Renal replacement therapy in acute kidney injury: an overview

Renal replacement therapy plays a key role in the management of acute kidney injury – a devastating condition in the critical care setting. This article reviews current evidence and provides a template to inform routine practice.

Despite our deepening understanding of the pathophysiology of ischaemic acute kidney injury (AKI), current treatment options remain limited. In the absence of specific therapies that will modify its natural history (Molitoris, 2003), patients must be tided over to the 'recovery' phase, often with the use of renal replacement therapy (RRT).

This article will review current opinion on the optimal provision of RRT in the critically ill AKI patient. An unravelling of underlying theory and nomenclature will be followed by discussions of important technical considerations and of more clinically pertinent issues of modality choice, dose and timing.

Physical processes and nomenclature

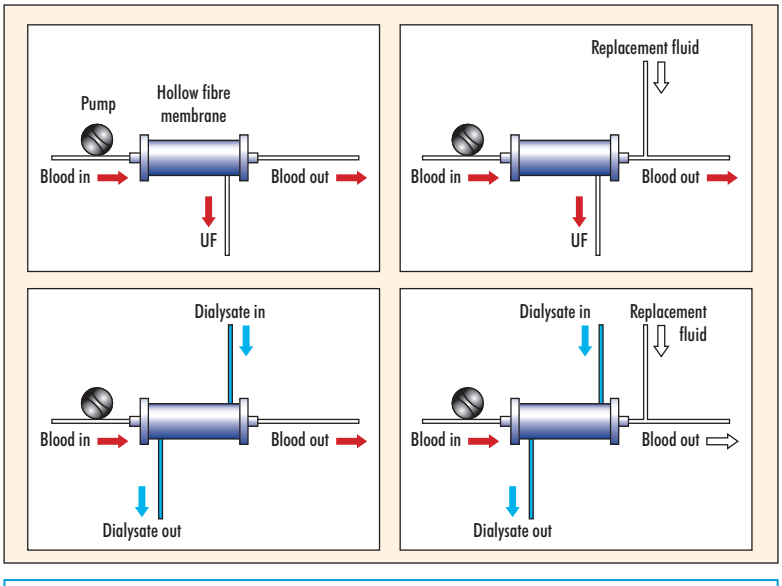
Our sometimes loose use of nomenclature such as 'filtration' and 'dialysis' necessitates a review of basic theory underpinning RRT. The two physical processes that may be used are convection and diffusion. Solute removal can occur by either; fluid removal through convection alone, which must therefore be at least a component of all RRTs.

Convection (or ultrafiltration) involves removal of plasma water by applying a hydrostatic pressure across a semi-permeable membrane. Within the constraints of membrane pore size, solutes follow by 'solvent drag'. Removal of small solutes (e.g. urea, potassium) is relatively inefficient so the high volume ultrafiltration that is needed to enhance it must be balanced with simultaneous fluid replacement in a process termed haemofiltration. By altering the relative rates of ultrafiltration and replacement, net fluid balance can be manipulated to achieve euvolaemia.

Haemodialysis relies predominantly on diffusion. Large concentration gradients across the semi-permeable membrane result in highly efficient removal of small solutes. Diffusion is less effective at removing larger molecules (e.g. β-2 microglobulin) than convection, which drags these solutes across the membrane en bloc. Fluid removal in haemodialysis is achieved by the addition of a small amount of ultrafiltration although the additive solute removal is minimal.

Both diffusive and (major) convective solute removal can be combined in haemodiafiltration. *Figures 1* and *2* illustrate the mechanics of these modalities, each of which may be performed either intermittently or continuously. *Table 1* describes nomenclature and use in more detail.

Figure 1. Graphic illustration of commonly used extracorporeal renal replacement techniques: a. Ultrafiltration (UF). b. Haemofiltration (replacement fluid infusion may be pre-dilutional – before the blood inlet – or, as in this figure, post-dilutional – after the blood outlet). c. Haemodialysis. d. Haemodiafiltration. Continuous arteriovenous techniques are generally pumpless. Adapted from Kanagasundaram and Paganini (2001).



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Technical considerations

Vascular access

In industrialized societies, the ready availability of safe, pump-driven hardware (*Figure 3*) means that most acute RRT is now provided using veno-venous access (Canaud et al, 1998) (*Table 1*). Insertion of these typically dual lumen devices should be performed with real-time ultrasound guidance if using an upper body approach (National Institute for Clinical Excellence, 2002). As these sites are usually already in use in the first stages of critical illness, the initial approach for RRT access is often femoral.

