Renal

Renal replacement therapy in critical care

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INTRODUCTION

Acute renal failure, also known as acute kidney injury (AKI), is defined as an abrupt (within 48 hours) reduction in kidney function. The AKI network defines the reduction in kidney function as the presence of any one of the following:[1]

- An absolute increase in serum creatinine of ≥ 0.3mg.dl^{-1} (≥ 26.4mcmol.L^{-1}),

- A percentage increase in serum creatinine of ≥ 50% (1.5-fold from baseline),

- A reduction in urine output (< 0.5ml.kg^{-1} per hour for more than six hours).

It is estimated that a third of patients in the critical care setting have an AKI[2] and approximately 5% will require renal replacement therapy (RRT).[3] The hospital mortality in patients with an AKI requiring RRT is as high as 60%.[4]

The initial management of AKI involves treating the underlying cause, stopping nephrotoxic drugs and ensuring that the patient is euvolaemic, with an adequate mean arterial blood pressure. However, no specific treatments have been shown to reverse the course of AKI, so RRT forms the basis of further management.

INDICATIONS FOR RRT

Indications for RRT are:

Acute kidney injury (AKI) with:

- Fluid overload (unresponsive to diuretics)

- Hyperkalemia (K$^+$ > 6.5)

- Severe metabolic acidosis (pH < 7.1)

- Rapidly climbing urea/creatinine (or urea > 30mmol.L^{-1})

- Symptomatic uraemia: encephalopathy, pericarditis, bleeding, nausea, pruritus

- Oliguria/anuria.

There are no universally accepted levels of urea, creatinine, potassium, or pH at which to start therapy. The figures quoted above are given as a rough guide. Initiation of RRT should be prompted more by the rate of change of renal parameters, and by the patient's overall condition, than by arbitrary levels.

There is some suggestion that starting RRT early (defined as a urea < 27mmol.l^{-1} in the PICARD study) may offer a survival benefit, however guidance on exact timing of RRT is still lacking.[5]

Summary

Acute kidney injury is common in the critically ill and RRT has a role in its management. It is also indicated in some cases of poisoning and in management of patients with severe sepsis. RRT is not universally available, however the next article describes how peritoneal dialysis may be a more cost-effective and safer technique in resource poor settings.

Table 1. *Examples of drugs/toxins removed or not removed by RRT.*

Removed	Not removed
Lithium	Digoxin
Methanol	Tricyclics
Ethylene glycol	Phenytoin
Salicylates	Gliclazide
Barbiturates	Beta-blockers (except atenolol)
Metformin	Benzodiazepines
Aminoglycosides, metronidazole, carbapenems, cephalosporins and most penicillins	Macrolide and quinilone antibiotics Warfarin

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Overdose with a dialysable drug or toxin

Some drugs are removed by RRT but some are not. As a general rule, drugs are cleared by RRT if they are water soluble and not highly protein bound (Table 1).

Severe sepsis

Recent studies have investigated the role of haemofiltration in removal of inflammatory mediators in patients with severe sepsis and septic shock. A number of small studies (with 25 subjects or less) have suggested that high volume haemofiltration (40-85ml.kg^{-1}.h^{-1}) may reduce vasopressor requirements and possibly improve survival in patients with septic shock, irrespective of whether they have AKI.[6,7,8,9] However, strong recommendations cannot be made about the role of RRT in this area until larger, well designed trials have been completed.

TYPES OF RRT IN USE IN INTENSIVE CARE

RRT encompasses peritoneal dialysis and renal transplantation but for the purpose of this article we will focus on the forms of RRT most extensively used in the intensive care setting. These are:

Intermittent haemodialysis (IHD)

Continuous renal replacement therapies (CRRT)

a. Continuous venovenous haemofiltration (CVVH)

b. Continuous venovenous haemodialysis (CVVHD)

c. Continuous venovenous haemodiafiltration (CVVHDF)

d. Slow continuous ultrafiltration (SCUF)

e. Continuous arteriovenous haemofiltration (CAVHD).

