AHD Objectives

Acute Kidney Injury and RRT in the ICU:

1. What is the prevalence of AKI in the ICU and what percentage of patients require RRT?
2. What are the indications for initiating RRT?
3. Name complications of RRT
4. List the most common types of RRT. What are the indications for IHD and what are the disadvantages? What is the most frequently used modality of RRT in the ICU?
5. What do the addition and composition of replacement fluids serve to regulate?
6. List examples of non-renal indications of RRT
7. When is termination of RRT indicated?

Acute kidney injury and renal replacement therapy in the intensive care unit

Peter Faber and Andrew A Klein

ABSTRACT

Background: Renal replacement therapy (RRT) is now offered as a routine treatment in most intensive care units (ICU) in the UK for patients suffering from acute kidney injury (AKI). It is important for all ICU staff to understand the underlying principles of the available therapeutic options and the possible complications thereof.

Aims and objectives: The objective of this review was to provide an accessible theoretical and practical update on the management of RRT. In addition to a detailed discussion of the underlying principles and indications for the various modes of RRT, we will discuss the assessment of kidney function, possible complications and anticoagulation during RRT, following a review of the current literature.

Search strategies: Pubmed, Medline and the Cumulative Index to Nursing and Allied Health Literature were searched using the keywords renal function, RRT, dialysis, renal failure kidney injury, together with intensive care, intensive therapy and critical care. We included only studies published in English from 1998 to 2008 and from these identified and included additional publications. The 12 most relevant publications are referenced in this review.

Conclusion: AKI is associated with increased mortality in ICU, and RRT should be considered early in the disease process. Continuous haemofiltration is the most common modality of treatment in this group of patients, and a detailed knowledge of the management of such patients is required.

Key words: Acute kidney injury • Anticoagulation • Complications of renal replacement therapy • Renal replacement therapy

INTRODUCTION

In the intensive care unit (ICU), the prevalence of acute kidney injury (AKI) is approximately 50–60%, with 15–20% of patients requiring renal replacement therapy (RRT). In the majority of cases, the pathology of AKI is acute tubular necrosis because of hypoxic tubular injury, associated with severe systemic disease. As opposed to chronic renal failure, AKI is potentially reversible following appropriate and timely intervention. Such early recognition and treatment of imminent AKI is important as hospital mortality may exceed 50% in patients requiring RRT following AKI (Brar *et al.*, 2008). The distinction between chronic renal failure and AKI is often made from the history or patient records. The development of AKI compounds the prognosis of underlying disease, and it is therefore pertinent to treat any renal impairment in parallel with other interventions to improve patient outcome.

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ASSESSING NORMAL RENAL FUNCTION

Glomerular filtration rate (GFR) is the single best measure of overall renal function and is defined as the volume of plasma cleared of a substance per unit of time: GFR (mL/min) = urine concentration (mg/mL) × urine volume (mL/min)/plasma concentration (mg/mL). In the healthy adult, the normal GFR is approximately 100 ± 25 mL/min and is traditionally measured using an infusion of the polysaccharide inulin. As inulin is neither secreted nor reabsorbed in the kidney, the clearance of inulin equals GFR (Rahn *et al.*, 1999). However, inulin and newer biomarkers are not commonly used in clinical practice and instead the endogenous metabolites urea and creatinine are used as surrogate markers to assess GFR (Sterner *et al.*, 2008).

However, nutritional state, age, gender, volume of distribution and muscle mass may have a significant effect. Creatinine clearance is a more accurate measure of GFR than serum creatinine or urea alone. In the absence of 24-h urine collections, one widely used equation to estimate creatinine clearance is the Cockroft-Gault formula (Cockroft and Gault, 1976): creatinine clearance (mL/min) = [(140 − age) × body weight in kg]/serum creatinine in μmol/L. A correction factor of 1·05 is applied for women and 1·23 for men. Local biochemistry laboratories now routinely include estimated GFR following the Modification of Diet in Renal Disease Study (Levey *et al.*, 1999).

ACUTE KIDNEY INJURY

The risk, injury, failure, loss and end-stage (RIFLE) definition of AKI (Bellomo *et al.*, 2004) allows the risk of renal dysfunction, kidney injury and failure to be estimated. The onset of end-stage renal disease is defined as the need for dialysis for more than 3 months.