Femoral catheters should be of an adequate length (≥24 cm) to reach the inferior vena cava, where optimal flow rates are probably achieved (Uldall, 1996). They should be removed and replaced at least weekly (Uldall,

1996) and replaced by upper body access once the patient starts to mobilize.

Subclavian catheters should be used with caution as future ipsilateral permanent arterio-venous access may be compromised by inducing downstream venous stenoses. This route is best avoided in those likely to progress to end-stage renal disease (ESRD). As a similar contingency, non-dominant arm veins should be preserved for future arterio-venous access.

Internal jugular access tends to have fewer procedure-related and long-term complications (Uldall, 1996). Infection may be more common (Kairaitis and Gottlieb, 1999), especially in patients with tracheostomies (Canaud et al, 1998). Local policy will determine the frequency of catheter change, but softer, silicone catheters, used with subcutaneous tunnelling, may be most appropriate for prolonged RRT (Canaud et al, 2004).

Catheter failure is a major cause of under-delivery of, especially intermittent, RRT (Kanagasundaram et al, 2003). Overtly poor flows and high access pressures are obvious manifestations of dysfunction, but may not reveal more subtle access recirculation, a phenomenon where cleared blood, just returned to the patient, is re-circulated to the device, significantly reducing treatment efficiency. It is worse at higher blood flows so is generally only a problem in intermittent modalities. Correct choice of catheter length can help prevent the problem. Ultrasound dilution technology can quantify recirculation (Depner et al, 1995), although observed under-delivery of the prescribed dose can suggest its presence without the need for this hardware.

Catheter-related bacteraemia and exit site infection are, perhaps, the most significant complications of temporary access (Kairaitis and Gottlieb, 1999). Fastidious insertion technique and rigorous catheter care can reduce the risk (Deshpande et al, 2005) as may reserving the access solely for the purpose of RRT.

Figure 2. Hollow-fibre device shown in cross-section. Each of the thousands of hollow-fibres bundled into the device comprise a wall of a semi-permeable material and a lumen through which blood flows – collectively, the 'blood compartment'. In diffusive modalities, dialysate flows around the outside of the hollow fibres in the 'dialysate compartment'. Flow of this solution, constituted to restore physiological plasma solute concentrations, is usually in an opposite – or counter-current – fashion to blood to enhance concentration gradients. In purely convective modalities there is no dialysate flow. The dialysate compartment provides the space where ultrafiltrate initially accumulates after first being drawn across the membrane. Membrane properties dictate whether use is predominantly convective or diffusive.

Anticoagulation

Clotting of the extracorporeal circuit is a significant source of under-delivery of RRT and the most frequent cause of interruption in continuous renal replacement therapy

Table 1. Extracorporeal renal replacement therapy – nomenclature and use

Therapy	Definition	Use	Access	Abbreviation
Ultrafiltration	Plasma water removal Usually < 5 litres/day	Fluid overload Congestive cardiac failure	AV/VV continuous VV continuous AV/VV intermittent	SCUF CVVUF IUF
Haemodialysis	Diffusion-based process using dialysate and semi-permeable membrane	Azotaemia Acid/base disturbance Electrolyte balance Volume control	AV continuous VV continuous AV/VV intermittent	CAVHD CVVHD IHD
Haemofiltration	Convective-based process using plasma water exchange methods across semi-permeable membrane	Azotaemia Acid/base disturbance Electrolyte balance Volume control	AV continuous VV continuous AV/VV intermittent	CAVH CVVH IH
Haemodiafiltration	Combining diffusion and convection for both small and middle molecular loss	Azotaemia Volume control	AV continuous VV continuous AV/VV intermittent	CAVHDF CVVHDF IHDF

Modalities are described according to frequency, technique and, for continuous techniques, vascular access. Continuous renal replacement therapy (CRRT) is an umbrella term for continuous techniques. I = intermittent; C = continuous (= S = slow); H = haemofiltration; HD = haemodialysis; HDF = haemodiafiltration; UF = ultrafiltration; VV = veno-venous modality (via central venous catheter; requires blood pump); AV = arterio-venous modality (via arterial + venous cannulae; usually pumpless, systemic arterial pressure providing the driving force; potentially hazardous because of the need for arterial cannulation, it is now rarely performed except in mass casualty settings when bulky hardware may not be immediately available). This descriptive system has recently been complicated by the development of hybrids of intermittent and continuous techniques, referred to as 'sustained low efficiency dialysis' (SLED), 'extended daily dialysis' (EDD) and 'slow continuous dialysis' (SCD). Adapted from Kanagasundaram and Paganini (2001).

