

## Review

# Continuous haemofiltration in the intensive care unit

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## Abstract

Continuous renal replacement therapy (CRRT) was first described in 1977 for the treatment of diuretic-unresponsive fluid overload in the intensive care unit (ICU). Since that time this treatment has undergone a remarkable technical and conceptual evolution. It is now available in most tertiary ICUs around the world and has almost completely replaced intermittent haemodialysis (IHD) in some countries. Specially made machines are now available, and venovenous therapies that use blood pumps have replaced simpler techniques. Although, it remains controversial whether CRRT decreases mortality when compared with IHD, much evidence suggests that it is physiologically superior. The use of CRRT has also spurred renewed interest in the broader concept of blood purification, particularly in septic states. Experimental evidence suggests that this is a promising approach to the management of septic shock in critically ill patients. The evolution and use of CRRT is likely to continue and grow over the next decade.

**Keywords:** acute renal failure, blood purification, continuous renal replacement therapy, cytokines, haemodialysis, haemofiltration, multiorgan failure syndrome, sepsis, septic shock

## Introduction

"The difficulty lies, not in new ideas, but in escaping old ones, which ramify for those brought up with them, as most of us have been, into every corner of our minds."

*John Maynard Keynes (1933)*

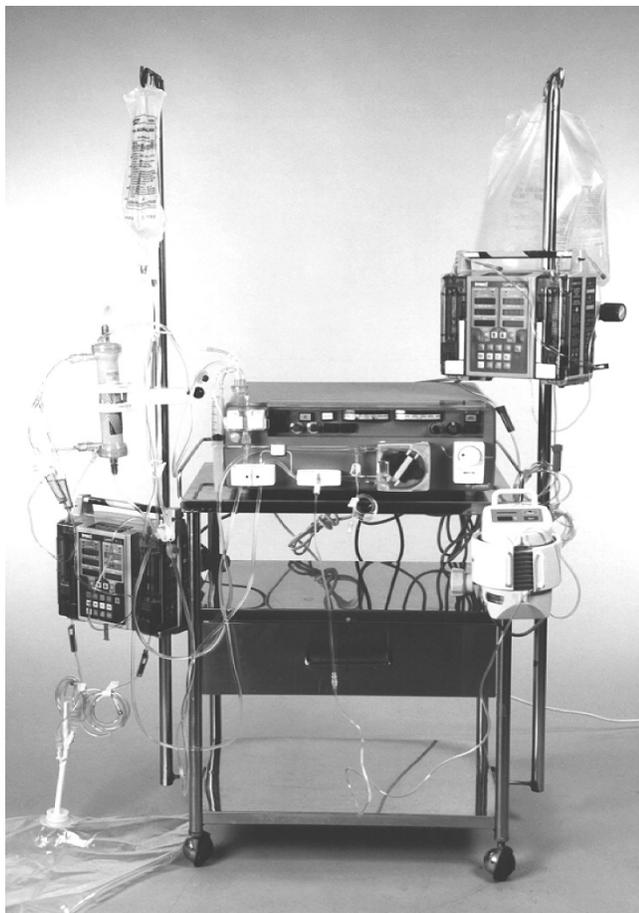
Since its first description [1] continuous hemofiltration, or 'continuous renal replacement therapy' (CRRT) as it is now called, has undergone remarkable growth [2]. In the modern ICU, CRRT is now performed using pump technology [3] and double-lumen central venous access [4]. In many ICUs, especially in Australia and in Europe, CRRT has become the dominant if not exclusive form of artificial

renal support [5]. Furthermore, there has been growing research into its role as adjuvant therapy in sepsis [6]. Modifications to standard CRRT circuits are also being explored in an effort to increase such anti-inflammatory potential [7]. In the present review, we describe the current technology and state of CRRT in the ICU, address some of the controversies that surround its application in critically ill patients, and attempt to give the reader a state-of-the-art view of its uses and clinical future.

