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Renal Replacement Therapy in Acute Kidney Injury: a Primer for Anaesthetists

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Contents

INTRODUCTION

Acute kidney injury (AKI) is an increasingly frequent complication in critically ill patients (1-3). Depending on the definition used and the population studied, the prevalence of AKI in patients admitted to intensive care units (ICU) varies between 25 and 60% (4-7).

Despite technological and pharmacological advances, the mortality associated with AKI is still high and occurs in up to 60% of ICU patients (8-12). Risk factors shown to be linked to decreased survival comprise advanced age, co-morbid illnesses and higher severity of AKI (12, 13). Patients who survive AKI remain at heightened risk of progression to chronic kidney disease and long-term dialysis dependence, prolonged hospitalisation, and greater rate of long-term mortality (1, 7, 14, 15). Given the heavy burden of these sequelae to the patient and to society, all possible measures should be undertaken to prevent their development.

Renal replacement therapy (RRT) is a mainstay of supportive therapy in severe AKI (16). Severe AKI, requiring renal replacement therapy, occurs in 5-13% of patients and has a mortality rate of 50-80% (1, 3, 7, 17, 18). The goals of renal support are to replace native renal function, which includes clearance of electrolytes and uraemic toxins, maintenance of acid-base balance and regulation of fluid balance; as well as to prevent further insults to the kidneys, to promote the recovery of renal function and to allow administration of medications and nutrition without limitation (16, 19-22).

Despite much progress has been made in the area of RRT, considerable controversy remains in numerous fundamental aspects, such as optimal timing of initiation, modality choice, therapy dosing, anticoagulation, as well as timing and approach to RRT discontinuation (2, 3, 8, 16, 23).

The aim of this booklet is to present an overview of current literature on renal replacement therapy for acute kidney injury in the adult intensive care unit. The topics of peritoneal dialysis and RRT in chronic kidney disease will not be covered in this document.

DEFINITION OF ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is defined as “an abrupt decrease in renal excretory function over a period of hours to days, resulting in accumulation of urea, creatinine and other waste products and in the dysregulation of fluid volume and electrolyte and acid-base balance” (6, 16, 24).

Currently the term Acute Kidney Injury is being used instead of previously used term of Acute Renal Failure, emphasising that even small decrements in kidney function reflecting minor degree of kidney injury, may lead to increased morbidity and mortality (24-26).

Several consensus groups worked on a system unifying the definition and classification of AKI (26). In 2002, Acute Dialysis Quality Initiative (ADQI) group introduced RIFLE criteria, grading severity of kidney injury as Risk, Injury and Failure, and classifying the outcomes as Loss or End-Stage Renal Disease. In 2009, Acute Kidney Injury Network (AKIN) modified the RIFLE system, removing GFR criteria and outcome classification among other changes (26). The characteristics of RIFLE and AKIN systems are summarized in Table 1 (26).

RIFLE classification		**AKIN classification**		
Stage	**GFR or serum creatinine criteria**	**Stage**	**Serum Creatinine criteria**	**Urine output criteria**
Risk	1.5 x ↑ in creatinine	1	≥ 1.5-2.0 times ↑ in creatinine	< 0.5 mL/kg/h for 6 hours

	or > 25% ↓ in GFR		or Absolute ↑ in creatinine ≥ 26.5 µmol/L	
Injury	2 x ↑ in creatinine or > 50% ↓ in GFR	2	2.0-3.0 x ↑ in creatinine	< 0.5 mL/kg/h for 12 hours
Failure	3 x ↑in creatinine or > 75% ↓ in GFR	3	≥ 3.0 x ↑ in creatinine or ↑ of creatinine to ≥ 354 µmol/L) with an acute ↑ of at least 44 µmol/L	< 0.3 mL/kg/h for 24 hours Or Anuria for 12 hours
Loss	Complete loss of kidney function > 4 weeks			
ESRD	Complete loss of kidney function > 3 months			

Table 1. Characteristics of RIFLE and AKIN classifications of acute kidney injury (25).

The most recent and commonly used definition of AKI was developed by the Acute Kidney Injury Working Group of KDIGO (Kidney Disease: Improving Global Outcomes) in 2012, merging the criteria from two previous systems (26). The definition and staging of AKI as per KDIGO guidelines are summarized in Tables 2 and 3 (22).

"AKI is *defined* as any of the following:	
1	Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours, **or**
2	Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days, **or**
3	Urine volume < 0.5 mL/kg/hour for 6 hours"

Table 2. Definition of AKI as per KDIGO guidelines (22).

