUS RENAL REPLACEMENT THERAPY: RENAL INDICATIONS

In current practice, the decision to initiate RRT is based most often on clinical features of volume overload and biochemical features of solute imbalance (e.g., azotemia, hyperkalemia). However, the best approach to evaluate timing for RRT initiation would be based on clinical criteria, including presence and degree of other organs' dysfunction, rather than biochemical evidence of uremia. Early intervention would allow for better control of fluids and solutes and promote return of renal function.[2–4]

The benefits of supporting other organs depend on the balance between the current load associated with the clinical conditions and the ability of the kidneys to manage fluid and the metabolic load, which means that kidneys have a finite capacity. Consequently, the initiation of RRT should be prompted by the ability of the kidneys to meet the demands being placed on them.[5,6] Although there are no randomized controlled trials for dialysis initiation for life-threatening indications, in current clinical practice there are accepted indications for starting RRT in AKI patients. These include refractory fluid overload; hyperkalemia (plasma potassium concentration >6.5 mEq/L) or rapidly rising potassium levels; signs of uremia such as pericarditis, neuropathy, or an otherwise unexplained decline in mental status; and severe metabolic acidosis (pH < 7.1).[2] In the absence of these life-threatening indications, clinicians tend to delay initiation of RRT when they suspect patients will recover on their own, and because of the concerns associated with the RRT procedure such as hypotension, arrhythmias, and complications with the vascular access and the use of anticoagulation. Another concern with "early" RRT initiation is that it could delay renal recovery because of some factors mentioned earlier, such as hemodynamic instability, and vascular catheter-related bacteremia and sepsis.[3] Table 163.1 describes the indications for CRRT from the absolute versus relative indications perspective.[4]

Fluid Overload

Fluid overload may occur as a complication of acute kidney injury or as a complication of other critically clinical syndromes such as congestive heart failure, iatrogenic fluid overload in shock, and acute respiratory distress syndrome. There is increasing evidence that fluid overload in critically ill patients with AKI is associated with adverse outcomes as shown in Table 163.2.[7–14] With most of the data coming from observational studies, the question if a positive fluid balance has a direct causative effect on patient outcome or if it is a marker of clinical severity remains to be answered. Nevertheless, one randomized controlled trial in patients with acute distress respiratory syndrome provided evidence of a causal relationship.[15]

In terms of type of RRT to be used in patients with fluid overload, CRRT offers some advantages over intermittent hemodialysis (IHD). Bouchard et al.[7] showed that patients on CRRT were more likely to progress with a lower percentage of fluid accumulation compared with patients treated with IHD. In that observational study, mean fluid accumulation in patients treated with CRRT on the tenth day of treatment was lower than 10%, as compared with patients treated with IHD, in whom mean fluid accumulation on the tenth day was higher than 15% (with an increment from baseline mean fluid accumulation).[7] The study also showed that the adjusted odds ratio for death associated with fluid overload at RRT cessation was 2.52 (95% CI 1.55–4.08).[7] Another study that compared IHD with CRRT found similar results: median cumulative total fluid balances during the first 3 days of therapy were −4005 mL for patients treated with CRRT and +1539 mL for patients treated with IHD, and this negative did not correlate with a decrease in urine output.[16] Furthermore, for IHD patients during the treatment there was a significant decrease in the mean arterial blood pressure from baseline, whereas for CRRT patients the mean arterial blood pressure remained unchanged from baseline.[16]

CRRT allows continuous and slow fluid removal to at least match fluid inputs; on the other hand IHD fluid removal goals must be met in 3 to 4 hours of therapy that leads to transient intravascular underfilling, intradialytic hypotension, and recurrent injury to kidneys, which increases the risk of nonrecovery of renal function.[17,18] Likewise, a systematic review of 16 studies has found a higher rate of dialysis dependence among survivors who initially received IHD as compared with CRRT (RR 1.99, 95% CI 1.53–2.59).[19]

Fluid removal is an important goal and often is the major goal of RRT for AKI.[20–26] Although the interpretation of the studies assessing the relationship between fluid overload and mortality is difficult, because sicker patients may receive more fluids, and more severe AKI is often oliguric, CRRT should be considered for patients not achieving adequate fluid balance in IHD techniques.