INDICATIONS FOR RRT

The main indications for initiation of RRT are summarized in Table 1. The decision to start RRT often varies depending on clinical condition and local policies. The prognosis of the underlying pathology, when known, may be more important than the RIFLE score with regard to the initiation of RRT (Rondon-Berrios and Palevsky, 2007). Unnecessary or too early a commencement of RRT may subject patients to additional risks associated with the treatment itself. However, clinical studies have not demonstrated a worse outcome in groups of patients where RRT was initiated early compared with patients where RRT was commenced later.

VASCULAR ACCESS

Vascular access with a dedicated wide-bore (11·5–13·5 FrG) double-lumen dialysis catheter is required. Choice of access site may be determined by clinical condition, the presence of coagulopathy and the experience of the person inserting the catheter. A 15- or 20-cm catheter should be used for the right or left internal jugular vein, respectively. Recirculation and insufficient flow rates are prevented by correct catheter positioning, 1–2 cm above the right atrium for an internal jugular catheter. A 20-cm catheter should be used for *femoral* vein access, with the tip in the inferior vena cava.

Vascular access complications include catheter related bloodstream infection, abscess, arterial puncture, bleeding and vessel thrombosis. Pneumothorax or haemothorax is rare when the internal jugular vein is used for access. Additionally, the catheter may malfunction because of intraluminal thrombosis or kinking. In general, the order of preference for venous access should be the internal jugular vein followed by the femoral vein.

Compared with the internal jugular vein, access obtained through the subclavian vein is associated with twice the rate of infection (18% versus 9%) and a 50% incidence of vessel stricture and thrombosis. If the duration of RRT is expected to last more than 3 weeks, it is recommended to use tunnelled, cuffed catheters.

Table 1 Criteria for initiating renal replacement therapy

- Anuria or oliguria with associated organ oedema
- Hyperkalaemia (K > 6·5 mmol/L)
- Creatinine >350 mmol/L
- Urea >30 mmol/L
- Dysnatraemia (Na >160 or <115 mmol/L)
- Severe metabolic acidosis (pH < 7·1)
- Progressive uraemic encephalopathy or neuropathy with urea >20 mmol/L
- Severe myoglobinuria
- Dialysable toxin or drug metabolite after overdose
- Hyperthermia

COMPLICATIONS OF RRT

In addition to the early and late complications associated with vascular access, a multitude of other complications and side effects occur as a result of RRT. Most notable is haemodynamic instability, which occurs more frequently in intermittent haemodialysis (IHD) compared with continuous RRT. Bleeding complications occur less frequently with unfractionated heparin (UFH) compared with other alternative methods of anticoagulation. However, exposure to heparin may result in heparin-induced thrombocytopenia (HIT), requiring immediate termination of heparin. Patients requiring medium to longer term RRT may become depleted in, e.g. vitamins, amino acids, magnesium, phosphate and trace elements. This is not always obvious and will require appropriate substitution therapy. More noticeable problems can occur as results of prescription/operating errors and apparatus failure causing disconnections with subsequent risks of haemorrhage or air entrapment/emboli.

PRINCIPLES OF RRT

The most common types of RRT are

- IHD;
- Continuous RRT
  (i) Continuous venovenous haemofiltration (CVVH);

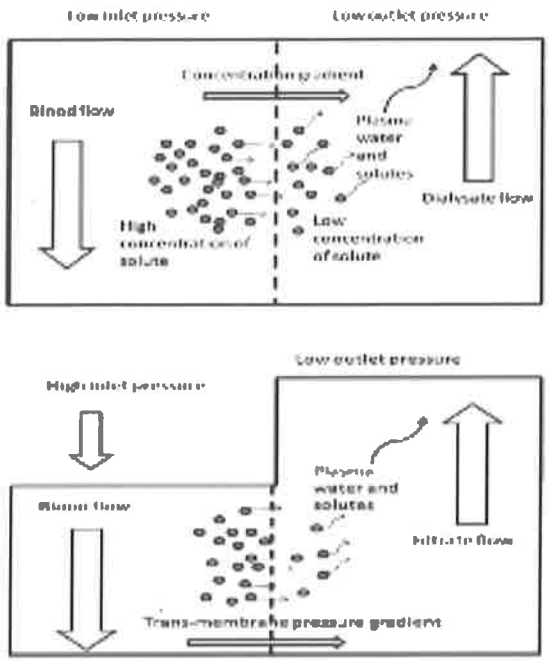

Figure 1 Principles of dialysis (top panel) and filtration (lower panel).

