Continuous renal replacement therapy for the critically ill patient

Since its introduction in 1977, continuous renal replacement therapy has advanced considerably and is now widely used in the management of renal insufficiency in critical illness. Acute kidney injury affects 3.2–18.3% of hospitalized patients, and 35% of critically ill patients (Palevsky et al, 2008; Selby et al, 2012). Whatever the underlying cause, acute kidney injury is associated with increased mortality and is a frequent reason for escalation to critical care for renal replacement therapy.

Table 1. Renal and non-renal indications for continuous renal replacement therapy

Renal	Fluid overload unresponsive to diuretic therapy
	Hyperkalaemia refractory to treatment
	Rapidly increasing urea level (>30 mmol/litre)
	Acidaemia (pH 7.1)
	Oligouria (<200 ml/12 hr) or anuria (<50 ml/12 hr)
	Uraemic complications, e.g. bleeding, pericarditis, encephalopathy
Non-renal	Drug overdose with a dialysable toxin
	Liver failure (raised ammonia)
	Patient requiring large amounts of blood products but at risk of developing pulmonary oedema or acute respiratory distress syndrome
	Cardiac failure with severe fluid overload or pulmonary oedema
	Hyperthermia and hypothermia

From Kishen et al (2009)

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Indications

Continuous renal replacement therapy is started when renal insufficiency has led to complications that are refractory to medical management, such as acidaemia, electrolyte disturbances, and more commonly oliguria unresponsive to diuretics, uraemia and volume overload (*Table 1*) (Silvester et al, 2001; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). In the UK continuous renal replacement therapy is usually delivered by the critical care team with minimal input from nephrologists, unlike practice in other countries.

There are no universally accepted levels of urea, potassium or pH at which to start continuous renal replacement therapy, but commonly used parameters are outlined in *Table 1*. Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that initiation of continuous renal replacement therapy should depend on the presence of modifiable conditions and biochemical trends, rather than individual urea and creatinine thresholds (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Principles of haemofiltration

The two main types of renal replacement therapy are dialysis (which is intermittent) and filtration (which is continuous). The key differences are described in *Table 2*. Both systems draw blood from a large vein using a pump to stream it through an extracorporeal circuit, and return processed blood into the venous system. Solutes are removed from the blood across a semi-permeable membrane either by diffusion (in haemodialysis), by convection (in haemofiltration) or by a combination of both (in haemodiafiltration) (*Figures 1* and *2*).

Table 2. Comparison of continuous venovenous haemofiltration and intermittent haemodialysis

	Continuous venovenous haemofiltration	Intermittent haemodialysis
Patient cohort	Critically ill	Chronic renal failure
Duration	Continuous, 24 hours	Short sessions three times a week
Blood flow	50–200 ml/min	300–400 ml/min
Mode of molecule clearance	Convection	Diffusion
Size of molecules cleared	Small–medium	Small
Anticoagulation	Required	Not needed
Access	Central venous access, Vascath	Intravenous fistula or long-term tunneled haemodialysis line
Solute control	Good electrolyte and fluid balance control	More rapid fluid and electrolyte shifts
Fluid balance control	Used in haemodynamically unstable patients	Used in stable patients, hypotension is common
Water supply	Packaged sterile water (expensive)	Filtered water (cheaper)

Figure 1. Diagram of haemodialysis circuit. Solutes move via diffusion from a high concentration in the blood compartment to a low concentration in the dialysate. The speed of movement depends on the magnitude of the diffusion gradient, which is maintained by a countercurrent. Intermittent haemodialysis machines have pumps, air detectors and pressure monitors throughout the circuit. Adapted from Yartsev (2016).