To optimize fluid overload managing patients' goals for fluid management must be defined initially and adjusted according to the patient's clinical condition as recommended by a recent Acute Dialysis Quality Initiative (ADQI) consensus. A proposed approach to achieve the target fluid balance using CRRT (replacement fluid technique) is to set a fix net ultrafiltration rate and use a variable replacement fluid rate. With this method, fluid balance is achieved by adjusting the amount of replacement fluids, the output is fixed to achieve a solute clearance goal, and replacement fluid rates are changed to allow flexibility in reaching net fluid balance goals. This method allows for constant solute clearance and dissociates clearance parameters from fluid balance. However, one of the disadvantages of this method is that it requires hourly calculations of the amount of replacement fluid to be given with risk for fluid imbalance if rate is not calculated correctly.[18]

TABLE 163.1

Absolute and Relative Renal Indications for Continuous Renal Replacement Therapy

INDICATIONS	ABSOLUTE	RELATIVE
Metabolic disorders	BUN > 100 mg/dL Hyperkalemia > 6 mEq/L with ECG abnormalities Hypermagnesemia >8 mEq/L with anuria and absent deep tendon reflexes	BUN > 76 mg/dL Hyperkalemia> 6 mEq/L Hypermagnesemia > 8 mEq/L Dysnatremia
Acidosis	pH < 7.15 Lactic acidosis related to metformin use	pH > 7.15
Oliguria/ anuria		AKIN class 1, 2, or 3
Fluid overload	Diuretic resistant	Diuretic sensitive

AKIN, Acute Kidney Injury Network; *BUN,* blood urea nitrogen; *ECG,* electrocardiogram.

TABLE 163.2

Studies That Showed an Association of Positive Fluid Balance and Adverse Outcomes in Adult Population

STUDY	NUMBER OF SUBJECTS	STUDY DESIGN	MAJOR FINDINGS
Payen et al. (2008)	3147	Secondary analysis of a multicenter observational cohort study (SOAP study), all patients were adult	Mean positive fluid balance was an independent risk factor for 60-day mortality
Bouchard et al. (2009)	618	Secondary analysis of a prospective multicenter observational study (PICARD study)	A >10% positive fluid balance was associated with significantly higher mortality within 60 days of enrollment. The adjusted odds ratio for death associated with fluid overload at dialysis initiation was 2.07
Fulop et al. (2010)	81	Retrospective single-center observational study	Volume-related weight gain of ≥10% and oliguria were associated with significantly increased odds ratio for mortality
Grams et al. (2011)	1000	Retrospective analysis of a randomized controlled trial (FACTT study)	Post AKI positive fluid balance was associated significantly with mortality in crude and adjusted analysis
Vaara et al. (2012)	283	Prospective, multicenter, observational cohort study in 17 Finnish intensive care units	Fluid overload was associated with an increased risk for 90-day mortality (odds ratio 2.6)
Bellomo et al (2012)	1453	Retrospective analysis of a prospective randomized controlled trial	A negative mean daily fluid balance during study treatment was independently associated with a decreased risk of death, with increased survival time, with significantly increased renal replacement-free days, and with intensive care unit–free days
Heung et al. (2012)	170	Retrospective single-center observational study	A higher degree of fluid overload at RRT initiation predicts worse renal recovery at 1 year
Dass et al. (2012)	94	Retrospective analysis of a single-center randomized controlled study (Nesiritide study)	Positive fluid balance in the immediate postoperative period was associated with risk of AKI in patients undergoing cardiovascular surgery
Kambhampati et al. (2012)	100	Prospective observational single-center study	Progressive positive fluid balance was associated with higher risk of AKI
Teixeira et al. (2013)	601	Secondary analysis of a multicenter observational study	Higher fluid balance and a lower urine volume were associated with 28-day mortality of AKI patients