Hybrid therapies e.g. Sustained low-efficiency dialysis (SLED)

The functional differences between the techniques listed above can be classified in terms of:

- The mechanism of solute removal (filtration versus dialysis)

- The duration of the treatment (continuous versus intermittent).

DEFINITIONS

Convection
Solute transport across a membrane together with a solvent (usually water) in response to a pressure gradient across the membrane.

Dalton
A unit of mass used to express atomic and molecular masses. It is the approximate mass of a hydrogen atom, a proton, or a neutron.

Diffusion
Solute transport from a compartment with high concentration to a compartment with low concentration.

Fick`s Law of diffusion
States that the rate of diffusion across a membrane is proportional to the concentration gradient across that membrane

Hydrostatic pressure
The pressure exerted by a fluid at equilibrium at a given point within the fluid, due to the weight of the fluid above. In the context of haemofiltration, this pressure is created by the rollerball pump system of the extracorporeal circuit.

Semipermeable membrane
A barrier, either cellulose or synthetic, that allows water, electrolytes and other molecules to pass through, while cellular components and larger molecules are held on one side.

Ultrafiltrate
Plasma water and solutes that pass through the semipermeable membrane.

Ultrafiltration
Transport of water across a membrane by a pressure gradient.

MECHANISM OF SOLUTE REMOVAL

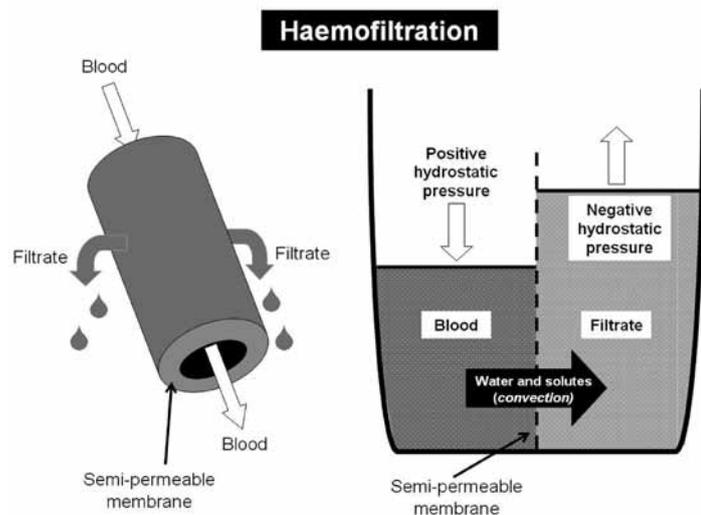### Filtration (convection) versus dialysis (diffusion)

Haemofiltration involves blood being pumped through an extracorporeal system that contains a semi-permeable membrane. The hydrostatic pressure that is created on the blood-side of the filter drives plasma water across the filter. This process is referred to as ultrafiltration. Molecules that are small enough to pass through the membrane (<50,000 Daltons) are dragged across the membrane with the water by the process of convection. The filtered fluid (ultrafiltrate) is discarded and a replacement fluid is added in an adjustable fashion, according to the desired fluid balance.

Haemodialysis involves blood being pumped through an extracorporeal system that contains a dialyser. Blood flows through the dialyser in one compartment, separated from crystalloid solution (dialysate) in a second compartment, by a semipermeable membrane. Solutes move across the membrane, down their concentration gradient (i.e. from high concentration to low) from one compartment of the dialyser to the other (Fick`s law of diffusion). For example, bicarbonate moves from dialysate to blood whereas urea and potassium move from blood to dialysate. In order to maintain these essential concentration gradients and enhance the efficiency of the system the dialysate flows in the opposite direction to the flow of blood (*countercurrent*). When removal of water is required, the hydrostatic pressure on the blood side of the membrane is increased in order to force water molecules into the dialysate compartment.

Haemodiafiltration is a combination of filtration and dialysis. There is no evidence to suggest that CVVDF has a survival benefit when compared to CVVH, but if may be a useful way of increasing clearance of small solutes.