(ii) Continuous venovenous haemodialysis;
(iii) Continuous venovenous haemodiafiltration (CVVHDF);
(iv) Slow continuous ultrafiltration (SCUF).

Dialysis is clearance of solutes and plasma water across a semi-permeable membrane (usual filter size 0·5–2·2 m^2) down a concentration gradient.

Filtration is achieved across a semi-permeable membrane down a pressure gradient.

Figure 1 illustrates the principles of diffusion and filtration. The dialysate and effluent ultrafiltrate are discarded and substituted with replacement fluid (appropriate amount and composition) before being returned to the patient together with the cleared blood.

INTERMITTENT HAEMODIALYSIS

Facilitated by a concentration gradient, dialysis is based on diffusion, whereby solutes cross a semi-permeable membrane. The clearance of solutes is determined by

- Concentration gradient between blood and dialysate;
- Molecular weight;
- Protein binding;
- Electrical charge;
- Size of solute;
- Characteristics of the membrane.

Most filters are designed to allow passage of molecules below a weight of 5000 Da, with decreasing diffusion up to 20 000 Da. This semiporous design facilitates the removal of urea and the retention of albumin and immunoglobulins. Corrective buffer and electrolyte solutions are required during dialysis. With increased blood and dialysate flow either side of the membrane, usually 500 mL/min, dialysis is effective in clearing small molecules, correcting acid-base disturbances and removing large volumes of fluid. Disadvantages include the potential for haemodynamic instability and the technical requirements for staff operating the machine.

CONTINUOUS VENOVENOUS HAEMOFILTRATION

CVVH is the most frequently used modality of RRT in the ICU. The main difference from dialysis is the presence of a pressure gradient across the semi-permeable membrane and the transmembrane pressure gradient (TMP). This is achieved by a positive hydrostatic pressure in the blood compartment side of the filter and/or a negative pressure on the dialysate side.

TMP =
(filter pressure + return venous pressure)/2
– effluent pressure.

The rate of ultrafiltration (Qf) across the membrane is, in addition to TMP, determined by the blood flow (Qb), dialysate flow (Qd) and membrane characteristics. Convection is the term used for the clearance of solutes following the ultrafiltrate across the membrane. Hence, convection is determined by Qf, membrane characteristics and molecular size. Haemofiltration is an effective method of removing smaller and middle-sized molecules. Because of haemoconcentration, a filtration fraction (Qf/Qb) of no more than 20% is recommended. The presence of many large molecules will reduce the lifespan of the filter. With CVVH filtration rates of 100–300 mL/min can be achieved.

CONTINUOUS VENOVENOUS HAEMODIAFILTRATION

The addition of a dialyser circuit to CVVH is termed CVVHDF; this combines the advantages of haemodialysis and CVVH, obtaining solute clearance rates and biochemical control comparable to dialysis with the haemodynamic stability and filtration rates of CVVH. Most modern filtration machines incorporate several individual and combined modes RRT. SCUF is

used primarily for fluid removal with minimal requirements for solute clearance.

REPLACEMENT FLUIDS

The blood is maximally concentrated at the effluent end of the filter, when the ultrafiltrate and essentially all plasma ions have passed to the dialysate compartment. Therefore, before the blood is returned to the patient, replacement fluids are added. The replacement fluid is pumped through the circuit warmer into either the effluent (post-dilution) or the affluent side (pre-dilution) of the filter. The addition and composition of replacement fluid serve to regulate haematocrit, electrolytes and pH value of the returned blood.

As pre-dilutional replacement fluid is added to the blood compartment side of the filter before filtration, there is a reduction in haematocrit, urea and electrolytes before filtration and/or dialysis. The dilution of blood will reduce the concentration gradients of the solutes and therefore their clearance. The advantage of pre-dilution is the potential for extended lifespan of the filter and the need for less anticoagulation.

Post-dilution refers to the addition of replacement fluid after the blood has passed through the filter. Although it is easier to control fluid balance using post-dilution, filter blockage or clotting is more common and higher levels of anticoagulation may be required. By combining pre-dilution and post-dilution techniques, the filtration fraction (ratio of ultrafiltrate to plasma water) can be increased.