Cardiovascular Instability

When applied to hemodynamically unstable patients, CRRT generally is viewed as superior to IHD techniques[27] based on several studies comparing changes in mean arterial pressure (MAP), systemic vascular resistance (SVR), and other hemodynamic parameters.[28,29] However, CRRT-associated hypotension remains a frequent problem in intensive care unit (ICU) settings. Several physiologic mechanisms have been described. In the early phase of CRRT (within 12 minutes after connection to the extracorporeal circuit), bradykinin release has been shown to be associated with the induction of temporary hypotension.[30] Another determinant of hemodynamic stability during CRRT is the ultrafiltration (UF) rate. Although the UF rate in CRRT is 5 to 6 times slower when compared with IHD, it may nonetheless lead to hypotension if the UF rate exceeds the rate of interstitial fluid movement into the plasma and depletes the intravascular compartment volume.[31] Similarly, rapid removal of urea with high UF rates may decrease plasma osmotic pressure, further decreasing the rate of interstitial fluid movement into the plasma. In the neonate there is an increased risk of hemodynamic instability if more than 10% of the neonate's blood volume is in the extracorporeal circuit. As a result, most neonates weighing less than 8 to 10 kg require blood priming to mitigate this hypotension.

Solute Removal: Uremic Symptoms and Signs

In critically ill patients, uremic syndrome is characterized by multiple-organ deterioration. The most serious consequences are observed in the cardiovascular, neurologic, hematologic, and immunologic systems. Critically ill patients with AKI have an increased protein catabolic rate with negative nitrogen balance and variable urea water distribution. An early and aggressive approach to hyperazotemia is an important therapeutic goal, because the reduction of the level of plasma urea could reduce the rate of complications of acute kidney injury and improves survival because higher blood urea nitrogen also was associated with mortality in logistic regression models.[32] For example, early initiation of CRRT based on blood urea nitrogen levels (<60 mg/dL) in patients with posttraumatic acute kidney injury had a better survival rate as compared with patients with a late CRRT initiation (blood urea nitrogen > 60 mg/dL).[33]

After the initial prescription of CRRT, it is important that providers frequently reassess the response to prescribed CRRT dose using quality measures focused on CRRT dose, such as delivered clearance; ratio of delivered to prescribed dose; effective treatment time; and other measures of solute control. CRRT prescription may require additional modifications, which is why it is important that solute control should be adapted to the changing clinical needs of critically ill patients.[34]

Metabolic Acidosis

In AKI, metabolic acidosis is the most common acid-base abnormality and is due to reduced regeneration of bicarbonate and failure to excrete ammonium ions. Acidosis is related to increased mortality resulting from myocardial electrical and contractility alterations. Severe refractory metabolic acidosis, usually defined as a pH value less than 7.10 or 7.15, is considered a standard indication for RRT. Under most circumstances, RRT can correct abnormal blood pH within 24 to 48 hours.[35,36] Specific physiologic end points of acid-base intervention with RRT in the critically ill population have not been defined. A complete correction of blood pH is not necessary nor a rapid correction in most if not all critically ill patients.

Four different buffers have been used to correct acidemia in RRT (i.e., bicarbonate, lactate, citrate, and acetate). The most widely used buffer solution is bicarbonate. In IHD, bicarbonate concentrations usually vary between 31 and 39 mEq/L and in commercial solutions used for CRRT, between 25 and 35 mEq/L. Despite a lower concentration, bicarbonate levels more often are normalized with continuous venovenous hemodiafiltration (CVVHDF) than with IHD (71.5% vs. 59.2%, $p = .007$).[36] When using CRRT for treating acidosis, clinicians must consider that different modalities also may cause different acid-base disturbances. In a retrospective study, continuous venovenous hemofiltration (CVVH) was associated with a lower incidence of metabolic acidosis than CVVHDF (13.8% vs. 34.5%; $p < .0001$) and a higher incidence of metabolic alkalosis (38.9% vs. 1.1%; $p < .0001$).[37]