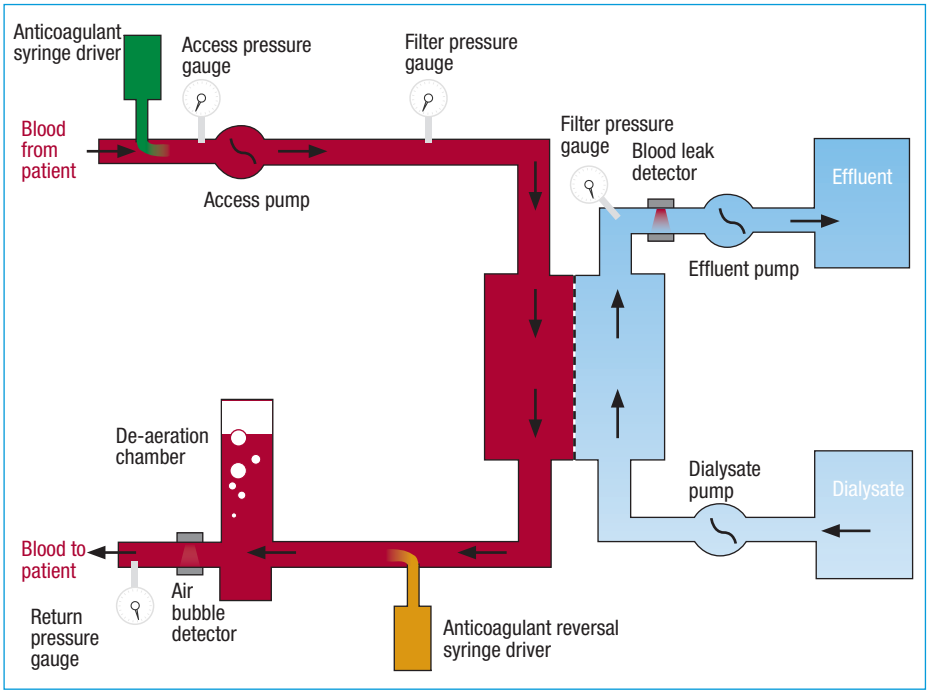
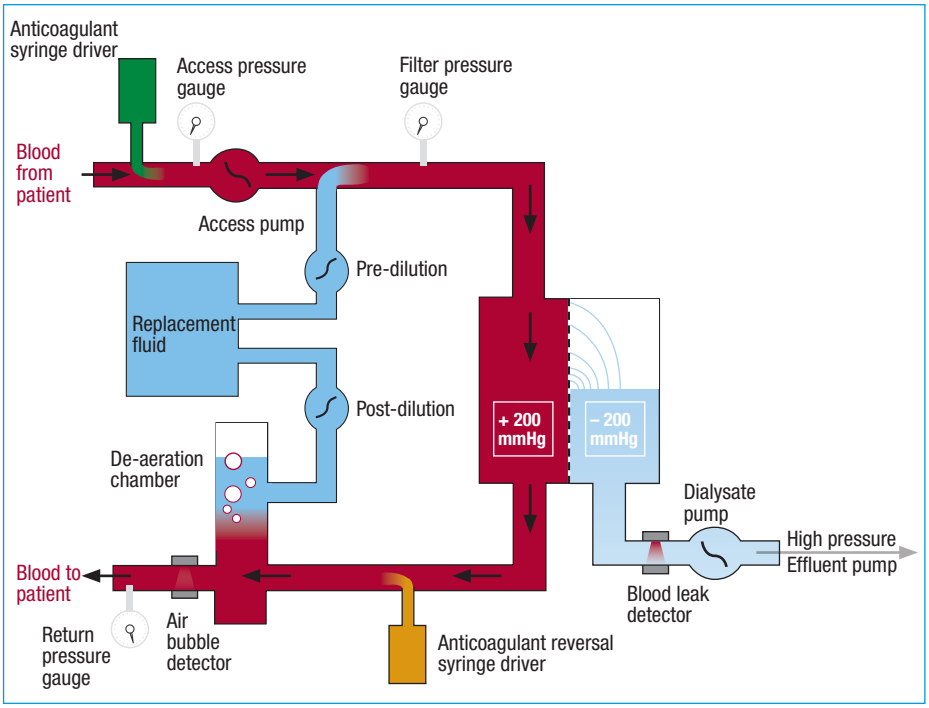


Figure 2. Diagram of continuous venovenous haemofiltration circuit, where blood is filtered via convection. Solvent and solutes are both forced from a high pressure in the blood compartment to a low pressure in the effluent circuit. The transmembrane pressure determines the rate of ultrafiltrate production. Continuous venovenous haemofiltration machines have pumps, air detectors and pressure monitors throughout the circuit. Additional fluid can be added pre- or post-filter. Anticoagulation and fluids can be added at various points. Haemodiafiltration uses the same circuit plus dialysate solution (seen in *Figure 1*) as it combines convection and diffusion. Adapted from Yartsev (2016).