## The technology

Continuous arteriovenous therapies were first used for CRRT because they are simple and do not require a peristaltic blood pump. As such, they may have a place under

Figure 1

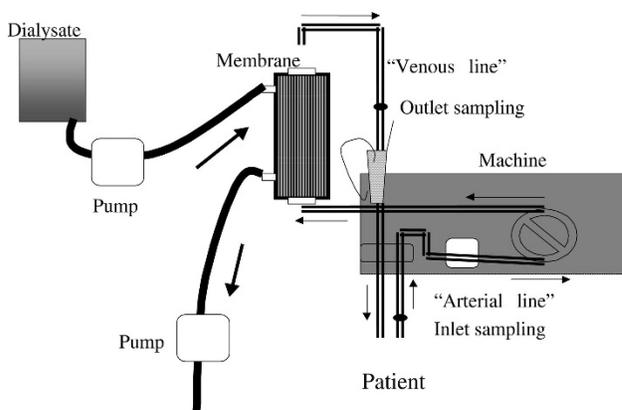


A 'makeshift' CRRT circuit, using a simple and inexpensive blood pump with pressure alarms and air trap. Ultrafiltration is controlled using standard ICU-type volumetric pumps. Replacement fluid administration is similarly controlled.

emergency circumstances or in developing countries. However, the morbidity associated with arterial cannulation is substantial [8], and the cost of a simple blood pump module is only £2500. Thus, if one can afford to have an ICU at all, one can afford to have venovenous CRRT, which is much safer for the patient (Fig. 1) [8–10]. All CRRT modalities should now be venovenous.

Once venovenous therapy is applied, blood flow rate must be controlled. A peristaltic pump module is necessary to achieve this goal. This module must have the appropriate air-trap and pressure monitors to ensure patient safety. In this setting, either continuous venovenous haemofiltration (CVVH) or continuous venovenous haemodialysis (CVVHD), or a combination of both [continuous venovenous haemodiafiltration (CVVHDF)], may be chosen. All techniques will deliver excellent uraemic control provided ultrafiltrate flow and/or dialysate flow is adequate. In fact, with sufficient blood flow ( $\geq 200$  ml/min) and membrane surface ( $\geq 0.8$  m<sup>2</sup>),

Figure 2



The design of a CVVHD circuit using a simple blood pump, volumetric pumps for dialysate control and a double lumen catheter for vascular access.

CVVH without pump-driven ultrafiltrate control initially will spontaneously deliver high ultrafiltration rates (1.5–2 l/h), and thereby high solute clearances without the need for counter-current dialysate flow [11]. To facilitate nursing care, however, ultrafiltration or dialysate flow should be pump-controlled (Figs 1 and 2). All new machines for CRRT possess such technology. If only a simple blood module is available, ultrafiltration (and replacement fluid) or dialysate flow rate can be controlled by means of a standard volumetric pump. Such volumetric pumps are ubiquitous in the ICU [12].

If it is necessary to combine diffusive and convective clearance, as in CVVHDF, this can be achieved by using the pump to control dialysate inflow and outflow. If the clearance is purely diffusive (dialysate inflow rate = dialysate outflow rate) and the membrane is low-flux (cellulose-based), then therapy is more appropriately called CVVHD. A consensus nomenclature has been published [13\*] that facilitates uniformity of communication and more precise exchange of ideas and clinical experience. The authors of that nomenclature currently prefer to use CVVH with pump-driven ultrafiltrate control because of its greater ability to remove middle molecules (most soluble mediators of sepsis are middle molecules), its safety, and ease of operation by nursing staff. This CVVH-based approach to the treatment of acute renal failure (ARF) has now been extended to include high-volume haemofiltration [7,14\*] and more complex circuit modifications [15,16] that are aimed at increasing blood purification in septic shock or at removing excess plasma water during cardiac surgery [17].

### Clinical application of continuous renal replacement therapy

CRRT offers extraordinary advantages over IHD and peritoneal dialysis. With CRRT, volume control is continuous

and immediately adaptable to the changing clinical circumstances (the immediate need for blood or blood products in a patient who is at risk for adult respiratory distress syndrome or who is on extracorporeal membrane oxygenation) that are common in the care of critically ill patients. Because of this adaptability, CRRT can immediately treat volume overload or, even better, prevent it without inducing acute volume depletion. The avoidance of intravascular volume depletion and hypotension prevents treatment-associated ischaemic renal injury, which is seen with standard IHD [18\*\*].