CRRT can be effective to manage patients with lactic acidosis. In one of the largest series, six patients with metformin-associated lactic acidosis were treated with either CVVH (n = 3) or CVVHDF (n = 3). Metabolic acidosis, as well as metformin plasma concentrations, were reduced dramatically in the first 24 hours and/or normalized on the second day in every case with no rebound in acidosis.[38]

When the acidosis is severe or not controlled during dialysis, the highest concentration of bicarbonate levels should be used, and the therapy can be optimized to accommodate the patient's needs. Initiation of CRRT leads to increased bicarbonate and is the preferred modality in this setting, if tolerated, because it provides a greater rapid clearance, whereas CRRT offers more continuous and sustained correction of metabolic acidosis.[39]

Control of Electrolyte Derangements

Hyperkalemia

Hyperkalemia is a frequent complication of AKI. Its primary risk is bradycardia or asystole caused by alterations on cardiac conduction. Emergency intermittent hemodialysis is the preferred treatment for severe hyperkalemia because it provides a higher clearance than CRRT over a few hours. For patients who cannot tolerate IHD or if the hyperkalemia is not life threatening, CRRT also can be used for hyperkalemia. Potassium concentrations between 0 and 4 mEq/L are commercially available, and higher volumes of replacement solution or dialysate and/or low or zero potassium levels can increase the pace of hyperkalemia correction with CRRT. Mild hyperkalemia can be treated with a potassium concentration of 2 mEq/L.[40] In severe cases, 0 mEq/L can be used with frequent potassium monitoring (e.g., every 2 to 4 hours).

Hyponatremia and Hypernatremia

Abnormal sodium values frequently are observed before the initiation of RRT, with reports ranging from 39.6% to 80.0%. In patients with severe and chronic sodium disturbance, rapid correction of hyponatremia can cause osmotic demyelination or cerebral edema, and targeted extent of correction should not exceed 8 mmol/L in 24 hours.[41] Changes in sodium toward normal are slower with CRRT than IHD; in addition, in case of significant dysnatremia, lower volumes of replacement fluid and/or dialysate per hour and customized sodium levels can provide safely slower rates for correction.[39] During CRRT, hypernatremia can be corrected effectively and safely by adding small precalculated amounts of 30% NaCl to the dialysate/replacement fluid bags aiming for a Na^+ in the fluid that allows safe equilibration and correction of the serum Na^+.[42] To correct hyponatremia safely, precalculated amounts of sterile water can be added in a stepwise manner to achieve a fluid Na^+ that equals the desired target serum Na^+.[42] In this setting, frequent monitoring of sodium and glucose levels (e.g., every 2 hours) is mandatory.

RENAL REPLACEMENT VERSUS RENAL SUPPORT

The concept of renal replacement is the traditional and prevailing approach when there is little or no residual kidney function. The renal support approach, on the other hand, is based on the use of RRT techniques as an adjunct to add to kidney function, modify fluid balance, and control solute levels. CRRT as renal support could have beneficial effects of fluid removal in congestive heart failure, and during surgery in which intraoperative fluid removal using modified ultrafiltration has been shown to improve outcomes in pediatric cardiac surgery patients.[2] Bellomo et al. first reported nonrenal indications for CRRT; CVVH then was used to remove various cytokines.[43] Some CRRT nonrenal indications include severe sepsis and septic shock, severe acute pancreatitis, acute respiratory distress syndrome, and fulminant hepatic failure. In the following sections the concept of CRRT as renal support is described further.

NONRENAL INDICATIONS FOR CONTINUOUS RENAL REPLACEMENT THERAPY

Severe Sepsis and Septic Shock

Many endogenous mediators of sepsis such as cytokines can be removed using CVVH or CVVHDF. This observation has prompted many investigators to attempt to use CVVH as an adjunctive therapy in sepsis. Although it remains controversial as to whether CVVH offers additional benefit in patients with acute kidney injury and sepsis, available evidence does not support a role of CVVH for the removal of cytokines in patients without acute kidney injury. A study using CVVH with an effluent volume of 2600 mL/hr demonstrated a lack of effect of convection on serum levels of several cytokines; however, the authors find a significant effect on serum cytokines levels resulting from adsorption within the first hour of treatment.[44] A later randomized controlled trial in patients with severe sepsis without AKI

was not able to demonstrate a reduction in cytokine levels or complement levels in patients treated with isovolemic CVVH with a total effluent volume of 2000 mL/hr.[45] Thus, based on actual evidence, CRRT in patients with sepsis without AKI could not been recommended.