Diffusion-based dialysis systems use synthetic polysulfone membranes and are more effective at removing small molecules, e.g. urea, creatinine and electrolytes (<300 Da), than haemofiltration. Convective clearance is the ultrafiltration of large volumes of fluid, mainly plasma water, down a pressure gradient forcing a concomitant 'drag' of solutes across the membrane. As in the glomeruli, a pressure gradient from the blood compartment to the filtrate drives fluid across the membrane.

Convection is more effective at clearing middle and larger sized molecules (500–20 000 Da). Large molecule clearance depends on the pore size of the membrane. High flux membranes, usually made of synthetic polymers, are used in continuous venovenous haemofiltration to remove molecules up to 20 000 Da.

Most membranes need to be replaced after 24–72 hours of filtration, as a result of the accumulation of particles (often protein) in the filter, a process known as fouling. Filtered waste (ultrafiltrate) is discarded into bags by the machine. To maintain a neutral fluid balance, sterile isotonic replacement fluid, equal to the ultrafiltrate loss, must be added to the extracorporeal circuit. This can be done before or after the membrane; termed pre-dilution or post-dilution. Typically, the total fluid volume is divided equally between pre- and post-dilution, but the ratio can be altered. Increasing pre-dilution dilutes the blood in the membrane, thus prolonging the membrane life but reducing solute clearance. A balance must be made between these factors and patient-specific needs (Bersten and Soni, 2008; Ronco et al, 2015).

Hybrid therapies

Filtration methods can be adapted to optimize solute or fluid clearance. Haemodiafiltration combines convection and diffusion to achieve a balanced rate of filtration of both large and small solutes, consequently it is the most commonly used modality. Slow, continuous ultrafiltration is used solely to remove plasma water. Unlike haemofiltration or haemodiafiltration, there is no fluid replacement during slow, continuous ultrafiltration. Slow, continuous, low efficiency daily dialysis provides extended intermittent haemodialysis for 8–12 hours.

Studies indicate that haemodynamic instability during slow, continuous, low efficiency daily dialysis is less than in

> During continuous renal replacement therapy, intravascular volume control is titrated according to the patient's clinical needs.

intermittent haemodialysis, and comparable to continuous venovenous haemofiltration (Ronco et al, 2015). KDIGO guidance recommends that the choice of renal replacement modality is based on availability and experience with the specific modality, and the patient's haemodynamic stability (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

Haemodynamics and intravascular volume control

Haemodynamic instability (common in critically ill patients) generally requires continuous renal replacement therapy rather than intermittent haemodialysis as the rapid removal of fluid and solutes in intermittent haemodialysis can cause profound hypotension. During continuous renal replacement therapy, blood pressure is less affected than during intermittent haemodialysis, because continuous renal replacement therapy allows sufficient time for compensatory fluid shifts from the interstitium to maintain intravascular volume. A Cochrane systematic review reported that continuous renal replacement therapy achieved better haemodynamic stability than intermittent haemodialysis and decreased the need for vasopressors (Rabindranath et al, 2007).

During continuous renal replacement therapy, intravascular volume control is titrated according to the patient's clinical needs. This is achieved by altering the daily balance of fluid removal and replacement, prescribed as a 24-hour positive or negative balance. Balance can also be adjusted on an hourly basis to account for acute changes in clinical status. This facilitates the administration of intravenous fluid and medications to be given in the context of fluid overload.