Slow continuous ultrafiltration is used when the only requirement is water removal. Effectively, it is CVVH with a low filtration rate. It can remove up to 6 litres of fluid a day but solute removal is minimal.
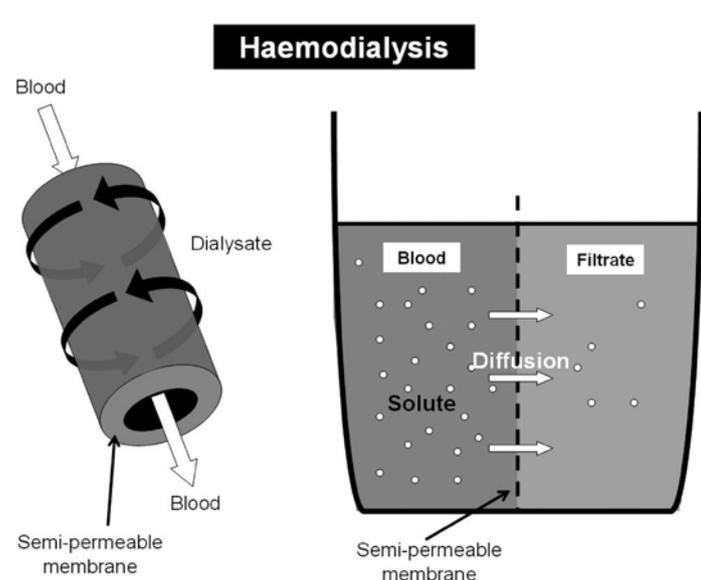
A

B

Figure 1. *Schematic diagram comparing the different modes of solute removal in A - haemofiltration; B - haemodialysis (redrawn from emcrit. org).*

DURATION OF TREATMENT

Intermittent (IHD) versus continuous (CRRT)

Intermittent haemodialysis involves dialysing with higher flow rates than CRRT for defined periods of time. A typical regime is 3-5 hours of dialysis 3 times a week. The high flow rates and rapid fall in plasma osmolality mean that it is only suitable for patients who are cardiovascularly stable. It forms the basis of long term RRT for chronic renal failure and is not commonly used in the critical care setting.

CRRT involves filtering and/or dialysing on a continuous basis. It allows better fluid management and creates less haemodynamic disturbance, but it is more expensive than IHD and requires continuous rather than intermittent anticoagulation. There is some evidence to suggest that CRRT is superior to IHD in patients with sepsis, cardiovascular instability or with a head injury. However, a large RCT comparing IHD with CRRT, in patients with an AKI and multiple-organ dysfunction syndrome, showed no difference in survival at 60 days.[10]

Sustained low efficiency dialysis (SLED) is an example of a hybrid therapy which aims to combine the logistic and cost advantages of IHD with the relative cardiovascular stability of CRRT. Treatments are intermittent but usually daily and with longer session durations than conventional IHD. Solute and fluid removal are slower than IHD, but faster than CRRT. Some are confident that hybrid therapies are the future of RRT in ICU, but there is little evidence to support this. At present, it is not a technique used in the UK.

WHICH FORM OF RRT SHOULD WE USE?

No single RRT technique has been shown to offer a survival benefit over the others in the critical care setting, so the decision about which technique to use depends on:

1. **What we want to remove from the plasma (Table 2)**

2. **The patient`s cardiovascular status**

- CRRT causes less rapid fluid shifts and is the preferred option if there is any degree of cardiovascular instability.

3. **The availability of resources**

- CRRT is more labour intensive and more expensive than IHD

- Availability of equipment may dictate the form of RRT.

Table 2. *How the choice of RRT can be determined by the aim of treatment.*

What do you want to remove?	Size of molecule (Daltons)	Example	Preferred type of RRT
Small molecules/electrolytes	< 500	Urea, creatinine, K^+, H^+, lithium	Dialysis or filtration
Middle molecules	500 – 5 000	Large drugs e.g. vancomycin	Filtration better than dialysis
Low molecular weight proteins	5 000 – 50 000	Cytokines, complement	Filtration
Water	18		Filtration better than dialysis

4. The clinician's experience

- It is wise to use a form of RRT that is familiar to all the staff involved.