(CRRT). The most appropriate method of anticoagulation will depend on the balance of risk between reduced circuit lifespan and bleeding in an individual patient.

Infusions of unfractionated heparin are the traditional method of maintaining circuit patency, at fixed rates (Martin et al, 1994) or guided by activated partial thromboplastin time monitoring (van de Wetering et al, 1996), although the most appropriate dose is still unclear.

With its short half-life prostacyclin is a suitable alternative in those at increased risk of bleeding, but drawbacks include its expense and systemic vasodilatory properties (Davenport et al, 1994).

Regional citrate anticoagulation is another alternative and although safe and effective (Kutsogiannis et al, 2000), it is also technically complex (see review in Kanagasundaram and Paganini, 2001).

A no-anticoagulation strategy can be achieved with regular circuit saline flushes (Ramesh Prasad et al, 2000). Although useful in patients at highest risk of bleeding, optimal circuit survival is unlikely. Other drawbacks include fluid loading and the risk of baro-traumatic membrane fibre rupture.

Finally, pre-dilutional fluid replacement during haemofiltration minimizes the haemoconcentration induced by large ultrafiltration volumes but introduces the inefficiency of removing replacement fluid before it even reaches the patient.

Membranes

The first consideration in membrane choice is biocompatibility – a measure of its propensity to activate complement, the coagulation cascade and leucocytes (Jones, 1998). Cellulosic membranes are considered the least biocompatible, synthetic the most, with modified cellulose composites somewhere in between. Potential benefits of increased biocompatibility include reduced renal damage (Schulman et al, 1991) and filter clotting (Sreeharan et al, 1982). Although these have not been uniformly corroborated in human AKI, the balance of evidence still favours the avoidance of bioincompatible materials (Kanagasundaram and Paganini, 2001). The financial disincentive against using biocompatible devices may indeed be negated by falling cost.

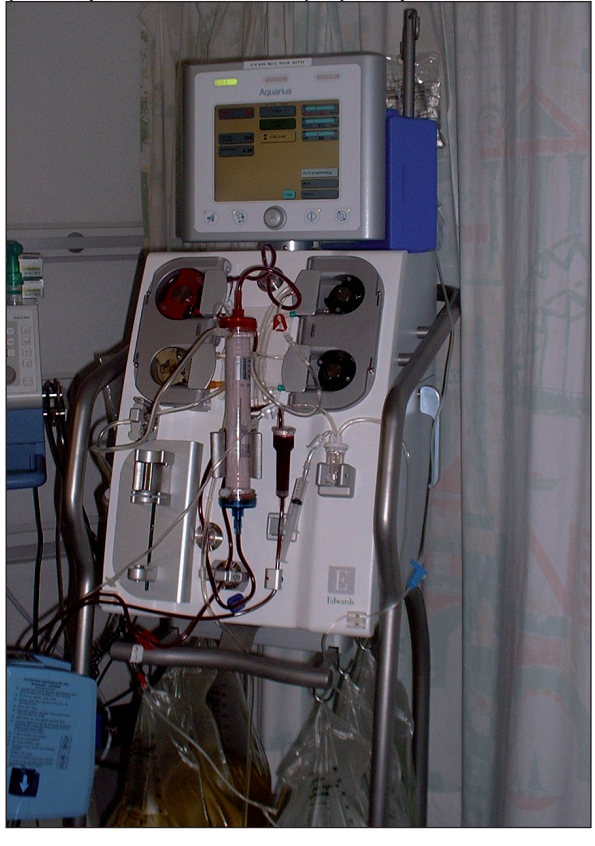


Figure 3. Modern, pump-driven, continuous veno-venous therapy in use. Much of the technology functions to provide a level of safety, precision and robustness not previously afforded in historical hardware.

The second consideration in membrane choice is its use. Materials with high hydraulic permeability, for instance, are needed for convective therapies. Intrinsic structure, membrane thickness and pore size are determinants of the utility of any one device and are discussed in detail in Kanagasundaram and Paganini (2001).

