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Renal replacement therapy in critical care

Lisa Gemmell MBChB FRCA FFICM[1], Robert Docking MBChB FRCA FFICM[2] and Euan Black MBChB FRCA FFICM[2,*]

[1]Specialty Trainee in Anaesthesia and Intensive Care Medicine, Queen Elizabeth University Hospital, Glasgow G51 4TF, UK and [2]Consultant in Anaesthesia and Critical Care, Department of Anaesthesia and Critical Care, Queen Elizabeth University Hospital, 1345 Govan Road, Glasgow G51 4TF, UK

*To whom correspondence should be addressed. Tel: +44 1414523093; E-mail: euan.black1@nhs.net

Key points

- Despite improvements in renal replacement therapy (RRT) technology, the mortality associated with acute kidney injury remains high.
- Within the adult critical care population in the UK, continuous modes of RRT are generally preferred although intermittent and hybrid therapies remain in use.
- Emerging evidence suggests that continuous modes of RRT are associated with reduced rates of long-term dialysis dependence.
- There is no benefit associated with high-intensity RRT as part of routine care.
- Research into the timing of commencement of RRT, drug dosing, and anticoagulation is required.

Acute kidney injury (AKI) affects up to 60% of intensive care unit (ICU) patients and is associated with mortality rates of between 15 and 60%. Up to two-thirds of patients with AKI go on to require renal replacement therapy (RRT).[1] Without the ability to replace native renal function, mortality from the complications of fluid overload, refractory hyperkalaemia, and metabolic derangement would be far higher. From the 1960s, hollow-fibre dialysers became available as a form of RRT and were able to be mass produced, with Scribner starting the first outpatient dialysis centres in the USA. Haemofiltration, as a form of RRT, began in the 1970s and is now an indispensable tool used as part of modern critical care management. Despite improvements in technologies, there has been only slow improvement in mortality since the 1980s. The reasons postulated for this include the lack of diagnostic tools available to detect early AKI, delayed initiation of RRT, inadequate delivery of RRT, and the inability to replace kidney function fully with current RRT modalities.

Little information exists on trends in the epidemiology of AKI; however, there are several reasons to suspect that its incidence is on the rise: the increasing age and comorbidities of the hospitalized population; an increase in the prevalence of risk factors for AKI such as chronic kidney disease and diabetes; and more widespread use of i.v. contrast for cardiovascular and other radiological procedures.

Mechanisms of RRT

Worldwide, RRT can be provided as peritoneal dialysis, intermittent haemodialysis (IHD), and continuous renal replacement therapy (CRRT), which includes continuous veno-venous haemofiltration (CVVH), continuous veno-venous haemodialysis (CVVHD) and continuous veno-venous haemodiafiltration (CVVHDF). The majority of UK critical care units use either CVVHF or CVVHDF.[2] Some units use hybrid therapies that combine IHD and CRRT; this technique is commonly known as slow low-efficiency daily dialysis. Slow continuous ultrafiltration (SCUF) is an alternative mode of RRT used to control fluid balance particularly in patients with diuretic-unresponsive cardiorenal syndrome.

The aims of RRT are solute and water removal, correction of electrolyte abnormalities, and normalization of acid–base disturbances. This is achieved via diffusion or convection which is, respectively, referred to as haemodialysis or haemofiltration. The system comprises an extracorporeal circuit filled by blood arising from a wide-bore double-lumen central venous catheter

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(see Fig. 1). Roller pumps control the speed of blood flow towards a semi-permeable polysulphone membrane consisting of multiple hollow fibres with pores throughout. The pore size affects the molecular size of substances that can pass through, allowing for passage of waste solutes whilst ensuring cells and other blood proteins remain within the intravascular compartment. Middle molecules are preferentially cleared by convective methods, rather than smaller molecules that are more reliably cleared by diffusion. This potentially allows for individualization of treatment modality. Blood that has passed through the length of the membrane is then returned via the same dedicated venous catheter to the patient. Anticoagulation is generally required to minimize the chance of thrombosis within the extracorporeal circuit.