Uraemic control with CRRT is vastly superior to that achieved with standard IHD [19\*\*]. Thus, patients treated with CRRT consistently maintain lower urea and creatinine levels [20]. Recent data [21\*,22\*] show that delivery of a greater 'dialysis dose' is associated with better outcome in critically ill patients. The preliminary results of a randomized controlled trial that compared daily IHD with IHD every 2 days in patients with ARF [23] also show a statistically significant increase in survival in those patients treated with daily IHD. The better level of uraemic control provided by CRRT may offer a survival advantage.

CRRT offers more rapid improvement and control of metabolic acidosis, and more rapid and reliable control of serum phosphate levels [24]. However, hypophosphataemia will develop during CRRT unless clinicians monitor serum phosphate levels and administer replacement as appropriate as soon as the serum phosphate is within the normal range. CRRT also allows better nutritional support. With standard IHD, adequate control of uraemia is difficult, and protein restriction is often applied to prevent high levels of serum urea. Such restrictions induce protein starvation and a highly negative daily nitrogen balance [25]. An aggressive, protein-rich nutritional policy can be implemented if CRRT is used [26]. Such a policy maintains nitrogen balance close to neutral and prevents protein malnutrition [27\*]. Amino acid losses through the filter do occur. However, they represent approximately 10% of administered amino acids, and such losses are not appreciably greater than those seen during a session of IHD or during peritoneal dialysis [28].

CRRT is mandatory in all patients who are at risk of or who have increased intracranial pressure (neurosurgical patients, patients with encephalitis or meningoencephalitis or acute liver failure). In a series of elegant studies [29,30\*], Davenport and coworkers showed that CRRT prevents the surge in intracranial pressure that is associated with intermittent therapies.

ICU patients with significant cardiac disease are best treated with CRRT. In patients with diuretic-resistant congestive cardiac failure, CRRT restores dry body weight, improves urinary output, decreases neurohumoral activation

and prolongs symptom-free and oedema-free time [31\*]. Clinical benefits have also been reported for cardiac surgery patients [32]. The possible mechanisms include decreased myocardial oedema, a decrease in left ventricular end-diastolic pressure, optimization of the Starling relationship, increased myocardial performance, and the removal of circulating myocardial depressant factors [33]. Finally, in an era of increasingly aggressive cardiac surgery and artificial mechanical heart support, a number of patients develop ARF in the setting of postcardiotomy cardiogenic shock. These patients require temporary mechanical heart support (left or right ventricular assist devices, extracorporeal membrane oxygenation, haemopump) and renal replacement therapy, they are dependent on vasopressor drugs, and they are haemodynamically fragile. The use of standard IHD can be lethal in such patients. CRRT, on the other hand, is easily tolerated and becomes a useful tool for control of intravascular and extravascular volume.

Patients with ARF and septic shock are particularly suited to CRRT. In these patients haemodynamic instability is very common, and oliguria and anuria are typical. If appropriate fluid resuscitation, nutrition, blood and blood products administration is to take place under optimal physiological circumstances, CRRT must be used. CRRT also appears to have beneficial effects on haemodynamics and inflammation in animal models of sepsis [34–36]. Accordingly, there is a strong biological rationale for using CRRT in septic shock and ARF. More recently, standard CRRT technology has been modified by using a more porous membrane [36]; by coupling continuous plasma filtration with continuous sorption [37]; and by increasing the plasma water exchange rate [38]. These modifications are aimed at moving CRRT from the simple treatment of ARF to the adjunctive treatment of sepsis.

### **Initiating continuous renal replacement therapy**

When standard IHD is used, the initiation of renal replacement therapy is often delayed by concerns about haemodynamic tolerance. With CRRT, renal replacement therapy can and should be started promptly and aggressively. Accordingly, we have proposed a set of indications (Table 1) that can be used as triggers for initiating artificial renal support in the ICU. Early initiation of CRRT may increase survival [39\*].