High-volume hemofiltration (HVHF) has been used to reduce the elevated and imbalance levels of proinflammatory and antiinflammatory mediators, the so-called peak-concentration hypothesis.[46] Two small randomized controlled trials investigated the effect of HVHF on sepsis. In the first study 8 hours HVHF at 6 l per hour reduced C3a, C5a, and IL-10 levels and also decreased vasopressor requirements as compared with standard CVVH at 1 L/hr; however, the effect was lost after 24 hours.[47] In the second study a dose of 35 mL/kg/hr was compared with 6 hours of 100 mL/kg/hr.[48] The study found a significant reduction of IL-6 levels; however, both studies were underpowered to find differences in mortality. More recently the high volume in intensive care IVOIRE study that compared standard volume hemofiltration at 35 ml/kg/h to high volume hemofiltration at 70 ml/kg/h in 140 critically ill patients with septic shock and AKI found no evidence that HVHF at 70 mL/kg/hr leads to a reduction of 28-day mortality or contributes to early improvements in hemodynamic profile or organ function.[49]

Continuous hemodiafiltration using a polymethylmethacrylate membrane hemofilter (PMMA-CHDF), which shows an excellent cytokine-adsorbing capacity, has been used for the treatment of severe sepsis/septic shock. Nakamura et al. found that PMMA-CHDF could remove efficiently various proinflammatory cytokines such as TNF, IL-6, and IL-8 from the bloodstream, resulting in early recovery from septic shock. Furthermore, PMMA-CHDF could remove antiinflammatory cytokines such as IL-10 from bloodstream, suggesting that it may improve immunoparalysis as well. These findings suggest that PMMA-CHDF could be useful for the treatment of patients with severe sepsis or septic shock as a cytokine modulator.[50]

Based on the current literature, the use of CRRT in patients with severe sepsis or septic shock and AKI does not differ substantially from treatment of other forms of AKI in critically ill patients. However, current clinical practice supports broader indications and earlier initiation with higher dose of CRRT for patients in septic shock.[51]

Continuous Renal Replacement Therapy in Sepsis and Multisystem Organ Failure

Patients with multiple organ dysfunction syndrome (MODS) frequently develop AKI and are more likely to receive CRRT when renal support is indicated. In these patients, in addition to providing more time to achieve fluid balance and metabolic homeostasis, CRRT has been used with the concept of modulator of the immune response. The effects of CRRT on modulating the levels of inflammatory mediators have been studied for two decades. Different techniques have been developed; high-volume hemofiltration (HVHF), high-adsorption hemofiltration, high-cutoff membranes, and hybrid systems such as coupled plasma filtration absorbance. Experimental and small human clinical studies have suggested that HVHF may improve hemodynamic profile and mortality; however, larger trials failed to confirm this effect. In the IVOIRE trial, HVHF at 70 mL/kg/hr showed no benefit on mortality, early improvements in hemodynamic profile, or organ function as compared with contemporary standard-volume HF (SVHF) at 35 mL/kg/hr. In a recent systematic review and meta-analysis there was no difference in 28-day mortality or recovery of kidney function, length of ICU and hospital stay, vasopressor dose reduction, and adverse events using HVHF for septic AKI. Pilot trials in septic patients using high-permeability hemofilters, with increased pore size, which facilitates the filtration of inflammatory mediators, have demonstrated positive immunomodulation, altering neutrophil phagocytosis as well as mononuclear cell function ex vivo. More studies are needed to confirm these effects.