Haemofiltration

Haemofiltration is a convective process whereby a hydrostatic pressure gradient is used to filter plasma, water, and solute across a membrane. This is analogous to the process within the renal corpuscle. The underlying mechanism is that of 'solute drag' where appropriately sized molecules are pulled along with the mass movement of solvent, traditionally termed ultrafiltration (UF). The convective transport is independent of solute concentration but determined by the direction and magnitude of the transmembrane pressure (TMP). Measures that result in a higher flow rate will increase UF production and in turn increase solute clearance. Equally, measures that increase the negative pressure across the membrane, including the pump on the effluent line, can have a marked effect. This fluid, known as effluent, is discarded. Owing to the high volumes produced, the circulating volume of the patient is replaced with a balanced crystalloid buffer solution (see Fig. 2).

Haemodialysis

In haemodialysis, solute clearance is achieved by diffusion across the membrane. The space outside the blood-containing fibres within the 'filter' is filled with dialysate, which is pumped in a counter-current fashion to the flow of blood. Dialysate is reconstituted to include a buffer (which may be either acetic acid or bicarbonate) and essential electrolytes dissolved in ultrapure water rendered devoid of toxins and impurities. Diffusion occurs down concentration gradients allowing rapid

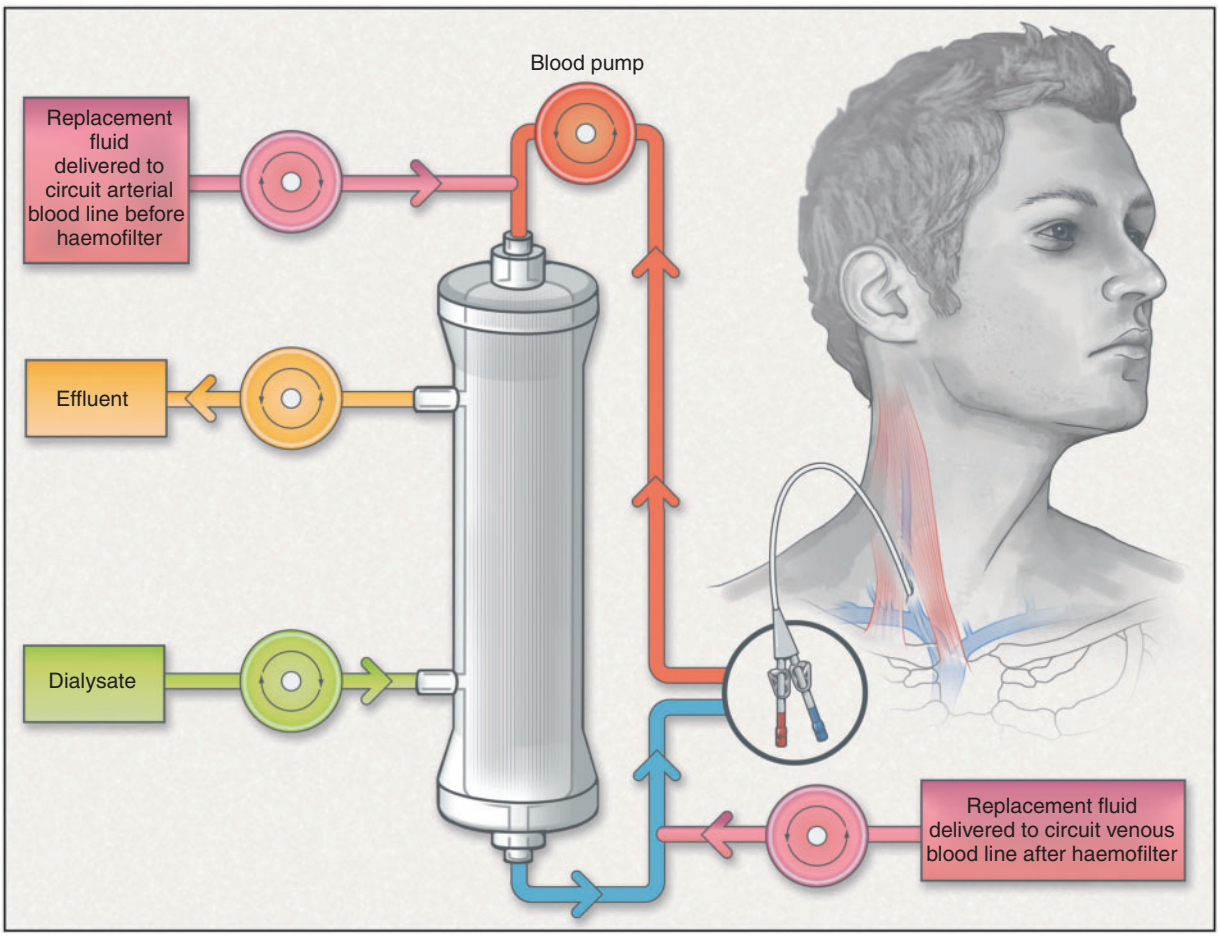

Fig 1 Circuit components. Continuous renal replacement therapy requires a central double-lumen veno-venous catheter, an extracorporeal circuit and haemofilter, a blood pump, and an effluent pump. Depending on the type of continuous renal replacement therapy, dialysate, replacement fluid pumps, or both are required. In continuous veno-venous haemofiltration, solutes and plasma water are forced across the semipermeable membrane by high ultrafiltration rates (convection). Simultaneously, replacement fluid is infused into the blood with the use of a replacement pump. In continuous veno-venous haemodialysis, solutes and plasma move across the semipermeable membrane into the dialysate compartment of the haemofilter by means of diffusion. In continuous veno-venous haemodiafiltration, solutes and plasma water are removed by diffusion, convection, and ultrafiltration. Reproduced with kind permission from Massachusetts Medical Society and Copyright Clearance Centre's RightsLink Service, Tolwani A, *NEJM* 2012; 67: 2505–14 (licence no. 3840241141696).

