Renal Replacement Therapy in Intensive Care Unit

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Abstract

Acute renal failure requiring renal replacement therapy (RRT) is a frequent complication in critically ill patients with high morbidity and mortality. Early prediction of who is going to need RRT is clinically useful in the intensive care unit (ICU). Patients’ with diuretic resistant pulmonary edema, hyperkalemia / metabolic acidosis refractory to medical therapy and uremic complications (pericarditis, encephalopathy, bleeding) are candidates who need RRT as an earlier intervention with continuous haemofiltration, which might be beneficial to the patient and even prevent clinicians from implementing unnecessary, futile and perhaps injurious escalations in medical therapy (e.g. low-dose dopamine, mannitol boluses, further fluid loading, introduction of additional vasoactive drugs) to rescue kidneys that are beyond rescuing. Recent evidence also suggests that RRT may be useful as an immunomodulator and best initiated early in the course of the patient’s illness with multiple system involvement.

Introduction

Continuous hemofiltration was first described more than 20 years ago and it has undergone remarkable changes over these periods, which have made it one of the great success stories of intensive care medicine.

RRT encompasses hemodialysis and its progeny – peritoneal dialysis, continuous hemofiltration, continuous hemodialfiltration, intermittent hemodialysis, slow efficiency daily dialysis and extended daily dialysis.

Need for renal replacement therapies (RRT) in patients with acute renal failure (ARF) is a common and increasing problem in ICUs. Leading cause of ARF in patients in intensive care units is sepsis as a part of multi-organ dysfunction syndrome (MODS).

Patients in medical wards who develop acute renal failure are conventionally treated conservatively and in most cases correction of underlying cause leads to recovery and for few some form of RRT may be required. The principle (non) intervention in these patients is fluid restriction. This is difficult in critically ill patients of intensive care, as they require large amounts of carrier fluids for antibiotics and other drugs and nutrition in order to arrest catabolism and preserve physiologic reserve. In addition, patients in intensive care units often have multi-system involvement, and these systems may be further injured by fluid overload, electrolyte and acid base imbalance. In essence renal replacement therapy is required to either prevent endogenous poisoning or fluid overload. It is also important to remember that urinary output does not represent renal function: the kidney may be able to filter fluid, but not to clear metabolic waste.

Indications for Starting Renal Replacement Therapy

It is better to start renal replacement therapy early rather than wait for complications of ARF to develop. Fluid balance is a major stimulus for starting CRRT in critically ill patients because large volumes of daily intravenous fluids are required to maintain intravascular volume, and for drug delivery and nutrition.

The most commonly cited clinical indications for renal replacement therapy are:

- Fluid overload
- Metabolic acidosis
- Oliguria (urine output <200 mL/12 h)
- Anuria / extreme oliguria (urine output <50 mL/12 h)
- Hyperkalemia ([K] >6.5 mEq/L)
- Clinically significant organ (especially pulmonary) edema
- Uremic pericarditis
- Uremic neuropathy/myopathy
- Severe dysnatremia ([Na] <115 or >160 mEq/L)
- Hyperthermia
- Drug overdose with filterable toxin (lithium, vancomycin, procainamide, etc)
- Imminent or ongoing massive blood product administration

Modes of Renal Replacement Therapy

Renal replacement therapy utilizes dialysers that enable solute and solvent to move across semi-permeable membranes in either a convective or diffusive or ultrafiltration fashion. The principle of blood purification by means of semi-permeable membranes during RRT is based on the understanding of the mechanisms of fluid and solute transport across such membranes.

RRT can either be intermittent (IRRT performed for less than 24 hours in each 24 hour period, two to seven times per week) or continuous (CRRT performed continuously without any interruption throughout each day).

Intermittent hemodialysis (IHD) is the most efficient – large amounts of fluid can be removed and electrolyte abnormalities can be rapidly corrected. However, this is not suitable in unstable patients: 20-30% of patients with ARF who are being hemodialysed become hypotensive, with huge associated osmotic shifts – disequilibrium syndrome. Many ICU patients are intolerant of such shifts. Moreover it appears that the hemodynamic changes that occur during hemodialysis (hypotension) may worsen the pre-existing renal injury by increasing the ischemic insult.

Peritoneal dialysis (PD) has the advantage of being simple and cost effective. The major disadvantages of PD are – poor solute clearance, poor uremic control, risk of peritoneal infection and mechanical obstruction of pulmonary and cardiovascular...
Continuous hemodiafiltration techniques were developed to overcome these deficiencies. In critical illness the phenomenon of capillary leak increases the interstitial volume and makes patients edematous. This makes the clearance of solute difficult to calculate and carry out. Continuous techniques lead to more effective urea clearance and more controlled fluid removal.