Figure 2 illustrates CVVH with pre-dilution and CVVHDF with post-dilution replacement fluid. Replacement fluids with different concentrations of electrolytes, glucose, lactate and osmolarity are commercially available, and choice of replacement fluid is determined by clinical situation. Examples include Monosol® (Baxter, Thetford, UK), Hemasol® (Hospal, Lyon, France) and Prismasol® (Gambro, Lakewood, CO, USA) with or without lactate buffer and added potassium. Lactate-containing replacement fluids (e.g. Monosol) are cheaper and have a longer shelf life compared with bicarbonate-containing solutions. However, in severely acidotic patients with conditions where lactate is not metabolized to bicarbonate, lactate-free replacement solutions should be used in combination with a bicarbonate buffer.

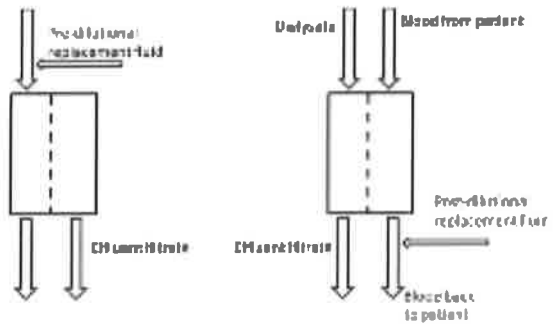

Figure 2 Principles of pre-dilutional and post-dilutional replacement fluid for continuous veno-venous haemofiltration (CVVH) and continuous veno-venous haemodiafiltration (CVVHDF).

ANTICOAGULATION

Anticoagulation is required to prevent clotting of the extracorporal circuit and filter. If there are no contra-indications to anticoagulation, it is standard practice to prime the filter-circuit with saline containing heparin (5000 IU/L). Subsequently, to achieve an activated partial thromboplastin time (APTT) value of 1·5–2 times baseline, unfractionated heparin (UFH) of 5–15 IU/kg/h is infused into the afferent side of the filter. The APTT or alternatively activated clotting time (ACT, aiming for 180–220 s) is checked at regular intervals on the efferent side of the filter and the dose of heparin adjusted accordingly. The plasma anti-thrombin III (AT-III) concentration needs to be above 0·5 μmol/L (normal plasma concentration approximately 2–3 μmol/L) for heparin to exert optimal effect. If the filter keeps clotting or APTT/ACT does not increase despite increased amounts of heparin, the AT-III levels should be measured. It may be necessary to correct low levels of AT-III by administering fresh-frozen plasma or AT-III concentrate. During haemodialysis, the normal plasma concentration of AT-III is decreased to approximately 0·6–1·2 μmol/L. Heparinoids, e.g. danaparoid or hirudins (Amanzadeh and Reilly, 2006), may in cases of heparin-induced thrombocytopenia substitute unfrationated heparin. Heparanoids require monitoring of platelet concentration and antifactor Xa activity. A regime of danaparoid infusion of 200 U/h to obtain anti-Xa activity <1 IU/mL can be used. The thrombin inhibitors hirudin and lepirudin require ecarin clotting time and APTT monitoring. Other alternatives include low-molecular-weight heparin (LMWH), which is associated with a lower incidence of HIT but a variable half-life in renal failure and incomplete reversal by protamine sulphate. The incidence of bleeding complications is approximately 11% and 2% for LMWH and UFH, respectively. The platelet inhibitor prostacyclin is less commonly used.

CHOICE AND DOSE OF MODALITY

The choice of RRT modality should be guided by the indications for RRT, condition of patient and local protocols. The amount or dose for efficient IHD is characterized by the clearance, K, expressed as the

volume of blood cleared of a solute over time, litres per hour. As previously mentioned, K depends on Qb, Qf and Qd. These parameters are determined by machine settings and membrane type. However, K is an instantaneous measurement and, therefore, to achieve an index of overall dialysis efficacy, normally >1·2 (Ricci and Ronco, 2008), K is multiplied by the dialysis time (t, hours) and subsequently divided by the volume of distribution of the solute, usually urea (Vurea): dialysis efficacy = Kt/Vurea.