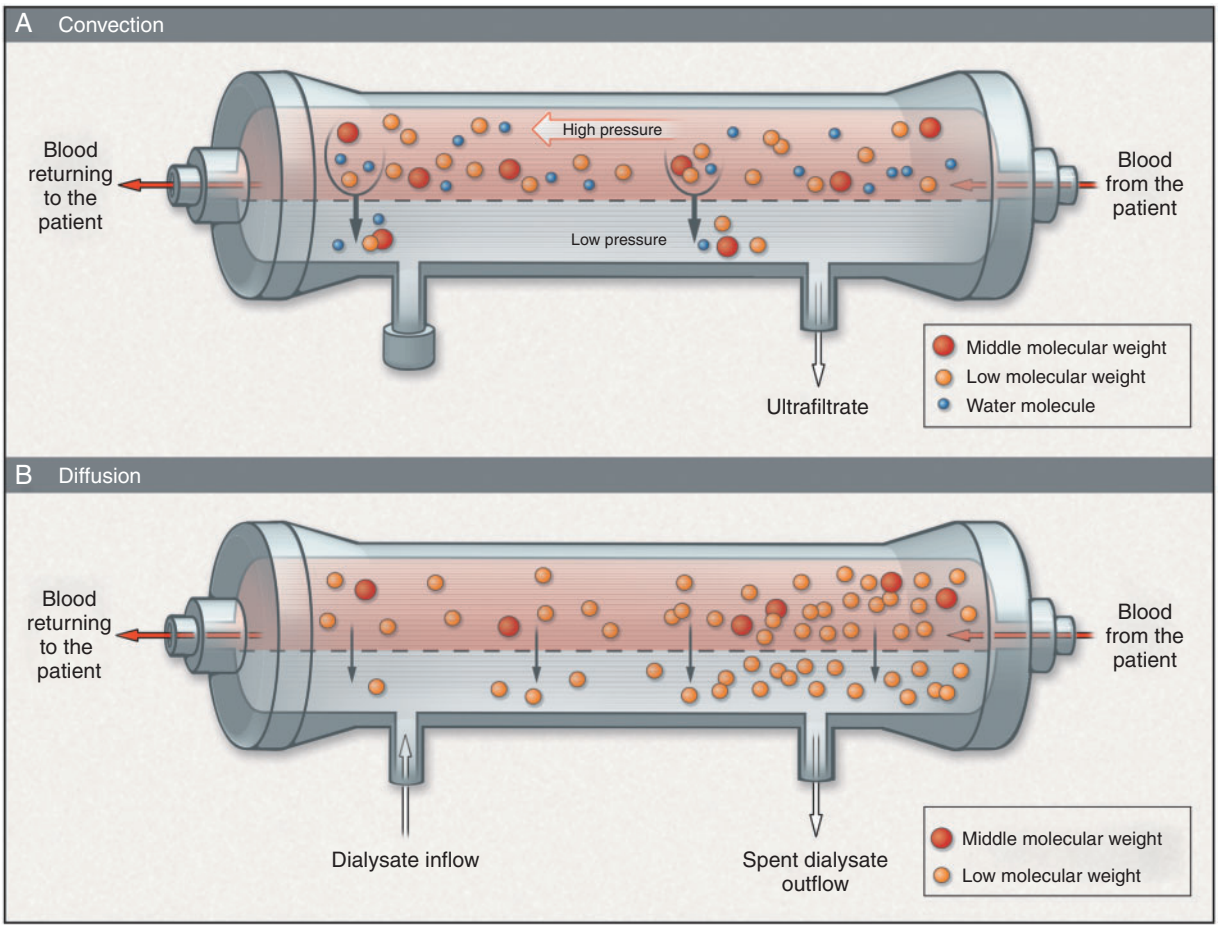

Fig 2 Transport of solutes across a semipermeable membrane. As shown in (A), convection occurs when solutes are transported across a semipermeable membrane with plasma water in response to a hydrostatic pressure gradient (i.e. created across the membrane). As shown in (B), in diffusion, movement of solute across a semipermeable membrane is driven by a concentration gradient between the blood and the dialysate. Solutes move from the side with the higher concentration of particles to the side with the lower concentration. Dialysate fluid is pumped through the haemofilter in a counter-current direction and solutes are removed from the circulation via the process of diffusion. The waste dialysate is produced as effluent. Reproduced with kind permission from Massachusetts Medical Society and Copyright Clearance Centre's RightsLink Service, Tolwani A, *NEJM* 2012; 67: 2505–14 (licence no. 3840241141696).

equilibration of solutes across the membrane (see Fig. 2). The purpose of this counter-current flow system is to maintain a waste-solute concentration gradient (i.e. always lower on the dialysate side of the membrane, similar to solute movement within the Loop of Henle).

It is worth noting that during CVVHDF, replacement and dialysate fluids are required to perform the hybrid function; this is achieved with the same fluid solution.

The RRT membrane

Two types of RRT membrane exist: cellulose based or synthetic. Exposure to an extracorporeal circuit and the interaction between blood and the membrane is known as biocompatibility. Less biocompatible membranes increase the likelihood of harmful side-effects associated with RRT.

Cellulose-based membranes trigger activation of inflammatory pathways, which may increase the longevity of AKI. Studies suggest that the use of more biocompatible membranes may lead to faster restoration of renal function and improved patient outcomes.[3] In short, it can be assumed that the most biocompatible membrane available should be used for RRT.