Timing

In the absence of life-threatening complications directly related to renal failure, the decision about when to initiate continuous renal replacement therapy is a topic of much debate. This decision is further complicated by the fact that the terms 'early' and 'late' are open to individual interpretation, as demonstrated by the varied definitions used in clinical trials. It is arguable that early initiation of continuous renal replacement therapy may achieve better control of fluid volume and electrolytes and improve the removal of uraemic toxins. However, early initiation may unnecessarily expose patients to continuous renal replacement therapy who would have otherwise spontaneously recovered.

Two meta-analyses have concluded that early initiation of continuous renal replacement therapy reduces mortality (Seabra et al, 2008; Karvellas et al, 2011). However, much of the data came from retrospective cohort studies with significant pre-intervention differences between study groups. More recent randomized controlled trials showed no difference in results (Gaudry et al, 2016; Zarbock et al, 2016). The pilot study of a multicentre randomized controlled trial attempting to resolve this issue found no difference in mortality between early or late therapy (Wald et al, 2015).

Dose of renal replacement therapy

The dose (or intensity) of continuous venovenous haemofiltration refers to the volume of ultrafiltrate produced per hour. It is commonly prescribed as an hourly exchange rate (e.g. 1500 ml/hr). The flow rate should be tailored to a patient's ideal body weight (ml/kg/hr). Considerable, but inconclusive, research has been devoted to determining the best dose for the critically ill. A widely used dose is 25 ml/kg/hr (Palevsky et al, 2008; Bellomo et al, 2009). KDIGO guidelines recommend 20–25 ml/kg/hr in continuous renal replacement therapy for acute kidney injury, but to achieve this it may be necessary to use higher doses while minimizing interruptions to total filter time (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012).

The use of high volume haemofiltration in the treatment of sepsis is an area of interest to critical care physicians. Initially, the removal of soluble inflammatory mediators seemed a promising hypothesis, but this approach has not improved clinical outcomes (Bouman et al, 2002). Ronco et al (2000) demonstrated better survival with 35 ml/kg/hr compared to 20 ml/kg/hr in sepsis, but no survival benefit from increasing filtration rates to 45 ml/kg/hr. Multiple subsequent randomized controlled trials have not demonstrated any benefit (Tolwani et al, 2008; Bellomo et al, 2009; Joannes-Boyau et al, 2013). A Cocharane systematic review concluded that high volume haemofiltration (35–48 ml/kg/hr) increased the risk of hypothermia without reducing mortality or furthering kidney recovery. Sub-group analysis in septic patients discerned no benefits from high dose filtration (Fayad et al, 2016). Higher doses use more replacement fluid, may shorten membrane life and are more costly, which needs to be considered if there is little evidence for any clinical benefit.

Intravenous access

Early methods of continuous renal replacement therapy used arteriovenous access with arterial flow providing the driving pressures for the extracorporeal circuit and filtration. Modern continuous renal replacement therapy uses double lumen central venous access (10–14 Fr catheter) and a pump in the machine to circulate blood. This avoids the risks associated with large bore arterial cannulation and leads to better controlled rates of filtration (Bellomo and Ronco, 2000). *Table 3* describes the advantages and disadvantages of different central venous access sites.

Anticoagulation

Interruption of continuous renal replacement therapy ranges from 8–28% of total filtration time. The most frequent cause is clotting within the membranes of the circuit filter. Maintaining extracorporeal circuit patency with anticoagulation minimizes breaks in filtration, reduces the differences between prescribed and delivered filtration doses, and lessens the blood loss that results from circuit changing. When blood comes into contact with artificial surfaces, the clotting cascade is activated. Anticoagulation helps to reduce this and increases the life of circuits and membranes. Commonly used anticoagulants include unfractionated heparin, sodium citrate and prostaglandins. KDIGO recommends the use of regional citrate anticoagulation for continuous renal replacement therapy, and unfractionated heparin for patients with contraindications

Table 3. Preferred sites for central venous access and the risks and benefits of each site

Site in order of preference	Risk	Benefits
Internal jugular vein	Swings in intrathoracic pressure may reduce flow rates	Straight route, especially on the right side (kinking less likely)
	Left internal jugular vein lines can damage the thoracic duct	Right internal jugular vein has the least recirculation during filtration
Femoral vein	Highest infection risk	Fairly straight routes (kinking less likely)
		Often provides good flow when tip in the inferior vena cava
Subclavian vein	Risk of pneumothorax	Cleanest site
	Can cause subclavian venous stenosis which can jeopardise future arteriovenous fistula placement	Most comfortable
	Swings in intrathoracic pressure may reduce flow rates	

to citrate. Sodium citrate achieves anticoagulation by chelating calcium which inhibits clot formation in the extracorporeal circuit. Sodium citrate anticoagulation can be achieved by using a number of different methods depending on the machine and fluids used.