### **Controversies**

Several controversies surround the use of CRRT, including the following: does CRRT increase survival?; does the anticoagulation that is needed in CRRT constitute an important disadvantage of CRRT?; do the costs of CRRT compare favourably with other modalities?; should ICU or haemodialysis nurses manage the CRRT circuit?; and should CRRT be used in patients without ARF who have severe sepsis or septic shock?

### Survival

Does CRRT increase survival? This issue would be best addressed with a randomized controlled trial comparing CRRT with IHD in critically ill patients with ARF. Such a trial would require close to 800 patients to have an 80% power of detecting a 10% absolute decrease in mortality at an  $\alpha$  of 0.05 [40]. Randomization would have to be stratified according to illness severity, cause of ARF and hospital. CRRT and IHD would have to be standardized.

The task of designing and conducting such a trial is daunting. Nevertheless, a similar randomized controlled trial was recently attempted in the USA. The results of the trial were reported at meetings, and have been published in part in abstract form [41]. Unfortunately, randomization failed to divide patients into comparable cohorts; patients randomized to CRRT were more severely ill according to Acute Physiology and Chronic Health Evaluation II and III scores, and included a higher percentage of males. Accordingly, no meaningful comparisons can be made. That study also had limited statistical power, and patients with a mean arterial pressure below 70 mmHg were excluded from the study; these are the very patients who are most likely to benefit from CRRT. Finally, patients were allowed to crossover (32 out of 131 who had an adequate trial of therapy), making analysis even more difficult. However, one interesting finding did emerge; patients treated with CRRT who survived were more likely to have renal recovery than patients treated with IHD (92.3% versus 59.4%;  $P < 0.01$ ) [42]. These findings suggest that mortality may not be an appropriate and achievable end-point for future trials, but that renal recovery could be.

The only other randomized controlled trial of some size (100 patients) [43] showed a 15% survival advantage with CRRT. In that study, however, five patients randomized to IHD were excluded from analysis because IHD could not be completed due to severe haemodynamic instability. Their inclusion and the use of therapeutic failure as an outcome measure would give CRRT a greater than 20% advantage over IHD.

As pointed out by Silvester [43] in a recent review, when renal recovery is used as the outcome measure and recent patient series are analyzed, CRRT appears significantly superior. In addition, of all of the retrospective series or prospective comparisons so far published, none has ever shown any trend in favour of IHD and all have shown a trend in favour of CRRT.

### Continuous anticoagulation

The need for continuous anticoagulation has been considered an important disadvantage of CRRT. This concern is not supported by evidence. CRRT can easily be conducted without any anticoagulation in patients who are at risk of bleeding [44] without significantly compromising the life of

**Table 1**

#### Potential indications for CRRT in the ICU

- Nonobstructive oliguria (urine output  $< 200$  ml/12 h) or anuria
- Severe acidaemia (pH  $< 7.1$ ) due to metabolic acidosis
- Azotaemia ([urea]  $> 30$  mmol/l)
- Hyperkalaemia ( $[K^+] > 6.5$  mmol/l or rapidly rising  $[K^+]$ \*)
- Suspected uraemic organ involvement (pericarditis/encephalopathy/neuropathy/myopathy)
- Progressive severe dysnatraemia ( $[Na^+] > 160$  or  $< 115$  mmol/l)
- Hyperthermia (core temperature  $> 39.5^\circ\text{C}$ )
- Clinically significant organ oedema (especially lung)
- Drug overdose with dialyzable toxin
- Coagulopathy requiring large amounts of blood products in patient with or at risk of pulmonary oedema/ARDS†