In ICU, CVVH and CVVHDF are most commonly used, and modern technology has led to increased safety and ease of use. For CVVH, the dose equals the ultrafiltration rate. Studies have reported that an ultrafiltration rate ≥35 mL/kg/h leads to improved outcome and lower filtration rates should be avoided (Ronco *et al.*, 2000).

NON-RENAL INDICATIONS

Non-renal indications for RRT include the removal of water-soluble drugs and toxins during cardiopulmonary bypass in sepsis and acute lung injury. Additionally, RRT has been used to reduce pyrexia and support patients in acute cardiac failure. The clinical improvement in these conditions may be a combination of the removal of inflammatory markers and more specific renal support. Targeted removal of inflammatory mediators, predominantly by adsorption filters, has failed to translate into significantly improved clinical outcome. An explanation could be that proinflammatory and anti-inflammatory mediators are eliminated in equal proportions and the observed improvement in haemodynamics is primarily attributed to a reduction in body temperature and fluid removal. Some success has been reported in children with cerebral oedema resulting from the accumulation of branch-chained amino acids in maple syrup urine disease.

PREPARATION AND PRESCRIPTION FOR RRT

Before starting RRT, the tubing and filter should be primed with 0·9% saline containing heparin 5000 IU/L. The priming of the circuit serves to remove air and detect any leaks before treatment is started. Additionally, priming may also mitigate contact activation between the blood leucocytes and the filter. The washback (0·9% saline) is the fluid used to flush the tubing of the machine when extracorporal blood is returned to the patient after treatment is finished. Heparin infusion (with or without loading dose) should be started, as per unit protocol. An appropriate replacement fluid is then chosen according to clinical condition and treatment indication. Bicarbonate 8·4% at 30 mL/h is initially used as buffer if lactate-free replacement fluids are required. The replacement fluid regime should also be chosen: 30% pre-filter and 70% post-filter is the most common.

The filter itself may vary; modern hollow fibre, high-flux (high K_m) filters are made of biocompatible fibres (approximately 10 000 fibres/m) and include polymethyl methacrylate, polysulphone, polyamide and polyacrylonitrile. These differ slightly in pore size and adsorption characteristics. Pressure transducers, either side of the filter, monitor the TMP with alarms for high negative afferent (pre-filter) and high positive efferent (post-filter) pressures. Additional alarms monitor temperature, leaks and the presence of air in the circuit. The pump speed is initially set to allow a blood flow of ≥200 mL/min. Fluid replacement or turnover is the substitute for the generation of ultrafiltrate. In general, the higher the turnover the more efficient is the removal of solutes. Subsequently, based on the patient's fluid balance, the hourly fluid removal rate is programmed into the treatment cycle. The machine will then calculate and operate at an ultrafiltration rate in accordance with the programmed replacement fluid and fluid removal rate. For patients with AKI, an ultrafiltration production rate of ≥35 mL/kg/h is recommended. Most machines operate in cycles of 6–12 h before requiring reprogramming.

TERMINATION OF THERAPY

Predicting successful weaning from RRT is difficult; a spontaneous urine output >400 mL/day is relatively reliable (Gibney *et al.*, 2008). In general, treatment is stepped down or intermittently paused once the patient's clinical condition improves and the requirement for additional supportive therapy is decreasing. Although widely used, dopamine and furosemide have not been shown to favourably affect the outcome of AKI. However, therapeutically forced urine production may ameliorate overall fluid balance and reduce dependence of RRT during recovery from the disease. Complete recovery (return of renal function to baseline) after survival and discharge from ICU and hospital is negatively associated with pre-existing renal disease, increasing age and vascular disease. Among patients surviving to hospital discharge, approximately 50–60% have regained complete renal function after 1 year, 30–40% have decreased renal function and the remaining 10–15% of patients continue to require RRT (Bagshaw, 2006).

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WHAT IS KNOWN ABOUT THIS TOPIC

- RRT in the ICU is an independent predictor of mortality.
- For vascular access, the internal jugular vein has the lowest incidence of complications.
- The main difference between dialysis and filtration is the presence of a pressure gradient across the semi-permeable membrane.
- Return of spontaneous urine production is associated with successful weaning of RRT.

WHAT THIS PAPER ADDS

- Provides a review of the indications for RRT.
- Discussion of principles behind haemodialysis and haemofiltration.
- Discussion of the practical management of RRT.

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