A specific caveat with the synthetic, polyacrylonitrile AN-69 membrane is the bradykinin-associated anaphylactic reactions that can occur with concurrent angiotensin-converting enzyme inhibition (Jones, 1998).

Buffer

Bicarbonate (rather than lactate or acetate) is the primary buffer for dialysate used in intermittent haemodialysis (IHD) for ESRD, a practice that has been propagated to patients with AKI.

In CRRTs, citrate-buffered solutions are used for regional citrate anticoagulation. In the remainder, concerns about exacerbating lactic acidosis with lactate-buffered solutions, particularly in those with liver failure, has led to the development of commercially-available bicarbonate-based fluids. The likelihood of benefit, especially in the sickest patients, seems to justify their current, widespread use (Davenport, 2001a).

Therapeutic considerations

Modality

A wide armamentarium now exists for the replacement of renal function in AKI (*Table 1*). Peritoneal dialysis has also been deployed (Ash, 2001) but is now rarely used and may be unsuitable in those with abdominal pathology or marked hypercatabolism (peritoneal dialysis providing limited clearance). The availability of industry-standard hardware for blood-based techniques in industrialized societies now generally relegates peritoneal dialysis to a secondary modality in AKI.

Theoretical benefits of continuous over intermittent forms of blood-based RRT include improved haemodynamic stability (Paganini, 1988) and increased dialysis dose delivery (Clark et al, 1994). High quality evidence of an advantage is lacking, however, in terms of both mortality (Mehta et al, 2001; Tonelli et al, 2002; Augustine et al, 2004; Uehlinger et al, 2005; Vinsonneau et al, 2006) and renal recovery (Augustine et al, 2004; Vinsonneau et al, 2006). Indeed, haemodynamic stabil-

ity, the mooted sine qua non for CRRT, can actually be maintained with modern IHD techniques (Paganini et al, 1996a). The one proven benefit of CRRT is in those with combined acute liver and renal failure with, or at risk of, cerebral oedema (Davenport, 2001b). Despite the broader lack of evidence, it seems nevertheless reasonable to recommend that the most haemodynamically unstable patients be treated with CRRT (*Table 2*).

The newer hybrid modalities (*Table 1*) deliver high prescribed doses and provide haemodynamic stability (Kumar et al, 2000; Marshall et al, 2001; Kielstein et al, 2004); their non-continuous nature facilitates out-of-intensive care unit (ICU) procedures while avoiding the higher anticoagulation requirements of CRRTs. No current data, however, corroborate any advantage over more established techniques.

The absence of evidence for an effect of 'intermittency' mirrors uncertainty over any real difference in physical process – convective, diffusive or combination. High-volume haemofiltration, through enhanced larger solute clearances, has been mooted as an inflammatory modulator but there is insufficient evidence to support its routine use, either in the presence (Bouman et al, 2002) or absence of AKI.

Given the wide array of different RRTs, it seems sensible to limit the range of techniques used in any one unit to allow the development of appropriate levels of medical and nursing expertise.

Prescription

The optimal method of RRT prescription remains unclear. Stumbling blocks in this population include wide inter- and intra-individual variability in two key determinants of dose – the catabolic rate (Clark et al, 1994; Kanagasundaram et al, 2003) and total body water (Kanagasundaram et al, 2003). Despite this, there is increasing evidence of a relationship between dose and outcome.

An analysis of a prospectively collected database from Cleveland, USA, has shown an influence of dose on survival in both intermittent and continuous techniques (*Figure 4*) (Paganini et al, 1996b).

IHD clearances in this study were relatively low by modern standards. In the absence of more robust data, one consensus group has since recommended that each session delivers a higher target, more consistent with chronic dialysis standards (Kellum et al, 2002) – i.e. a urea reduction ratio >65% (Renal Association and Royal College of Physicians of London, 2002) (see *Figure 4* for explanation).

The requisite frequency of IHD has been studied by Schiffl et al (2002) who suggest a survival advantage of daily over alternate daily treatments. Delivered doses were so low in the latter group, however, that observed effects may actually have been the result of significant underdialysis rather than augmented frequency. Daily IHD is nevertheless probably necessary in those with marked hypercatabolism or high ultrafiltration requirements.