5. Other specific clinical considerations

- Convective modes of RRT may be beneficial if the patient has septic shock.

- CRRT can aid feeding regimes by improving fluid management.

- CRRT may be associated with better cerebral perfusion in patients with an acute brain injury or fulminant hepatic failure.[11]

OPTIMAL FLOW RATES / DOSE OF RRT

The desired variables for RRT must be prescribed. The flow rate refers to the ultrafiltrate produced by the filtration process, as well as any effluent dialysate flow. The flow rate is a marker of solute clearance so it can simplistically be thought of as the dose of RRT.

Two recent randomised controlled trials have concluded that there is no benefit in increasing the flow rate from 20 to 35ml.kg^{-1}.h^{-1}:

The Randomised Evaluation of Normal versus Augmented Level of renal replacement therapy in ICU (RENAL) study randomised 1400 critically ill patients with AKI to intensive (35ml.kg^{-1}.h^{-1}) or non-intensive (20ml.kg^{-1}.h^{-1}) CRRT and no difference in mortality was seen in the two groups at 90 days.[12]

The Acute Renal Failure Trial Network (ATN) study compared intensive or less intensive dosing strategies for patients undergoing CRRT (35ml.kg^{-1}.h^{-1} versus 20ml.kg^{-1}.h^{-1}), IHD (daily versus alternate days) and SLED. The recovery of renal function and the mortality at 60 days were the same in both arms of the trial, but there were more hypotensive episodes in the intensive group.[13]

High volume haemofiltration may be of benefit in patients with septic shock, so there is currently a trend to increase flow rates in patients with septic shock and AKI. This is being investigated in the IVOIRE (Impact of High-volume Venovenous Continuous Hemofiltration in the Early Management of Septic Shock Patients With Acute Renal Failure) study.

PRACTICAL ISSUES

Vascular access

Venovenous RRT requires a double lumen vascular catheter placed in a central vein. The tip should be sited in the inferior vena cava for femoral lines or superior vena cava (1-2cm from right atrium) for internal jugular and subclavian lines. The catheters are usually made of polyurethane or silicone and need to be stiff enough to prevent collapse under high negative pressures, but soft enough to prevent kinking. The lumens can be arranged in various fashions but, as long as each lumen is at least 11 French gauge, there is no evidence that one design is superior to the others.

Good flow through the intravenous catheter is crucial to prevent stasis of blood in the circuit and clotting of the filter. There are a number of things to take into account when choosing the site of the vascular access (Table 3).

Extracorporeal circuits

Most CRRT techniques utilise a pump driven, venovenous circuit, as this provides a high constant flow rate. Arteriovenous techniques are described and were used historically, but are associated with catheter associated complications and are less reliable.

Anticoagulation

All modes of RRT that utilise an extracorporeal circuit will activate coagulation pathways and the premature 'clotting off' of a filter is a common problem. Even a small amount of clot formation will reduce filter performance, but if a filter clots off completely the blood contained in the circuit is lost and there an interruption in treatment while a new circuit is prepared.

Clot formation in the filter will trigger the transmembrane pressure alarm, whereas clot in the venous catheter will trigger the access pressure alarm. Kinking of the catheter or a collapsing vein can also

Table 3. *Considerations when choosing where to site the central venous catheter.*

Line Site	Advantage	Disadvantage
Internal jugular vein	• Straightest route (esp right side) and, overall, the preferred site	• Swings in intrathoracic pressure reduce flow • Often occupied by other lines
Subclavian vein	• Cleanest site • Most comfortable for patient	• Exposed to intrathoracic pressure changes (as above) • Subclavian vein stenosis* • Pneumothorax
Femoral vein	• Fairly straight route and often provides good flows when tip in IVC	• Highest risk of infection (especially in obese patients)

