

RENAL REPLACEMENT THERAPY IN CRITICAL CARE TUTORIAL OF THE WEEK 194

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Dr Andrew Baker, Anaesthetic ST5,
Dorset County Hospital, Dorchester, UK

Dr Richard Green, Consultant Anaesthetist,
Royal Bournemouth Hospital, Bournemouth, UK

Correspondence to: andrewkellasbaker@doctors.org.uk



SELF ASSESSMENT

- Which of the following statements comparing Dialysis with Filtration are true:
 - Dialysis depends on diffusion whereas filtration depends on convection
 - Filtration is more effective than dialysis at removing small molecules
 - Filtration is more effective than dialysis at removing cytokines
 - Dialysis is not as effective as Filtration at removing water
- Which of the following statements are true regarding the differences between Continuous Renal Replacement Therapy (CRRT) and Intermittent Haemodialysis (IHD):
 - CRRT is more cost effective than IHD
 - IHD is preferable to CRRT in patients who are cardiovascularly unstable
 - IHD offers an overall survival benefit when compared with CRRT
 - CRRT is preferable to IHD in patients with a coexistent acute brain injury
- Are the following statements regarding RRT True or False:
 - Poor vascular access often contributes to the clotting of a filter
 - RRT has an established role in septic shock with normal renal function
 - Protein bound drugs are not easily removed by CRRT/IHD
 - The hospital mortality of patients with AKI on RRT is approx 60%

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 $\geq 0.3 \text{ mg.dl}^{-1}$ ($\geq 26.4 \text{ mcmol.l}^{-1}$)
- A percentage increase in serum creatinine of $\geq 50\%$ (1.5-fold from baseline)
- A reduction in urine output ($< 0.5 \text{ ml.kg}^{-1}$ per hour for more than six hours).

It is estimated that a third of patients in the critical care setting have an AKI² 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 is the cornerstone of further management.

INDICATIONS FOR RRT

Indications for RRT are:

1. Acute kidney injury (AKI) with:

- Fluid overload (refractory to diuretics)
- Hyperkalemia ($K^+ > 6.5$)
- Severe metabolic acidosis ($pH < 7.1$)
- Rapidly climbing urea/creatinine (or urea $> 30\text{mmol.l}^{-1}$)
- 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 only. Initiation of RRT should be prompted more by the rate of change of renal parameters and by the patients overall condition than by arbitrary levels.

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

2. Overdose with a dialyzable 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. [Please see Table 1]

Table 1. Examples of drugs/toxins that are either removed or not removed by RRT

Removed	Not removed
<ul style="list-style-type: none">• Lithium• Methanol• Ethylene glycol• Salicylates• Barbiturates• Metformin• Aminoglycosides, metronidazole• carbapenems, cephalosporins and most penicillins	<ul style="list-style-type: none">• Digoxin• Tricyclics• Phenytoin• Gliclazide• Beta-blockers (except atenolol)• Benzodiazepines• Macrolide and quinilone antibiotics• Warfarin

3. Severe sepsis

There has been recent interest in the potential for haemofiltration to remove inflammatory mediators in patients with severe sepsis/septic shock. A number of small studies (with 25 subjects or less) have suggested that high volume haemofiltration ($40\text{-}85\text{ml.kg}^{-1}.\text{hr}^{-1}$) may reduce vasopressor requirements and possibly improve survival in patients with septic shock irrespective of whether they have an AKI.^{6,7,8,9} However, strong recommendations cannot be made about the role of RRT in this area until larger, well designed trials address the issue.