Severe Acute Pancreatitis

It has been reported that hypercytokinemia plays a pivotal role in the pathophysiology of severe acute pancreatitis and that higher levels of plasma cytokines could be related to adverse outcomes. Abe et al. evaluated the efficacy of CVVHDF using a polymethyl methacrylate (PMMA) membrane hemofilter to remove cytokines in the treatment of severe acute pancreatitis. In that study, patients with blood IL-6 level of at least 400 pg/mL were placed on CVVHDF using a PMMA hemofilter (n = 82). Mean blood IL-6 level, which was 998 pg/mL on admission to the ICU, was significantly lower (335 pg/mL) after 3 days' treatment of PMMA-CHDF ($p < .01$). Patient heart rate, blood lactate level, and intraabdominal pressure also decreased significantly ($p < .01$). The mortality rate among patients who received CVVHDF using a PMMA hemofilter was significantly lower (6.1%) as compared with historical controls (25%). Authors suggest that this technique could improve outcomes in patients with severe acute pancreatitis.[52]

Fulminant Hepatic Failure

Fulminant hepatic failure can be described as a potentially fatal condition, including hepatic encephalopathy and coagulopathy associated with acute hepatic dysfunction. Shinozaki et al. used high-flow dialysate continuous venovenous hemodiafiltration (HF-CVVHDF), in which a conventional CVVHDF machine is connected to an IHD machine to induce a high flow rate of dialysate.[53] With this method, the dialysate flow rate is about 500 mL/min at maximum, equivalent to about 50 times the dialysate flow rate during ordinary CVVHDF. In this study, authors analyzed data from 90 patients with fulminant hepatic failure who underwent this blood purification technique. They reported that improvement in the level of consciousness was achieved in 33 (70.2%) of 47 cases. They also reported a significantly higher survival rate and that lower blood ammonia levels were achieved in patients treated with HF-CVVHDF.[53]

Treatment of Acute Distress Respiratory Syndrome

As with severe acute pancreatitis, cytokines play an important role in the pathophysiology of acute respiratory distress syndrome (ARDS). They increase capillary and alveolar permeability, which results in pulmonary interstitial edema. The use of CVVHDF using a cytokine-adsorbing hemofilter with a membrane made of polymethylmethacrylate (PMMA) was evaluated in the treatment of 51 patients with ARDS complicated by acute renal injury. Matsuda et al. compared 32 patients treated with CVVHDF using a PMMA hemofilter to 19 historic control patients, in whom IHD plus CVVH were used for metabolic and volume control.[54] By day 3 of therapy blood levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-8 significantly decreased in patients treated with CVVHDF using a PMMA hemofilter

than in patients treated with IHD + CVVH. The 28-day cumulative survival rate in the CVVHDF group was significantly higher (68.8%) than that in the IHD group (36.8%).[54] These results suggest that cytokine removal therapy using CVVHDF with PMMA hemofilter could be useful to treat patients with ARDS and AKI, but a prospective randomized controlled trial is warranted to establish the efficacy of this new technique.

Continuous Renal Replacement Therapy in Heart Failure

Although diuretics are the mainstay of therapy for acute decompensated heart failure (ADHF), improved understanding of the pathophysiology of kidney dysfunction in the context of ADHF and limitations of conventional therapy have led clinicians to employ different forms of extracorporeal therapy. Intermittent isolated UF (IUF), slow continuous ultrafiltration (SCUF), and CVVH have been used as extracorporeal therapy to treat ADHF. In IUF and SCUF the extracorporeal blood circuit is adapted for isotonic fluid removal via a pressure gradient. In CVVH, the substitution fluid allows for correction of metabolic acidosis and electrolyte disturbances. In addition, recent evidence suggests that myocardial depressant factors such as IL-8 and antimonocyte chemoattractant protein-1, which is removed effectively via hemofiltration, may have adverse effect on cardiac function. Four randomized trials (UNLOAD, RAPID-CHF, CARESS-HF, and AVOID-HF) compared ultrafiltration to diuretic therapy in patients with acute decompensated HF.[55–58] The Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial showed that early use of UF in CHF patients resulted in significant weight loss and fluid removal and was well tolerated.[57] In the UNLOAD study, the safety and efficacy of SCUF were confirmed; they showed that UF leads to greater weight and fluid loss than intravenous diuretics, reduces overall HF resource in 90 days, and is an effective alternative therapy.[55] The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF) compared ultrafiltration to stepped pharmacologic therapy (bolus, high doses of continuous infusion loop diuretics, addition of thiazide diuretic, and intravenous inotrope and/or vasodilator). In the study, weight loss was the same in the two groups; however, UF therapy was associated with a higher rate of adverse events and higher increments in serum creatinine.[56] The most recent, AVOID-HF trial, showed a trend toward a longer time to new event of HF decompensation, with significantly fewer patients being rehospitalized for HF or cardiovascular causes at 30 days in the ultrafiltration group.[58] The results suggest no negative impact in renal function with excess fluid removed with adjustable UF. A number of questions and concerns still are unresolved, including the need for anticoagulation, complications related to extracorporeal circuit, and the effect of UF on renal function and long-term outcomes. Given the high cost, complexity of ultrafiltration, and the available evidence from these RCT, UF cannot be established as first-line therapy for AHDF.