* There is a significant chance of subclavian vein stenosis after large bore venous catheter insertion. This is problematic if an arteriovenous fistula is subsequently required for long term dialysis. However mortality of patients on CRRT is high and those who survive are not usually dialysis dependant.
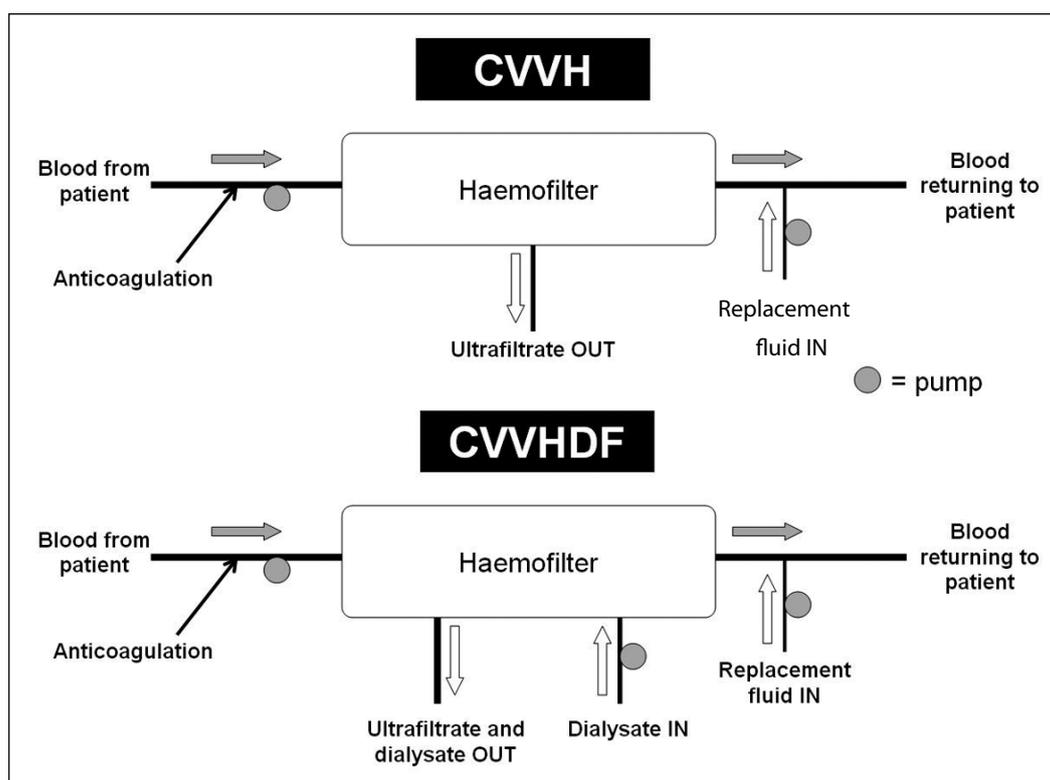
Figure 2. *Schematic represenation of CVVH and CVVHDF circuits.*

be responsible for triggering the access pressure alarm.

Non-pharmacological measures to reduce clot formation include ensuring the patient has an adequate central venous pressure, optimising vascular access and adding a proportion of the replacement fluid to the patient's blood before it passes through the haemofilter (this is *predilution*).

Guidelines published in 2009 by Intensive Care Society (UK) suggest that anticoagulation is NOT required when:[14]

- There is a already a degree of coagulopathy
    - INR > 2-2.5
    - APTT > 60 seconds
    - platelet count < 60 x 10^3.mm^{-3}

- There is a high risk of bleeding.

Anticoagulation should be considered in all other situations and the aim is to anticoagulate the filter and not the patient. In practice, this can be more difficult than it sounds. The forms of anticoagulation available are:

Unfractionated or low molecular weight heparins

Unfractionated heparin (UFH) [5-30kDa] is the most commonly used anticoagulant in the UK and a typical regime involves a 40-70IU.kg^{-1} bolus followed by a pre-filter infusion at 5-10IU.kg.$^{-1}$h^{-1}. It is the most cost effective anticoagulant and is fully reversible with protamine. The APTT should be monitored to avoid excessive anticoagulation but there is no evidence that elevating the APTT prolongs filter life.