[Please see glossary at end of tutorial for definitions of sepsis, severe sepsis, septic shock]

TYPES OF RRT IN USE IN CRITICAL CARE

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

1. **Intermittent haemodialysis (IHD)**
2. **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)
3. **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*)

MECHANISM OF SOLUTE REMOVAL: Filtration (convection) versus dialysis (diffusion)

Haemofiltration involves blood being pumped through an extracorporeal system that incorporates 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 incorporates a dialyzer. In the dialyzer, blood is separated from a crystalloid solution (dialysate) by a semi-permeable membrane. Solutes move across the membrane along their concentration gradient from one compartment to the other obeying Fick's laws of *diffusion*. For example, bicarbonate moves from dialysate to blood whereas urea and potassium move from blood to dialysate. In order to maintain concentration gradients and therefore enhance the efficiency of the system the dialysate flows *countercurrent* to the flow of blood. When removal of water is required the pressure on the blood-side of the membrane has to be increased forcing water molecules to pass into the dialysate.

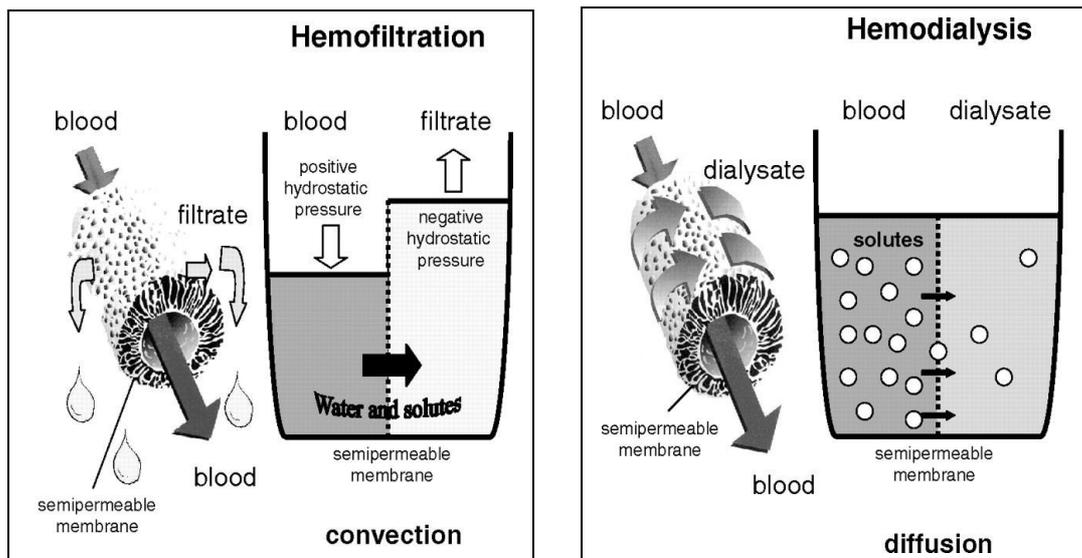


Figure 1. Schematic diagram comparing the different modes of solute removal in haemodialysis and haemofiltration. (Courtesy of emcrit.org)

Haemodiafiltration, as its name suggests, is a combination of filtration and dialysis. It has the benefits of both techniques but to a lesser extent than when the individual techniques are used on their own. There is no evidence to suggest that CVVDF has a survival benefit when compared to CVVH but 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.

DURATION OF TREATMENT: Intermittent (IHD) versus continuous (CRRT) (versus hybrid)

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 but is not often 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 coagulation. 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 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 currently a lack of evidence to support its use. 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 [Please see Table 2]

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

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.

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

When prescribing RRT one is often asked to define a flow rate. The flow rate refers to the ultrafiltrate produced by the filtration process as well as any effluent dialysis 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 to increasing the flow rate from 20 to 35ml.kg.⁻¹hr⁻¹:

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.⁻¹hr⁻¹)

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

Line Site	Advantage	Disadvantage
Internal jugular vein	<ul style="list-style-type: none"> • Straightest route (esp right side) and, overall, the preferred site 	<ul style="list-style-type: none"> • Swings in intrathoracic pressure reduce flow • Often occupied by other lines
Subclavian vein	<ul style="list-style-type: none"> • Cleanest site • Most comfortable for patient 	<ul style="list-style-type: none"> • Exposed to intrathoracic pressure changes (as above) • Subclavian venous stenosis* • Pneumothorax
Femoral vein	<ul style="list-style-type: none"> • Fairly straight route and often provides good flows when tip in IVC 	<ul style="list-style-type: none"> • Highest risk of infection (especially in obese patients)

* There is a significant chance of subclavian venous stenosis after large bore venous catheter insertion which 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.