The concept behind continuous renal replacement techniques (CRRT) is to dialyze patients in a more physiologic way, slowly, over 24 hours, just like the kidney. Intensive care patients are particularly suited to these techniques as they are, by definition, bed bound, and, when acutely sick, intolerant of the fluid swings associated with IHD. The techniques used are:

**SCUF (Slow Continuous Ultrafiltration):**

SCUF is the removal of water from the patient’s blood as it travels through the filter. Water removal is referred to as ultrafiltration. SCUF is a therapy designed to only remove surplus water. The amount of water removed is not sufficient to remove wastes. SCUF does not require the use of replacement fluid, and fluid removal is 300ml to 500ml per hour.\(^2,7,8\)

**CVVH (Continuous Venous-Venous Hemofiltration):**

CVVH is the removal of large amounts of water across the filter membrane for the purpose of clearing wastes. When large volumes of water are washed across the membrane, solutes are dragged along with the water (convection). Hemofiltration is the removal of water over and above the surplus water removed during ultrafiltration. To prevent hypovolemia, water removed during hemofiltration must be given back before the blood is returned to the patient. This is referred to as replacement. CVVH is the use of replacement fluid without dialysis fluid, plus or minus fluid removal. The ultrafiltration rate is high, and replacement electrolyte solution is required to maintain hemodynamic stability. This mode is also very effective for clearing mid sized molecules, such as inflammatory cytokines. It is hypothesized that removal of such mediators may play a role in improving outcome in sepsis.\(^2,7,8\)

**CVVHD (Continuous Venous-Venous Hemodialysis):**

CVVHD is the infusion of dialysis fluid into the filter canister. The dialysis fluid (dialysate) surrounds the blood filled filter segments. Solutes that are small enough to fit through the membrane of the dialysis filter will move from an area of high concentration to low concentration (diffusion). The dialysate determines the solutes that will be removed. If we want to remove solutes, the concentration in the dialysate is lower than the blood concentration. If we want to give something to the patient, the concentration in the dialysate is higher than the blood. CVVHD is the removal of wastes by diffusion only, without the use of hemofiltration (replacement fluid). It can be administered with or without fluid removal from the patient.\(^2,7,8\)

**CVVHDF – (Continuous venous venous hemodiafiltration):**

This is the most popular method of dialysis in ICU, combines convective and diffusive dialysis. Both small and middle molecules are cleared, and both dialysate and replacement fluids are required.\(^2,7,8\)

Most of these modes can remove up to 1 litre per hour of fluid. It is rare that this volume of fluid removal is required in intensive care.

**Advantages of using CRRT**

- Suitable for use in haemodynamically unstable patients.
- Precise volume control, which is immediately adaptable to changing circumstances.
- Very effective control of uremia, hypophosphatemia and hyperkalemia.
- Rapid control of metabolic acidosis
- Improved nutritional support (full protein diet).
- Available 24 hours a day with minimal training.
- Safer for patients with brain injuries and cardiovascular disorders (particularly diuretic resistant CCF).
- May have an effect as an adjuvant therapy in sepsis.
- Probable advantage in terms of renal recovery.

**Disadvantages of using CRRT**

- Expense – probably more than the IHD.
- Anticoagulation – to prevent extra corporeal circuit from clotting.
- Complications of line insertion and sepsis.
- Risk of line disconnection.
- Hypothermia.
- Severe depletion of electrolytes – particularly K+ and PO\(_4\), where care is not taken.

**Slow low efficiency dialysis (SLED) & Extended daily dialysis (EDD):**

Slow low efficiency dialysis is an increasingly popular extra corporeal renal replacement therapy for patients with renal failure in the intensive care unit (ICU). This is ‘hybrid’ technique, which has advantages of both intermittent and continuous methods. Advantages of SLED are efficient clearance of small solutes, good hemodynamic tolerability, flexible treatment schedules, and reduced costs.\(^7,8\)

**Controversies in the choice of RRT in the ICU:**

The continuous replacement of renal function must facilitate fluid and solute homeostasis, nutrition and vital organ function, and, where possible, hasten the recovery of renal function. Difficulties with anticoagulation, biocompatibility, mobility and cost remain obstacles to be overcome. The use of continuous renal replacement therapy (CRRT) to remove systemic inflammatory mediators is yet to be confirmed. Although survival benefits of CRRT over intermittent dialysis remain controversial, the slow continuous removal of fluid, acid and solute has a number of advantages, especially where patients are haemodynamically unstable.\(^2\)

In patients who are haemodynamically stable, the RRT modality does not appear to influence important patient outcomes, and therefore the preference for CRRT over IRRT in such patients does not appear justified in the light of available evidence. CRRT was shown to achieve better haemodynamic parameters such as MAP. Future research should focus on factors such as the dose of dialysis and evaluation of newer promising hybrid technologies such as SLED.\(^9\)