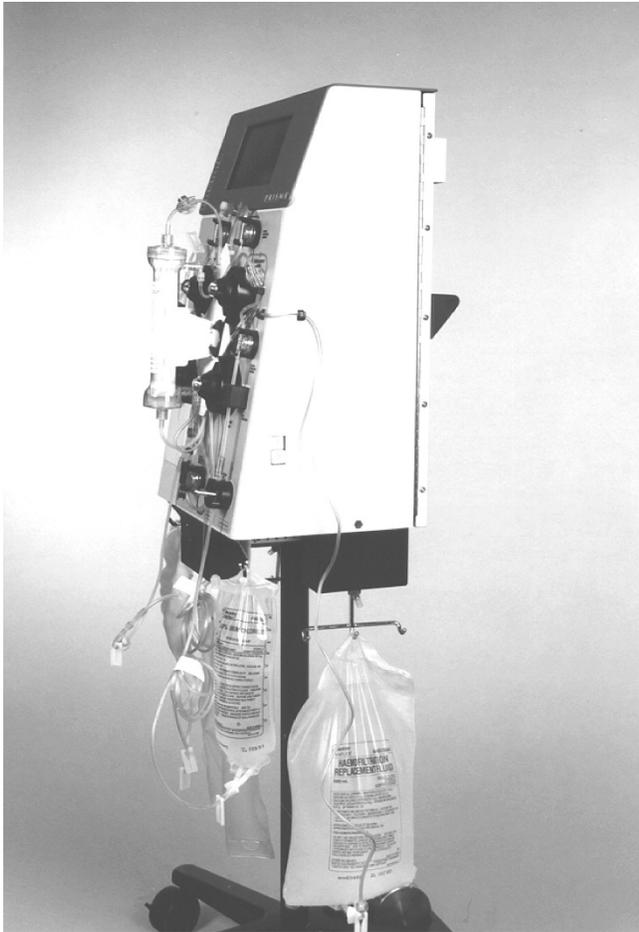
Any one of these indications constitutes sufficient grounds for considering the initiation of CRRT. Two of the above criteria make CRRT highly desirable. Combined disorders suggest the initiation of CRRT even before some of the above-mentioned 'limits' have been reached. \*IHD removes potassium more efficiently than CRRT. However, if CRRT is started early enough, hyperkalaemia is easily controlled. †For example, a fulminant liver failure patient with adult respiratory distress syndrome (ARDS), an international normalized ratio  $> 3$  and spontaneous epistaxis. Unless volume is rapidly removed, as fresh frozen plasma is rapidly given, the patient is very likely to develop pulmonary oedema.

the filter. If anticoagulation is used, it is typically in the form of low-dose heparin and has minimal effects on systemic coagulation. If filter life is significantly impaired despite low-dose heparin, then regional anticoagulation strategies exist that expose the patient to minimal systemic anticoagulation while achieving excellent circuit or filter anticoagulation [45]. In a unit with a good understanding of these principles and a flexible approach to circuit maintenance, anticoagulation is not a major issue during CRRT.

### Costs of continuous renal replacement therapy

The matter of cost has been analyzed by several authors [46], and the general consensus is that the difference in cost between CRRT and IHD is minimal. In our hospitals there is no appreciable cost difference between CRRT and IHD. Severe ARF is a disease of critically ill patients, and in many countries, such as Australia, intensivists have taken over the task of treating ARF without any reference to nephrological opinion or intervention [47]. On the other hand, in the USA nephrologists mostly control the prescription and application of CRRT. In other countries, there may be a combined approach or a predominance of one group over another. It has been our belief for some time that the ideal arrangement is one of full collaboration between intensivist and nephrologist [48]. Such collaboration should be encouraged whenever possible. If this is not possible, we strongly encourage the combined training of