Filter fluid

During haemofiltration, bicarbonate ions are freely filtered and therefore need to be replaced. Previously, standard lactate-based fluids were used as buffers, with the lactate subsequently being metabolized in the liver. In the context of critical illness, impaired hepatic function can lead to lactic acid accumulation. To compensate for this, bicarbonate-based buffer solutions have become commercially available. These fluids may be added to the circuit before the haemofilter (pre-dilution) or mixed with the blood in the venous drip chamber (post-dilution). Pre-dilution replacement reduces the incidence of filter clotting but reduces the effective clearance of solutes. Post-dilution replacement is, therefore, the ideal, but a compromise is often made to maintain the integrity and lifespan of the filter. Although there is no mortality benefit associated with the use of bicarbonate-based fluids, there is evidence for improved control of acidosis and cardiovascular instability. The question as

to whether or not tailoring the dose of bicarbonate to match individual patient needs can affect outcome requires further research.[4]

Mode

The superiority of continuous over intermittent techniques remains controversial. Advocates for continuous techniques claim that they are associated with the following advantages:

- Enhanced haemodynamic stability.
- Superior management of fluid balance.
- Enhanced clearance of inflammatory mediators, which may provide benefit in septic patients.
- Better preservation of cerebral perfusion among patients with acute brain injury or fulminant hepatic failure.

In the absence of a survival benefit, both modalities continue to be used based on local preferences. International [Kidney Disease: Improving Global Outcomes (KDIGO)] consensus favours CRRT for haemodynamically unstable patients.[5] In addition, there is mounting evidence from observational studies that the use of CRRT at initiation reduces long-term dialysis dependence compared with IHD.[6]

The decision as to which mode of RRT is used should therefore be based on both the clinical condition of the patient and the capabilities within the unit providing RRT.

Timing

The timing of commencement of RRT in critically ill patients is highly subjective but may influence outcome. The classical criteria for initiating therapy include:

- Hyperkalaemia (potassium >6.5 mmol l^{-1} or rapidly rising).
- Refractory fluid overload.
- Metabolic acidosis.
- Certain drug and alcohol intoxications.
- Signs of uraemia, such as pericarditis or encephalopathy.

These criteria are based on expert opinion rather than evidence arising from randomized controlled trials.

It is worth emphasizing that RRT involves several risks, including those related to cannula insertion, as well as the side-effects of biocompatibility, fluid shifts, and altered drug metabolism. In addition, there is an increased nursing workload and a significant cost. These downsides must be balanced against the benefits of RRT, and consideration must also be given to the fact that spontaneous recovery of the kidneys may occur.

Some observational studies have suggested that earlier initiation of RRT correlates with improved survival; however, randomized controlled trial evidence is limited to the cardiac ICU population.[7] Two recently published trials have reported conflicting results which may relate to the populations studied: a single-centre study involving predominately surgical patients (47% cardiac) reported a benefit of early initiation,[8] whilst a multicentre study involving mainly medical patients reported no benefit of early treatment.[9] Multicentre research is ongoing which should help to address this issue in a general ICU setting. A significant issue regarding studies on timing relates to the previous lack of consensus regarding definitions of AKI.

Over and above the classical criteria, a decision to institute RRT should consider the severity of other organ failure and the trajectory of the patient's illness. It is also increasingly accepted that RRT can be used when managing fluid overload, hyperthermia and toxicity related to acute hepatic failure or drugs.

Discontinuation of therapy

RRT is usually continued until the patient shows evidence of recovery of native renal function. The primary manifestation of recovery is often an increase in urine output: a urine output of more than 400 ml per day is a reasonable cut-off value equating to correct identification of the majority of patients with renal recovery from RRT-dependent AKI. Recovery may also be evidenced by a progressive decline in serum creatinine during steady-state RRT. More objective assessment of recovery is obtained by the measurement of creatinine clearance. In one large randomized controlled trial, renal support was discontinued when the measured creatinine clearance exceeded 20 ml min^{-1} and was left to the discretion of providers when in the range of 12–20 ml min^{-1}.[10]

Dosing of RRT

A key element of the RRT delivery is dose. Until recently, little evidence existed for dosing, which led to wide variations in clinical practice.