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.

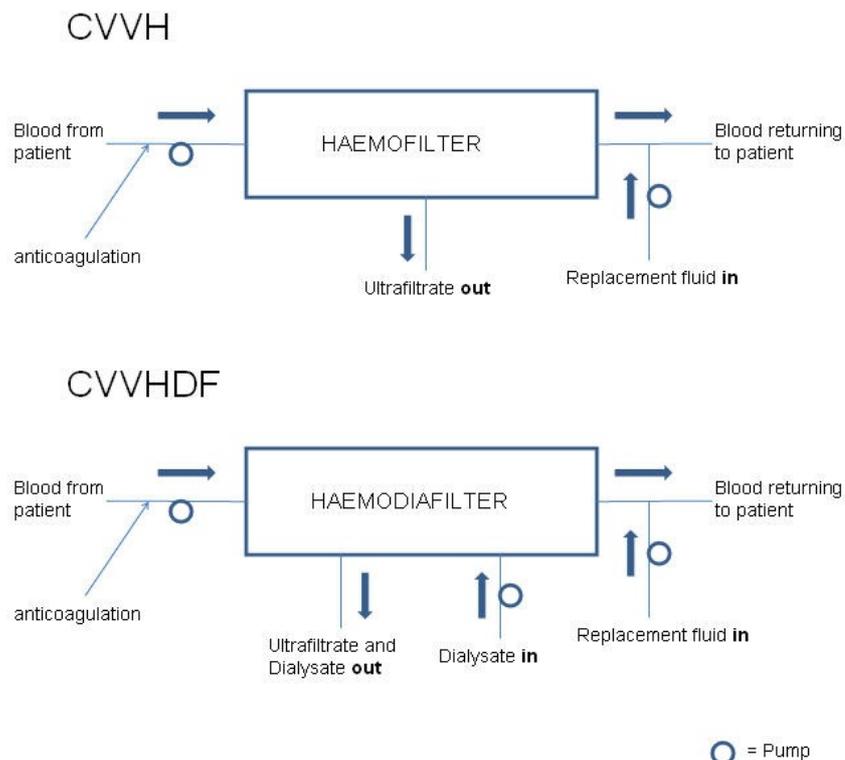


Figure 3. Schematic representation of CVVH and CVVHDF circuits

More detailed diagrams of the circuits used for CVVD and CVVHDF are include in the Appendix at the end of this tutorial

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 be responsible for triggering the *access pressure* alarm.

Non-pharmacological measures that can be taken 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 patients blood before it passes through the haemofilter (this is *predilution*). Guidelines published in 2009 by Intensive Care Society suggest that anticoagulation is NOT required when:¹⁴

- There is already a degree of coagulopathy
 - INR > 2-2.5
 - APTT > 60 seconds
 - platelet count < $60 \times 10^3 \text{.mm}^{-3}$
- There is a high risk of bleeding
- The patient is receiving activated protein C.

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 40-70 IU.kg⁻¹ bolus followed by a *pre-filter* infusion at 5-10 IU.kg⁻¹.hr⁻¹. It is the most cost effective anticoagulant and is fully reversible with protamine. The APTT should be monitored to avoid excessive anti-coagulation 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 0.25-0.35 IU.ml⁻¹). The half life of LMWHs is longer than for UFH (2-6 hrs versus 1.5-3hrs) 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 E2) inhibit platelet function and can either be used on their own or in combination with heparin whereby they have a synergistic effect. Prostaglandins have a short half life (several minutes) so are administered as an infusion (2.5 – 10 ng.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 hypoxemia. The other downside 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. This form of anticoagulation is limited by the metabolic derangements that it can cause: Hypocalcaemia, hypomagnesaemia (Mg^{2+} is also chelated), hypernatraemia (sodium load in sodium citrate), metabolic alkalosis (citrate is metabolised to bicarbonate), metabolic acidosis (caused by the citrate especially if the body's citrate handling is impaired e.g. liver failure).