Unfractionated heparin is given as a bolus, then as a continuous infusion (5–10 IU/kg/hr) into the extracorporeal circuit, before the membrane (Kishen et al, 2009). Its benefits are its low cost, reversibility (with protamine), ease of monitoring (through activated partial thromboplastin time), short half-life of 90 minutes and extensive clinical experience (Ronco et al, 2015). Regional anticoagulation with heparin can be achieved by infusing protamine after the filter. Prostacyclin inhibits platelet aggregation and can be used with or without heparin. Prostacyclin is significantly more expensive than heparin, can cause vasodilation and hypotension but has a shorter half-life.

Anticoagulants should be avoided in patients with impaired coagulation (international normalized ratio >2.5, activated partial thromboplastin time >60 seconds, platelets <60x10^9/litre) and also those who have had recent surgery (Kishen et al, 2009). In such cases, higher pump speeds and pre-dilution can reduce circuit and membrane clotting.

Pharmacokinetics

Acute kidney injury impedes the clearance of many drugs, but once continuous renal replacement therapy is initiated, the removal of water-soluble drugs is accelerated. Commonly used drugs removed by continuous renal replacement therapy are outlined in *Table 4*. Drug clearance is increased by high filtration rates, long filtration sessions, high flux membranes, post-dilution and the patient's residual renal function. In addition, critically ill patients often have low albumin levels and volume overload, reducing the proportion of protein bound drug. Higher levels of unbound soluble drug result in greater clearance and lower therapeutic levels (Vaara et al, 2012).

Without standardized dosage, the pharmacokinetic effects of continuous renal replacement therapy are difficult to gauge accurately. Ideally, drugs should be individually titrated to measured blood levels. However, therapeutic levels of many medications cannot be measured and therefore dosage is based on old pharmacokinetic models (Vaara et al, 2012).

When to stop

Decisions to stop continuous renal replacement therapy are hindered by the unpredictability of kidney recovery in critically ill patients and the challenges of assessing renal function during continuous renal replacement therapy. While receiving continuous renal replacement therapy the blood markers of kidney function (creatinine and urea) are the combined result of continuous renal replacement therapy and underlying renal clearance.

Current guidelines recommend stopping continuous renal replacement therapy when intrinsic kidney function has been restored, i.e. when creatinine clearance is at a minimum of 20 ml/kg, and electrolytes, fluid and pH are normal (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). In the Acute Renal Failure Trial Network Study renal support was ceased when creatinine clearance >20 ml/min, urine flow >20 ml/hr or there was a spontaneous fall in serum creatinine level. Studies have shown that urine output is the safest indicator for cessation (Ronco et al, 2015). Urine output exceeding 400 ml/day, in the absence of diuretics, has a positive predictive value for successful

Table 4. Drugs that are removed by continuous renal replacement therapy

Removed	Lithium
	Methanol
	Ethylene glycol
	Salicylates
	Barbiturates
	Metformin
	Aminoglycosides
	Carbapenems
	Cephalosporins
	Penicillins
	Metronidazole
Not removed	Digoxin
	Tricyclics
	Phenytoin
	Gliclazide
	Beta blockers (except atenolol)
	Benzodiazepines
	Warfarin
	Macrolide
	Quinolones