For continuous techniques, dose is the sum of all effluent fluids expressed as millilitres per kilogram body weight per hour. It is important to note that the addition of dialysate and the targeting of negative fluid balance both add to the summative dose. Dosing of intermittent techniques is difficult because of urea kinetics and fluid shifts in the critically ill: because of this, most studies assessing IHD measure dose in relationship to frequency and duration of sessions.

The notion of a relationship between treatment dose and patient outcome was first postulated in a single-centre study, in which patients randomized to post-dilution haemofiltration at a dose of 35 ml kg^{-1} h^{-1} or above had significantly improved survival compared with those randomized to 20 ml kg^{-1} h^{-1}.[11] Similar results were seen using IHD in a daily *vs* alternate day study.[12] These papers led to the widespread adoption of high dose prescribing. There has recently been a challenge to this practice: two large multicentre trials[10,13] both failed to detect any reduction in mortality associated with more intensive RRT and instead provided quality evidence that effluent flow rates above 25 ml kg^{-1} h^{-1} do not improve patient outcomes in ICU. This has led to international consensus guidelines supporting delivery of 20–25 ml kg^{-1} h^{-1}.[5] It should be noted that in these trials delivery of at least 85% of prescribed treatment time was achieved, highlighting the importance of minimizing filter-downtime. Given that CRRT dosing is intrinsically related to weight, it is surprising that little evidence exists as to the optimal measure of weight that should be used (ideal, pre-morbid, or actual).

Drug dosing in CRRT

Patients receiving RRT are often on multiple medications, many of which are vital to their care and require appropriate dosing. The pharmacokinetics of drugs in critically ill patients requiring CRRT is complex: the disease state can lead to an increased volume of distribution, an extended drug half-life or an alteration in protein binding capacity.[14] These variables make generalized dosing recommendations difficult. Drugs with low protein binding are removed by CRRT more readily, whereas those with a higher volume of distribution have lower clearance by CRRT.

The mechanical processes of CRRT may also affect drug clearance. Changes to the dialysate or blood flow rate altering the transmembrane pressure (TMP) lead to changes in drug

clearance. Membrane pore size is directly proportional to the degree of drug removal by CRRT. Modern CRRT treatments result in a creatinine clearance of around 25–50 ml min^{-1}. Recommendations with regard to drug dosing are often based on expert consensus in conjunction with the known pharmacokinetic and pharmacodynamic properties of individual drugs.

Dosing of drugs therefore relates to the effects of the AKI, the effect of the RRT modality, and the behaviour of the drug itself. Beta-lactam antibiotics require to be kept above the minimal inhibitory concentration for as long as possible for effective treatment and have relatively benign toxic effects so can be dosed either more frequently or at close to normal dose to achieve maximal benefit. Antifungals, such as fluconazole, however, undergo significant tubular reabsorption in health and therefore undergo greater clearance during CRRT and require adjustment in dosing for this reason. Drugs such as vancomycin with narrow therapeutic indices require regular level monitoring and benefit from delivery by continuous infusion to avoid rapid under- or overdosing.[15]

Vascular access

The site of insertion of the vascular cannula is crucial to the success of RRT: treatment is impossible without adequate blood flows, and poor flows risk premature filter clotting. KDIGO has recently listed a preference of site for vascular access catheters for RRT.[5] These are:

- First choice – right internal jugular.
- Second choice – femoral.
- Third choice – left internal jugular.
- Fourth choice – subclavian.

The subclavian is the least preferred anatomical position because of the higher rate of stenosis formation during chronic use. Except for the obese patient, the femoral site is no longer considered at higher risk for bloodstream-related infections and in addition may be quicker to insert. The right internal jugular site should be used in preference to the left because of improved delivery of RRT.[16]

Position of the catheter tip improves flow; therefore, perhaps not site, but length remains a more important feature of vascular access. Optimal flow rates are obtained with the catheter tip in the right atrium for internal jugular lines and within the inferior vena cava for femoral access.[17] Further considerations relating to flow include the central venous pressure of the patient and kinking of the catheter. When not in use, locking lines with citrate reduces catheter-associated infection.