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 0.6–1.2m² and a pore size allowing the passage of molecules up to 50,000 Daltons.

Replacement fluid

Replacement fluids vary slightly in their composition but are 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, however, 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 $2\text{L}\cdot\text{h}^{-1}$ and up to 40% for rates of $4.5\text{L}\cdot\text{h}^{-1}$)

Pharmacokinetics while on RRT

Some say that while a patient is receiving RRT drugs should be dosed as if the GFR is $10\text{-}50\text{ ml}\cdot\text{min}^{-1}$ but, unfortunately, it is probably not as simple as that 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:

<i>Protein binding</i>	Drugs that are highly protein bound (e.g. warfarin, diazepam, propranolol and phenytoin) are only cleared by RRT in small amounts. However, as the patients protein levels fall the free fraction of the drug increases and so does its clearance.
<i>Size of drug molecule and mode of RRT all (convective versus diffusive)</i>	Small molecules (<500 Daltons) are cleared by types of RRT but as molecule size increases diffusion becomes less effective.
<i>Timing of RRT (intermittent versus continuous)</i>	Drugs given between sessions of IHD or SLED will not be cleared until the subsequent session.
<i>Dose of RRT</i>	Reduced flow rates/ shorter sessions will reduce clearance of drugs.
<i>Membrane permeability</i>	The high-flux haemofilter membranes used in CRRT are permeable to most non-protein-bound drugs.
<i>The patient's residual GFR</i>	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: 5,000 IU bolus followed by a pre-filter infusion at $500\text{ IU}\cdot\text{hr}^{-1}$
- Aim to anticoagulate filter but ensure $\text{APTTR} < 2$

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/24hrs)

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]

Exchange rate/treatment dose:

- 1500ml.hr.⁻¹ (75kg x 20ml.kg.⁻¹hr.⁻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. [Please see Table 4].

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

Hourly flow rate	Hourly exchange rate for a 75kg patient (l.hr. ⁻¹)	CVVH	CVVHDF	
		Ultrafiltration rate (l.hr. ⁻¹)	Ultrafiltration rate (l.hr. ⁻¹)	Dialysate flow rate (l.hr. ⁻¹)
Standard flow rate (20ml. ⁻¹ kg. ⁻¹ hr. ⁻¹)	1.5	1.5	0.75	0.75
High flow rate* (35ml. ⁻¹ kg. ⁻¹ hr. ⁻¹)	2.6	2.6	1.3	1.3

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

COMPLICATIONS

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

- Complications related to the vascath (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 ARF 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 232µmol.l.⁻¹.⁴

OVERVIEW/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.
- Lifespan of the circuit is dependant on good quality vascular access and appropriate anticoagulation.
- Pharmacokinetics while on RRT needs to be looked at 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.

ANSWERS TO QUESTIONS

1. TFFT
2. FFFT
3. TFFT

GLOSSARY OF USEFUL PHYSIOLOGICAL TERMS

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 force of gravity. 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.

Sepsis	The diagnosis of “Sepsis” requires the presence of proven infection with two or more features of the Systemic Inflammatory Response Syndrome (SIRS): <ul style="list-style-type: none">• Temperature > 38 or < 36°C• Respiratory rate > 20• Heart Rate > 90• White Blood Cell count < 4 or > 12.
Severe Sepsis	Sepsis with evidence of organ dysfunction
Septic Shock	Severe Sepsis with hypotension that is refractory to fluid resuscitation.
Ultrafiltrate	Plasma water and solutes that pass through the semipermeable membrane.
Ultrafiltration	Transport of water across a membrane by a pressure gradient. In haemofiltration, it is the process by which plasma water and filterable solutes are separated from whole blood.

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Appendix

The arrangement of a haemofiltration and a haemodiafiltration circuit (available at: www.smilegroup.com.tw/t2-2.asp)