Low molecular weight heparins (LMWH) [4.5-6kDa] are only used for RRT in 4% of intensive care units in the UK.[15] They are dependant on renal elimination, so in this setting their dosing needs to be guided by anti-factor Xa levels (aiming for 0.25-0.35IU.ml^{-1}). The half life of LMWHs is longer than for UFH (2 - 6hours versus 1.5 - 3hours) and their effect can only be partially reversed with protamine. There is not a huge amount of data on the use of LMWH in CRRT and there is no evidence to suggest that they are superior to UFH.[16]

Prostaglandins

Prostaglandins (prostacyclin or prostaglandin E$_2$) inhibit platelet function and can either be used on their own or in combination with heparin, with which they have a synergistic effect. Prostaglandins have a short half life (several minutes) so are administered as an infusion (2.5–10ng.kg^{-1}.min^{-1}). The anticoagulant effect stops within 2 hours of discontinuing the infusion, making them a useful alternative to heparin in patients at high risk of bleeding. The main side effect is vasodilation, which may include a reduction in hypoxic pulmonary vasoconstriction leading to hypoxaemia. The other disadvantage is that they are expensive and so are only used as second line therapy.

Regional citrate anticoagulation

Regional citrate anticoagulation is an effective therapy, especially when there is an increased risk of bleeding. It is often used as an alternative to heparin in the USA, but it is rarely used in the UK. Sodium citrate is infused into the circuit pre-filter which chelates calcium and inhibits clot formation. The calcium citrate complex is freely filtered so a calcium infusion is required post-filter.

Others

There is no evidence to suggest newer heparin alternatives such as danaparoid, hirudin, fondaparinux or argatroban are better than UFH/LMWHs.

Filters

The properties of a filter that have an impact on its function are:

Biocompatibility

The degree to which the membrane will activate the patient`s inflammatory and coagulation pathways. The greater the biocompatibility of a membrane, the less activation it will cause.

Flux

The permeability of the filter. High flux membranes are hydrophobic and may have more or larger pores allowing more water and solute to move across the membrane.

Adsorption

The ability of larger solutes to adhere to the surface of the membrane. A highly adsorptive membrane offers the potential benefit of adsorbing mid sized molecules, including inflammatory mediators, but only until it is saturated with them (usually after the first few hours).

Thickness

Thinner membranes allow greater movement of solute by diffusion and also favour convective movement.

Surface area

The surface area of the membrane determines the available area for diffusion and ultrafiltration.

Filters are either cellulose-based or synthetic. Synthetic filters, such as polysulphone and polyamide, are more biocompatible and are higher-flux membranes so seem more suitable for CRRT, however, there is no conclusive evidence that they improve outcome. In practice, most filters used for CRRT are synthetic, high-flux membranes with a surface area of $0.6–1.2m^2$ and a pore size allowing the passage of molecules up to 50,000 Daltons.

Replacement fluid

Replacement fluids vary slightly in their composition, but all are balanced salt solutions with either a lactate or bicarbonate buffer.

Lactate based solutions are stable and hence the cheaper and more practical option, however their buffering capacity depends on the conversion of lactate into bicarbonate. Under normal physiological conditions the body converts lactate into bicarbonate on an equimolar basis. This is not always the case in critically ill patients, particularly if they have impaired liver function or already have a lactic acidosis. In these situations, RRT using a lactate based replacement fluid can worsen the patient's acidosis, so a bicarbonate based replacement solution should be used. If this is not possible, and serum lactate levels are not excessive, then an alternative option is to continue with the lactate based replacement solution and commence an intravenous infusion of bicarbonate.

Bicarbonate based replacement solutions have a more reliable buffering capacity, but need to be prepared just prior to use. At present, there is no evidence to suggest that the choice of replacement fluid has an impact on survival or renal recovery.