Anticoagulation

As with all extracorporeal circuits, the use of RRT mandates the consideration of anticoagulation. This can be systemic or regional.

Systemic heparin anticoagulation is the most commonly used method. It is ubiquitous, cheap, and its activity is routinely tested as part of coagulation screening. Because the treatment is systemic, patients are at risk of haemorrhage, and often a balance between the risk of bleeding and risk of circuit clotting must be addressed in several patient populations. In addition, heparin resistance (attributable to reduced concentrations of antithrombin III in the critically ill) and heparin-induced thrombocytopenia (HIT) mean alternative forms of anticoagulation must be available.

If patients develop HIT and associated thrombosis then systemic anticoagulation with either the heparinoids (such as danaparoid) or direct thrombin inhibitors (such as argatroban) is required. If patients merely have HIT antibodies and no evidence of thrombosis then RRT circuit anticoagulation can be maintained with prostacyclin or citrate, provided systemic anticoagulation is unnecessary.

The use of regional anticoagulation with citrate is increasing and has been recommended by international consensus guidelines.[5] Citrate chelates calcium and thus inhibits platelet aggregation and coagulation. Because the majority of the citrate–calcium complex is removed in the effluent during both convection and diffusion, a systemic calcium infusion is necessary in order to avoid hypocalcaemia.

There are several benefits to the use of regional citrate anticoagulation: it avoids systemic anticoagulation; it does not cause HIT; and studies have suggested reduced requirements for blood products and increased filter lifespan compared with heparin.[18] Potential disadvantages include metabolic complications and the need for a protocolized infusion. The electrolyte disorders potentially associated with the use of citrate include: alkalosis (attributable to the conversion of citrate to bicarbonate), acidosis (due to citrate accumulation), hypocalcaemia, and hypomagnesaemia (attributable to binding with the citrate–calcium complex). Any protocols must thus monitor for such abnormalities. It is important to note that citrate provides no prophylaxis against deep vein thrombosis.

Fluid balance

Mean fluid balance is a significant and independent predictor of mortality in ICU and is significantly more positive in AKI patients who die compared with survivors.[19] The extent of fluid accumulation is negatively associated with survival, as is the duration of fluid overload in patients receiving RRT. Fluid overload during AKI is also associated with a decreased likelihood for renal recovery. Use of beds with inbuilt scales can allow for trending of patient weight during RRT treatments. SCUF, as a form of RRT, can be used for patients whose primary problem is fluid overload.

Development of chronic kidney disease

Among survivors of AKI, a proportion become dialysis dependent.[6] A further subset of patients recovering from AKI never return to their baseline renal function: ongoing evidence of renal dysfunction has been described in as many as 40% of survivors. Indeed, the more severe the AKI the higher risk of renal dysfunction long term. ICUs should have formalized regional pathways for specialist nephrology input. Whilst the patient remains in ICU, nephrologists can provide necessary expertise in the evaluation and management of those with complicated renal disease. For patients with non-resolving AKI, long-term follow-up should be arranged after discharge from both ICU and hospital.

Controversies

It has been hypothesized that patients with sepsis may benefit from more intensive CRRT dosing owing to the removal of circulating inflammatory mediators. Current evidence for high-volume haemofiltration (defined by effluents greater than 50 ml kg^{-1} h^{-1}) suggests it has no influence on mortality or dialysis dependency and no consistent effect with regard to serum

cytokine concentrations, but can lead to a reduction in vasopressor requirements.[20] This technique is associated with increased episodes of electrolyte disturbance and the risk of decreased plasma concentrations of antimicrobials in a high-risk population.

There is an interest in the development of sensitive early biomarkers of AKI given the low sensitivity and delay in increase of serum creatinine. There is no current level 1 evidence supporting the use of any single biomarker for the diagnosis of AKI, but using a panel of different markers may increase utility. There may be a further role for their use in detecting patients who are recovering from AKI.[21]

Declaration of interest

None declared.

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