KEY POINTS

- Acute kidney injury is common among critically ill patients.
- For haemodynamically unstable patients continuous renal replacement therapy should be used rather than intermittent therapies.
- The administration of continuous renal replacement therapy should be tailored towards individual patient needs, based on current best evidence available.
- Circuit durability depends on good vascular access, adequate anticoagulation, and appropriate machine and blood pump settings.
- The effect of continuous renal replacement therapy on drugs must be taken into consideration in order to avoid under- or overdosing.
- Survivors of acute kidney injury who received continuous renal replacement therapy should routinely be followed up, ideally by a nephrologist.
- No one system of continuous renal replacement therapy has been shown to be consistently superior to another in the setting of critical illness.

discontinuation in >80% of patients (Uchino et al, 2009), whereas reinitiating continuous renal replacement therapy is associated with increased mortality (Uchino et al, 2009). Whether too early discontinuation of continuous renal replacement therapy with subsequent re-initiation is by itself harmful or an indicator of disease severity requires further investigation. Withdrawal of continuous renal replacement therapy must also be considered when kidney function fails to recover and the patient is not suitable for long-term renal replacement.

Complications of continuous renal replacement therapy

Before initiating continuous renal replacement therapy, the benefits must be weighed against risks, e.g. common complications include haemodynamic instability, volume and electrolyte disturbances. Intravascular catheter-related complications such as pneumothorax and arterial cannulation have been reduced with use of ultrasound guidance. Other line complications include arrhythmias, thrombosis, infection and stenosis from repeated line insertion. Extracorporeal circuits risks include air emboli, sensitivity reactions, hypothermia, thrombosis and thrombocytopenia. Continuous anticoagulation can cause bleeding and heparin-induced thrombocytopenia, but the use of regional anticoagulation has reduced these risks (Kishen et al, 2009).

Outcomes

After a critical illness complicated by acute kidney injury requiring continuous renal replacement therapy it is difficult to predict which patients' renal function will return to normal, and which will have chronic renal impairment. Follow up of patients who have received continuous renal replacement therapy is poor, as demonstrated by Kirwan et al (2015) who assessed the follow up of patients that received continuous renal replacement therapy for acute kidney injury; 57% of patients had their creatinine level measured 3–6 months post discharge and only 12% received specialist nephrology follow up. When renal function was assessed, the rate of chronic kidney disease, stage 3 or greater, rose from 49% to 70% (Kirwan et al, 2015).

Current literature on the impact of continuous renal replacement therapy on long-term kidney function is limited and complicated by large variations in study design and patient heterogeneity. A systematic meta-analysis assessing renal recovery in survivors of critical illness who received continuous renal replacement therapy or intermittent haemodialysis found that intermittent haemodialysis was associated with a higher rate of dialysis dependence compared with continuous renal replacement therapy. However, this finding was limited to observational studies and no difference was found when analysis included randomized controlled trials (Schneider et al, 2013). More recently Wald et al (2014) demonstrated an association between continuous renal replacement therapy, used in the treatment of acute kidney injury, and a lower risk of chronic dialysis when compared to intermittent haemodialysis. To understand outcomes there is a need for more detailed follow up and a large-scale investigation into long-term complications.

Costs

Continuous therapies cost considerably more per day than intermittent therapies, with haemofiltration sterile fluid and staffing costs contributing much of this. Consequently, some intensive care units opt to switch patients requiring continuous renal replacement therapy to intermittent haemodialysis once they are haemodynamically stable.

Future developments

Current biomarkers of renal function are often inconsistent. A rise in the creatinine level is only seen once kidney damage has taken place, and during continuous venovenous haemofiltration the levels are not representative of renal function. More reliable biomarkers to determine the onset, severity and treatment response of renal failure are necessary. Biomarkers currently under investigation (e.g. neutrophil gelatinase-association lipocalin, cystatin C, interleukin 8 and kidney injury molecule 1) should be considered in future studies.

Conclusions

There is no doubt that without continuous renal replacement therapy, most critically ill patients would be unable to receive adequate renal replacement therapy. However, there remain a number of areas of uncertainty in its optimum use, including clarity on when to start and stop therapy, and the optimum dose in different cases. A thorough understanding of the theory and practice of continuous renal replacement therapy is essential for anyone working on a critical care unit. **BJHM**

Conflict of interest: none.

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