Figure 3



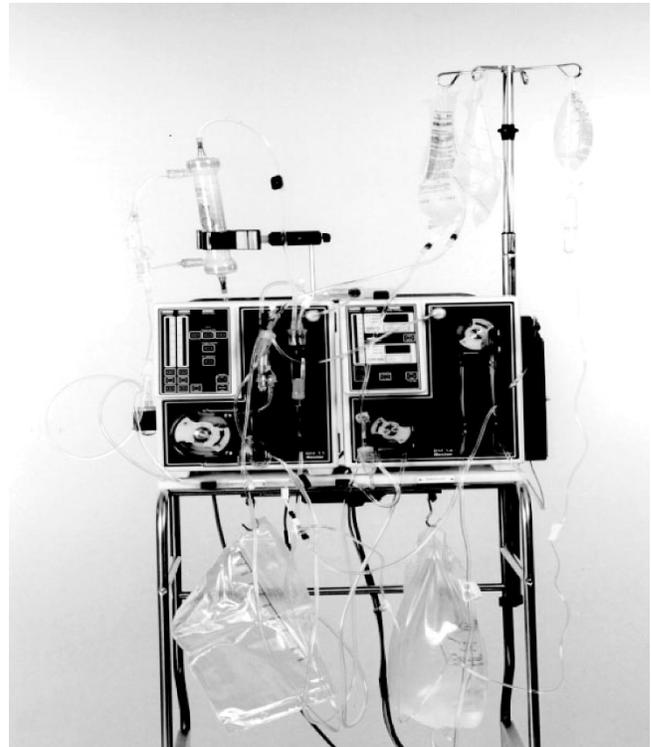
Prisma CRRT machine (Hospal, Lyon, France). This is from a new generation of devices that have been developed to be simple to operate and prime, and that possess more sophisticated alarm and monitoring functions.

physicians in both disciplines and believe that there is both a substantial body of knowledge and a strong need for the development of a new area of medical specialization: critical care nephrology. The subject matter for such practice and specialization has recently been gathered in the first textbook dedicated to this area [49].

#### Management of continuous renal replacement therapy by nurses

Another controversy related to CRRT is the issue of whether ICU nurses or haemodialysis nurses should set up, run and troubleshoot the CRRT circuit. In fact, both approaches are acceptable and their success depends on institutional logistics, continued nursing education, medical support, frequency of use and sufficient numbers of 'expert' nurses within a given ICU. Either using makeshift circuits (Fig 1) or increasingly sophisticated machines (Figs 3 and 4) with pressure alarms and graphic

Figure 4



Baxter BM 25 machine. This device was initially developed for intermittent haemofiltration. However, it has proven useful for continuous therapy. Although it does not have sophisticated graphic and alarm functions, it can achieve ultrafiltration rates of up to 10 l/h. This ability to achieve high ultrafiltrate rates makes this device ideal for high-volume haemofiltration therapy.

displays, a tertiary ICU must make CRRT a mandatory part of nursing (and medical) expertise and must provide the continuing education necessary to its success.

#### Continuous renal replacement therapy in severe sepsis or septic shock without ARF

Finally, there is much debate about whether CRRT should now be used in patients without ARF who have severe sepsis or septic shock [50,51]. The rationale for such use rests on the beneficial effects of CRRT in animal models of sepsis [7] and its ability to remove or adsorb many of the soluble inflammatory mediators of sepsis [52]. However, much work remains to be done before we can understand the effects of CRRT in severe sepsis/septic shock [53]. Accordingly, we do not believe the case exists yet for using CRRT as adjuvant treatment for severe sepsis.

#### Recent developments

The development of CRRT and its increasing use by intensivists has put a great deal of pressure on nephrologists to adapt and compete. Accordingly, hybrid strategies are now emerging. These strategies seek to reach a middle ground

between CRRT and standard dialysis. One such approach is called 'slow extended daily dialysis' [54]. With this approach, dialysis is extended to 6–12 h with intermediate blood flows and dialysate flows. This approach represents an improvement in the type of IHD applied to ICU patients, which may make it possible for IHD to return to the ICU in a more competitive manner in the next few years.

## Conclusion

CRRT is now firmly established as a form of artificial renal support in the ICU. In many units and in many countries, it has superseded IHD. Intensivists have begun to use CRRT independently, and are now exploring the opportunities that CRRT provides as an adjunctive treatment for severe sepsis. In particular, in patients such as those with heart failure, acute liver failure or cerebral oedema, the physiological advantages of CRRT over standard IHD are overwhelming. Once the appropriate training of nursing staff and medical staff has been achieved, CRRT is easy to conduct, is safe and flexible, and it will easily become the only form of artificial renal support in the ICU. The future may see CRRT move beyond its initial goal of providing renal support to the area of immune modulation in sepsis. However, many investigations and technological changes will be necessary to establish the efficacy of CRRT in sepsis.

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