Table 2. Clinical considerations in the choice of continuous or intermittent forms of renal support in the ICU setting

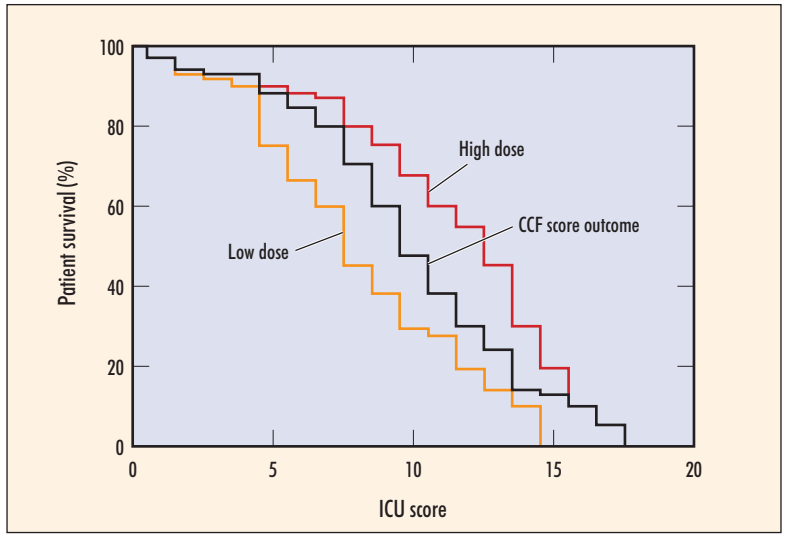
	Modality	
	Intermittent	**Continuous**
Haemodynamic instability	Less preferable	Yes
High fluid requirements	Less preferable	Yes
High potassium generation	Yes	No
Hypercatabolism	Yes	Yes
Cardiac dysfunction	Less preferable	Yes
Uraemic emergency (e.g. pericarditis)	Yes	Less preferable
Septic shock	Less preferable	Yes
High illness acuity	Less preferable	Yes
Bleeding	Yes	Less preferable
Off-ICU procedures (scans/surgery)	Fits in between interventions	May result in significant downtime

ICU = intensive care unit

Although 'TACurea' (*Figure 4*) defined CRRT dose in the Cleveland study, more recent practice has been to use ultrafiltration or dialysate flow rates.

From a practical perspective, ultrafiltration rates in continuous haemofiltration are equivalent to dialysate flow rates in continuous haemodialysis, which are so low that small solutes are fully equilibrated between dialysate and blood by the time the former exits the dialyser (Kanagasundaram and Paganini, 2001). The urea concen-

Figure 4. Survival among 512 intensive care unit (ICU) patients with acute renal failure according to urea clearance and Cleveland Clinic Foundation (CCF) ICU acute renal failure severity score. Outcome was not affected by dialysis dose at either low scores (indicating low acuity) or high scores, but survival was increased in patients with a higher delivered renal replacement therapy dose and intermediate severity scores. In intermittent haemodialysis (HD), high dose was defined as a urea reduction ratio (URR) > 58%, where URR = ((pre-HD urea – post-HD urea)/pre-HD urea) x 100%. In continuous renal replacement therapy, high dose was defined as a time-averaged concentration of urea (TACurea) of < 16 mmol/litre. Adapted from Paganini et al (1996).



tration of continuous dialysate effluent and ultrafiltrate will thus be similar. Pre-dilutional continuous haemofiltration (*Figure 1*) requires a proportionate, upwards adjustment of the prescribed ultrafiltration rate to account for the dilutional effects of the replacement fluid infusion.

Using this approach, an Italian single centre trial has demonstrated improved survival with higher doses of continuous veno-venous haemofiltration (*Figure 5*) (Ronco et al, 2000), benefits that have been confirmed elsewhere (Saudan et al, 2006).

Shortfalls in the delivered RRT dose arise in both IHD (Kanagasundaram et al, 2003) (owing to both clinical and technical factors) and CRRT (owing to circuit downtime). Because of this and because of the dynamic clinical state of the critically-ill patient (Kanagasundaram et al, 2003), both prescription of RRT and its delivery should be assessed at each session (for IHD) and daily (in CRRT).