Replacement fluid can be added pre- or post-filter in varying ratios. The benefit of adding some of the replacement fluid pre-filter is that it lowers the haematocrit of the blood, which reduces the likelihood of the filter clotting. The downside is that pre-dilution reduces solute clearance and a compensatory increase in flow rates should be considered. (15% for ultrafiltration rates of $2L.h^{-1}$ and up to 40% for rates of $4.5L.h^{-1}$).

Pharmacokinetics while on RRT

Some say that while a patient is receiving RRT drugs should be dosed as if the GFR is $10-50ml.min^{-1}$, but unfortunately it is probably not this simple since there are numerous variables. The most reliable guide to dosing is by measuring drug levels but this is not usually a feasible option, so referring to the drug manufacturer's recommendations is a reasonable place to start.

The factors that affect the pharmacokinetics while on RRT are:

Protein binding

Drugs that are highly protein bound (e.g. warfarin, diazepam, propranolol and phenytoin) are only cleared by RRT in small amounts. However, as the patient's protein levels fall, the free fraction of the drug increases along with its clearance.

Size of drug molecule and mode of RRT

Small molecules (<500 Daltons) are cleared by all (convective versus diffusive) types of RRT, but as molecule size increases diffusion becomes less effective.

Timing of RRT

Drugs given between sessions of IHD or SLED (intermittent versus continuous) will not be cleared until the subsequent session.

Dose of RRT

Reduced flow rates and/or shorter dialysis sessions will reduce clearance of drugs.

Membrane permeability

The high-flux haemofilter membranes used in CRRT are permeable to most non-protein-bound drugs.

The patient's residual GFR

This also needs to be taken into consideration.

Prescription of RRT

A typical prescription for a 75kg patient requiring CRRT for an AKI would be as follows:

Anticoagulation:

- Unfractionated heparin: 5000IU bolus followed by a pre-filter infusion at $500IU.h^{-1}$,

- Aim to anticoagulate filter but ensure APTTR <2.

Fluid balance over 24 hours:

- Aim for an even balance if the patient is euvolaemic,

- Aim for the appropriate negative balance if the patient is fluid overloaded ($<1500ml.24h^{-1}$).

Type of replacement fluid/Dialysate:

- Use solutions without potassium if serum potassium is high, but switch to potassium containing solutions as serum potassium normalises.

- Use a bicarbonate based buffer rather than a lactate based buffer if there are concerns about lactate metabolism or if serum lactate > $8mmol.L.^{-1}$ [Note - An intravenous bicarbonate infusion may be required if a lactate based buffer is used]

Table 4. *CRRT flow rates for a 75kg patient with an AKI.*

Hourly flow rate	Hourly exchange rate for a 75kg patient (L.h^{-1})	CVVH	CVVHDF	
		Ultrafiltration rate (L.h^{-1})	Ultrafiltration rate (L.h^{-1})	Dialysate flow rate (L.h^{-1})
Standard flow rate (20ml.kg^{-1}.h^{-1})	1.5	1.5	0.75	0.75
High flow rate* (35ml.kg^{-1}h^{-1})	2.6	2.6	1.3	1.3

*Consider high flow rates in patients with septic shock and AKI

Exchange rate/treatment dose:
- 1500ml.h^{-1} (75kg x 20ml.kg^{-1}·h^{-1})

The treatment dose is usually prescribed as an hourly 'exchange rate' which is the desired hourly flow rate adjusted for the patient`s weight. In the case of CVVH, the exchange rate simply represents the ultrafiltration rate, whereas in CVVHDF it represents a combination of the ultrafiltration rate and the dialysate flow rate. In CVVHDF, the ratio of ultrafiltration to dialysate flow is often set at 1:1, but it can be altered to put the emphasis on either the dialysis or filtration component (Table 4).

COMPLICATIONS

Complications common to IHD, CRRT, and hybrid therapies include:

- Complications related to the vascular access catheter (including line-related sepsis)
- Haemodynamic instability
- Air emboli
- Platelet consumption
- Blood loss
- Electrolyte imbalances
- Hypothermia
- Effects of anticoagulation (bleeding or specific side effects of the anticoagulant used e.g. heparin induced thrombocytopenia).