Continuous Renal Replacement Therapy in Acute Brain Injury

In patients with acute brain injury (ABI), AKI is a frequent complication, occurring in 8% to 23% of patients and recognized as an independent predictor of poor outcome. In patients with ABI, RRT presents a major problem because conventional intermittent hemodialysis may exacerbate reduction in cerebral perfusion and increase cerebral edema. Rapid urea removal from the plasma and water shift to the intracellular compartment can worsen brain edema. The phenomenon is known as dialysis disequilibrium syndrome. Mechanisms associated with this syndrome have been linked to the identification of different urea transporters in the brain of chronic uremic rats. Reduced intensity of dialysis leads to a slower removal of urea and increases the time for osmotic gradient adjustment in the brain.

The goal in patients with ABI and increased intracranial pressure (ICP) is to maintain cerebral perfusion pressure (CPP) higher than 60 mm Hg. Thus mean arterial pressure (MAP) has to be maintained to keep CPP (CPP = MAP – ICP). In IHD, intradialytic hypotension can cause a decrease in MAP and CPP and increase in ICP by compensatory cerebral vasodilatation. This may result in infarction or secondary injury. IHD should be avoided in these patients, because it is associated with a more significant increase in ICP compared with CRRT, which should be the first choice. Using CT scans to measure brain density, it has been shown that brain water content is increased after IHD, where no changes were observed after CRRT. In addition, CRRT also can be used to maintain hypernatremia and thereby reduce brain swelling. The KDIGO guidelines suggest "CRRT instead of intermittent RRT for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema."[4]

CONCLUSION

Continuous types of RRT are suggested in situations in which shifts in fluid balance and metabolic fluctuations are tolerated poorly. There are two specific situations in which continuous modalities are preferred. The first one is in the setting of intracranial hypertension and/or ABI, and the second one is to remove fluid and to achieve a target fluid balance in patients with fluid overload, including those with congestive cardiac failure or acute lung injury. CRRT allows continuous and slow fluid removal to at least match fluid inputs, and this type of RRT should be considered for patients not achieving adequate fluid balance in IHD techniques.

CRRT is also effective at removing biologically active substances, including cytokines, but there is still insufficient evidence to recommend the routine use of CRRT for the treatment of sepsis or for other nonrenal indications.

Key Points

1. Continuous renal replacement therapy (CRRT) is a key component of critically ill patients with acute kidney injury management.
2. Modality selection currently is driven by the availability of treatment, local expertise, and patient characteristics (mainly hemodynamic status and fluid overload).
3. Continuous types of renal replacement therapy are recommended in situations in which shifts in fluid balance and metabolic fluctuations are poorly tolerated.

4. Fluid management during CRRT in critically ill patients is a dynamic process.
5. The use of CRRT in patients with severe sepsis or septic shock and acute kidney injury does not differ substantially from treatment of other forms of acute kidney injury in critically ill patients. More studies are needed to further evaluate other nonrenal indications of CRRT.

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