There are no randomized controlled trials to guide the clinician in their choice of the best form of RRT for a given critically ill patient. Not surprisingly, in the absence of such a trial, there is much controversy and disagreement concerning the choice of RRT in the ICU. In the adult population, however, peritoneal dialysis is now used infrequently in developed countries. This lack of application is due to several factors that include insufficient solute clearance\(^6\) limited control of hyperkalemia, a high incidence of peritonitis, poor fluid removal
and unpredictable fluctuations in glycemia, abdominal leaks and respiratory dysfunction. Because of these factors, the major controversy pertains to the preferential use of CRRT vs. IHD. This controversy has generally divided practitioners across national or regional lines with Australian and European intensivists increasingly adopting CRRT and with American nephrologists choosing to remain with IHD. Although this controversy is likely to remain unresolved, some observations may assist the intensivist in appreciating the pros and cons of the options available. The first observation is that hemodialysis is associated with several clinically important complications like

- Systemic hypotension
- Arrhythmia
- Hypoxemia
- Hemorrhage
- Infection
- Line-related complications (pneumothorax)
- Seizure or dialysis disequilibrium
- Pyrogen reaction or haemolysis

The most important of these complications in critically ill patients with multiorgan dysfunction is the development of hypotension. Such hypotension is most severe in those patients that are most cardiovascullarly unstable. The physiological cost of such hypotension is clinically significant, as IHD may precipitate ischemia in specific organs such as the recovering kidneys, which have temporarily lost pressure-flow auto regulation. Such ischemia can be seen histologically as fresh ischemic lesions occurring with each episode of IHD potentially delaying renal recovery.

In addition to hemodynamic instability, the other major concern associated with episodic fluid removal with IHD is the intermittent fluid overload that occurs between treatments. In the extreme case, this can be unacceptable, as is the case for oliguric patients with acute respiratory distress syndrome (ARDS) who will not easily tolerate excess extra vascular water. CRRT is the obvious choice in such patients. Indeed CRRT may also improve respiratory function in patients with multiorgan failure and acute lung injury.

An important practical benefit of CRRT is its ability to continuously remove as much water and sodium as desired. This ability particularly impacts on patient nutrition, which can be delivered without restriction. The importance of feeding the critically ill adequately has been borne out by studies demonstrating a correlation between mortality and a progressive calorie deficit as well as an association between patient morbidity and cumulative protein intake. The advantage of CRRT is that uremic control can always be achieved and maintained even in septic patients while providing sufficient nutritional support. When compared with IHD, both CAVHD and CVVHD are superior in delivering the required daily nutrients. It should also be noted that the daily loss of free amino acids during CRRT is similar to that seen during a 4-hour hemodialysis session, i.e. approximately 1–2 g N 2 or 10% of the usual daily intake.

Another practical benefit of CRRT is that there is less risk of solute disequilibrium. Solute is thus extracted from the intravascular space by the dialyzer at a rate that is substantially faster than solute movement into blood from the intracellular and interstitial compartments. Such solute disequilibrium may be responsible for brain edema and has even more pronounced ill effects in the critically ill; particularly those with increased intracranial pressure. In high-risk patients, rapid solute movements may cause tonsillar herniation and death. CRRT, on the other hand, does not induce such surges in intracranial pressure and maintains cerebral perfusion pressure. CRRT is therefore the treatment of choice in all patients with, or at risk of, cerebral edema.

Other practical considerations regarding differences between CRRT and IHD include thermal loss, anticoagulation, and patient mobilization. The ability to cool febrile patients may be beneficial as it is often accompanied by amelioration of tachycardia and vasodilatation because this effect conceals some clinical signs of infection, the clinician should have a lower threshold for suspecting ongoing sepsis.

Anticoagulation of the hemofiltration circuit with heparin is safe and adequate in the vast majority of patients. In those at risk of bleeding, various alternative approaches are used including low dose heparin, regional heparinization, low molecular weight heparin, prostacyclin, citrate and no anticoagulation. It is not uncommon that persisting difficulties with circuit clotting are due to problems with vascular access. This can occur irrespective of whether continuous or intermittent treatment is being employed. Overall, the need for anticoagulation does not pose a sufficient obstacle to the use of CRRT in contrast to IHD.

Despite the demonstrable physiological benefits of using CRRT in critically ill patients, some believe that, in the absence of a proven effect on mortality, IHD should be regarded as the standard approach. The difficulty, however, is to demonstrate such a difference would require the randomization of more than a thousand patients in a multicenter study with standardization of other clinical management. Two attempts have been made to conduct such studies. Both have had difficulty with methodology, randomization and with recruitment of patients; neither has yet been published in full and neither has achieved conclusive results so far. Furthermore, it has been noted that as more ICUs change to using CRRT, such a trial will be harder to undertake.