PROGNOSIS OF PATIENTS WITH AKI ON RRT

Bagshaw et al looked at the outcomes in 240 patients with AKI requiring RRT and showed that, although the mortality rate was high (around 60%), the majority of survivors (78%) were free from RRT at one year. Of those requiring chronic RRT, 63% had pre-existing chronic renal impairment with a median pre-admission creatinine of 232mcmol.L^{-1}.[4]

SUMMARY

AKI is common and 5% of the critical care population receive RRT. There are various forms of RRT, but they all remove unwanted solutes using the processes of diffusion (dialysis) and/or convection (filtration). RRT can be administered continuously or intermittently.

No single form of RRT has been shown to offer a survival benefit over the others, but there are often other reasons why a particular technique may be preferable in a given situation. There is some evidence that high volume haemofiltration may improve survival in patients with septic shock but there have been no large randomised controlled trials in this area.

The lifespan of the circuit is dependant on good quality vascular access and appropriate anticoagulation. Pharmacokinetics must be considered on an individual basis, but there are some general rules, such as drugs which are protein bound are not easily removed.

60% of people receiving RRT for AKI will die during that admission but 80% of the survivors will be free from RRT one year later.

REFERENCES

1. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11**: R31.

2. Ostermann M, Chang RW: Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med* 2007; **35**: 1837–43.

3. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005; **294**: 813–8.

4. Bagshaw SM, Laupland KB, Doig CJ, Mortis G, Fick GH, Mucenski M, Godinez-Luna T, Svenson LW, Rosenal T. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. *Crit Care* 2005; **9**: 700-9.

5. Liu, KD, Himmelfarb, J, Paganini, E, et al. Timing of initiation of dialysis in critically ill patients with acute kidney injury. *Clin J Am Soc Nephrol* 2006; **1**: 915-9.

6. Honore PM, Jamez J, Wauthier M et al. Prospective evaluation of short-term, high volume isovolemic haemofiltration on the haemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. *Crit Care Med* 2000; **28**: 3581-87.

7. Joannes-Boyau O, Rapaport S, Bazin R et al. Impact of high volume haemofiltration on haemodynamic disturbance and outcome during septic shock. *ASAIO J* 2004; **50**: 102-9.

8. Ratanarat R, Brendolan A, Piccinni P et al. Pulse high-volume haemofiltration in critically ill patients: Effects on hemodynamics and survival. *Crit Care* 2005; **9**: 294-302.

9. Cornejo R, Downey P, Castro R et al. High-volume haemofiltration as salvage therapy in severe hyperdynamic septic shock. *Intensive Care Med* 2006; **32**: 713-22.

10. Vinsonneau, C, Camus, C, Combes, A, et al. Continuous venovenous hemodiafiltration versus intermittent hemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre, randomized trial. *Lancet* 2006; **368**: 379-85.

11. Davenport A, Will EJ, Davison AM. Continuous vs intermittent forms of haemofiltration and/or dialysis in the management of acute renal failure in patients with defective autoregulation at risk of cerebral oedema. *Contrib Nephrol* 1991; **93**: 225-33.

12. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S. Intensity of continuous renal-replacement therapy in critically ill patients (RENAL study). *N Engl J Med* 2009; **361**: 1627-38.

13. The VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008; **359**: 7-20.

14. J.J. Gatward, G.J. Gibbon, G. Wrathall and A. Padkin. Standards and Recommendations for the Provision of Renal Replacement Therapy on Intensive Care Units in the United Kingdom. Intensive Care Society (2009). Website: ics.ac.uk

15. Renal replacement therapy for acute renal failure: a survey of practice in adult intensive care units in the United Kingdom. *Anaesthesia* 2008; **63**: 959-66.

16. Oudemans-van Straaten HM, Wester JPJ, de Pont AC et al. Anticoagulation strategies in continuous renal replacement therapy: can the choice be evidence based? *Intensive Care Med* 2006; **32**: 188-202.