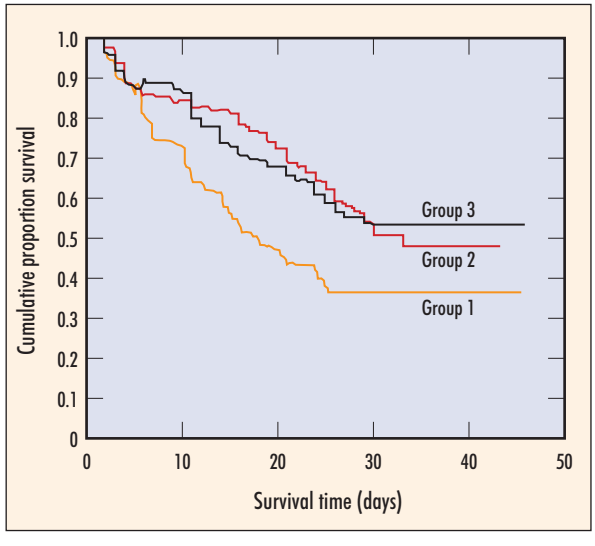
Although considerable uncertainty still exists matters of RRT prescription, we may be afforded some clarity from the results of two, major, multicentre dosing studies (the ATN and RENAL studies) that are due to report next year (Bellomo, 2006).

Timing of institution

The decision to institute RRT is relatively easy when faced with conventional indications such as refractory hyperkalaemia, refractory pulmonary oedema or severe metabolic acidosis (Kanagasundaram and Paganini, 2005). However, a consensus view on when to start treatment before such indications have developed is lacking.

As mortality rates are increased even in less severe AKI (Uchino et al, 2006) it has been suggested that RRT should be instituted before overt uraemia has developed.

Figure 5. Kaplan–Meier survival rates in continuous veno-venous haemofiltration patients randomized to three different ultrafiltration rates. Group 1 = 20 ml/h/kg body weight; group 2 = 35 ml/h/kg; group 3 = 45 ml/h/kg. Survival rates in group 1 were significantly lower than those in groups 2 and 3, which were not different. From Ronco et al (2000).



Countering this are concerns that RRT may expose the patient to the risks of anticoagulation and temporary vascular access and may actually hinder recovery of AKI (Conger, 1995).

Historical studies have yielded mixed results, are hampered by small numbers and do not translate easily to modern techniques. Contemporary studies have, unfortunately, failed to provide clarity.

Analysis of the prospective PICARD multicentre study database found that initiation of RRT at a serum urea >27 mmol/litre was associated with poorer survival (Liu et al, 2006) but these results are tempered by negative, prospective randomized study data (Bouman et al, 2002).

Despite this uncertainty, it would seem reasonable to start RRT when AKI is established and not immediately reversible, when complications might be anticipated but have not yet developed. A lower threshold for initiation should be considered when AKI is associated with increasing non-renal organ dysfunction. The initiation of RRT may be deferred when the underlying disease and non-renal organ failure are improving and when a declining rate of rise in serum creatinine levels may herald renal recovery. After RRT has been started, an improvement in the clinical condition and urine output would justify a period free of renal support to look for other signs of renal recovery.

Conclusions

The provision of RRT to the critically-ill patient with AKI is far from straightforward. Consideration of technique, timing and optimal therapeutic dosing in the individual patient must be viewed in the context of evolving evidence, developing technologies and the need for overall quality assurance. Regardless of where this expertise arises, the overview of practitioners with expertise in critical care nephrology seems to be essential to the safe and effective delivery of renal support.

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KEY POINTS

- Renal replacement therapy should be initiated once acute kidney injury is established and irreversible, before overt complications have developed and at a lower threshold with increasing levels of non-renal organ dysfunction. Initiation may be deferred if the underlying condition is improving and there are signs of renal recovery.
- Technical factors, including membrane and fluid choice, anticoagulation and vascular access, are important considerations when prescribing renal replacement therapy.
- The most haemodynamically unstable patients with acute kidney injury should be treated with continuous renal replacement therapy or, if available, one of the hybrid therapies.
- There is increasing evidence of a link between the dose of renal replacement therapy delivered to critically-ill acute kidney injury patients and their outcome. Intermittent haemodialysis may need to be administered daily in hypercatabolic or fluid loaded patients.
- In the critically-ill acute kidney injury patient, the effectiveness of therapy should be frequently assessed because of wide variability in clinical determinants of dose and shortfalls in the delivery of the prescribed renal replacement therapy dose.
- A limited number of different renal replacement therapy techniques should be used on any one unit to allow staff to maintain appropriate levels of experience.