Of all the patients in intensive care, those receiving RRT have the poorest prognosis and yet cost the most. It is therefore important to consider the costs of the treatment used in these patients including those of renal replacement and to relate them to the gains in life-years. Although the general principles of cost estimation apply throughout, they must be calculated for individual units to account for local factors such as salaries, costs of replacement or dialysate fluids, methods of anticoagulation and rates of depreciation of equipment purchased. One such costing analysis was carefully performed at Guy’s hospital in London. The costs of the two methods were found to be very close with the IHD being only 6% cheaper. CAVHD would be cheaper overall as a blood pump would not be required. In addition, recent data from a randomized controlled trial show that complete renal recovery is significantly more common with CRRT than with IHD. This finding suggests that there may be hidden costs in association with an IHD-based approach.

Renal Replacement Therapy and Sepsis

Many patients with ARF have severe sepsis, multiorgan dysfunction and a major systemic inflammatory response. In these patients, the blood purification achieved with CRRT may provide additional advantages that go beyond renal replacement therapy per se and move into the area of immunomodulation. In fact, the demonstrated ability that CRRT has to remove or adsorb putative mediators of organ dysfunction may represent yet another reason for its preferential application.
Recent investigations in animals and humans suggest that, if hemofiltration is to have an additional role in the management of sepsis, the rate of plasma water exchange will have to be increased.\textsuperscript{21,22} The effect of CRRT in sepsis may increase survival in patients with sepsis-associated ARF.\textsuperscript{23} In response to these developments, investigators are now seeking to augment the blood purification efficacy of CRRT in a direction more clearly aimed at immune system modulation. Initial experience is accumulating in the treatment of severe sepsis with organ dysfunction using high volume hemofiltration\textsuperscript{24} or coupled plasma-filtration with adsorption.\textsuperscript{25} Such experience suggests that, at the very least, these more aggressive approaches to blood purification can decrease the need for vasopressors therapy during septic shock.

More recently, the concept that convective CRRT in the form of CVVH is more effective at lowering circulating levels of soluble inflammatory mediators than diffusive CRRT in the form of CVVHD has been tested in a randomized controlled study.\textsuperscript{26} This elegant study demonstrated that for equal amounts of dialysate/replacement fluid administration rate, convective therapy achieves lower serum TNF concentrations than diffusive therapy. The findings of this study lend further support to the preferential use of convective therapy.\textsuperscript{2,26}

Another area where hemofiltration is proving remarkably useful is the control of fluid balance in patients requiring extra corporeal membrane oxygenation for cardiogenic shock after cardiac surgery. These patients often require massive amounts of clotting factors, which can only be given safely in the presence of continuous hemofiltration. Under such circumstances, fluid can be removed as the clotting factors are being administered and the development of ARDS/pulmonary edema can be prevented while the bleeding is controlled. Under such circumstances, hemofiltration can be performed without any need for circuit anticoagulation. We have also used hemofiltration to treat patients with ARDS in whom attempts to induce a negative fluid balance with loop diuretics result in a water diuresis but not a salt diuresis. In such patients, hypernatremia develops and extra vascular lung water is not decreased. Continuous hemofiltration under these circumstances achieves the normalization of serum sodium levels and the removal of extra vascular water while maintaining full hemodynamic stability. This process often achieves substantial improvements in gas exchange and lung compliance.

Lastly, it is worth remembering that CRRT also reduces energy expenditure by cooling the febrile patients and that no hormonal or trace element losses of significance take place during CRRT. Many patients with sepsis and congestive cardiac failure not responding to conventional therapy can be successfully treated in this way. The rationale of using a continuous therapy is to achieve a physiological, safe and progressive removal of fluid and solute. The cumulative clearance of urea and creatinine by a continuous method is superior (clinically and statistically) to that achieved by intermittent hemodialysis applied up to 4 times per week, even in septic patients. Indeed, IHD applied 6 times per week would be necessary to achieve the same uremic control seen with standard CRRT.\textsuperscript{1,16} The net result is that, in practice, uremic control is clearly superior during CRRT.\textsuperscript{1}

**Conclusion**

Artificial renal support remains a large component of the practice of critical care and may expand to the adjunctive management of septic shock.\textsuperscript{2} The clinician taking care of critically ill patients with multiorgan failure including severe ARF needs to understand the implications of recent changes in the area of renal replacement technology.\textsuperscript{27,28} The application of CRRT will continue to grow in intensive care units and that the intensivist will have to play an important role in it. In order to move forward, attention needs to be focused on this component of the care of critically ill patients and necessitates an approach that is completely different from that in chronic renal failure.\textsuperscript{29}

**References**

O R A T I O N S  /  A W A R D  2 0 1 1

Recommendations are invited from members for the following assignments so as to reach, Hon. General Secretary – API,
Dr. Sandhya Kamath by 15th December 2009.

Category No. (i) (General Medicine)
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