KDIGO Staging of AKI		
Stage	**Serum creatinine**	**Urine output**
1	1.5-1.9 times baseline **or** ≥ 0.3 mg/dL (≥ 26.5 µmol/L) absolute increase	< 0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	< 0.5 ml/kg/h For ≥ 12 hours
3	3.0 times baseline **or** Increase in serum creatinine to ≥ 4.0 mg/dL (≥ 353.6 µmol/L) **or** Initiation of renal replacement therapy **or** In patients < 18 years, Decrease in eGFR[1] to < 35 ml/min per 1.73 m^2	< 0.3 ml/kg/h for ≥ 24 hours **or** Anuria for ≥ 12 hours

[1]eGFR = estimated glomerular filtration rate

Table 3. Staging of AKI as per KDIGO guidelines (22).

MECHANISMS OF RENAL REPLACEMENT THERAPY

The aims of renal support are correction of electrolyte and acid-base abnormalities, achievement of euvolaemia, removal toxins and promotion of renal function recovery (19). Water and solute removal during renal replacement therapy is facilitated through following mechanisms: diffusion, ultrafiltration and convection (20).

Diffusion

Diffusion is a movement of water and solute down the concentration gradient from an area of high concentration to the area of low concentration (Figure 1) (27). In diffusive clearance (haemodialysis), blood is pumped through extracorporeal tubing across a semi-permeable membrane, on the opposite side of which dialysate is running in the counter-current direction to the blood flow (20, 27). Dialysate is a solution, containing ultrapure water, essential electrolytes and a buffer. Depending on the relative concentrations of the molecules in the plasma and dialysate, solutes can be added or removed from the plasma to achieve equilibrium between two substances (20).The prescription of potassium in the dialysate can be modified and usually varies between 0 and 5 mmol/L, with the chosen concentration depending on the serum potassium concentration (3, 4). Generally, bicarbonate or a bicarbonate precursor, such as lactate, acetate or citrate, is used as a buffer (3, 4). In patients with liver failure or septic shock the bicarbonate precursor should be avoided as it needs to be metabolised by patient (3, 4). The total amount of solute transported per unit of time is determined by the type of membrane (porosity, thickness, surface area), characteristics of the solute (molecular weight, charge and protein binding), rate of blood and dialysate flows, duration of dialysis (10). The substances that can be most efficiently removed by diffusion are small molecular weight solutes, like urea, creatinine, potassium and other ions (20).

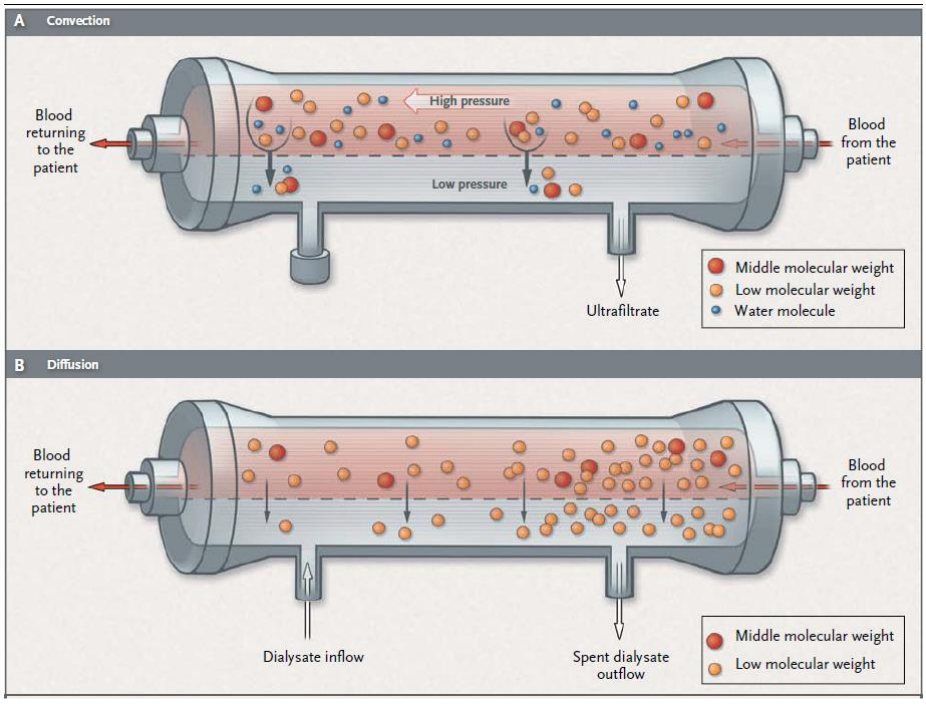


Figure 1. Transport of solutes across a semipermeable membrane (6).

Ultrafiltration

Ultrafiltration is a variety of filtration where plasma water is forced through a semi-permeable membrane by hydrostatic pressure (6).

Convection

During convective dialysis (haemofiltration), a transmembrane pressure gradient causes plasma water to filter across the highly permeable membrane (as in ultrafiltration), dragging along the low- and middle-molecular weight substances (Figure 1) (6, 20). Examples of middle-sized molecules are β2-microglobulin, inflammatory cytokines (tumour necrosis factor, IL-6, IL-8, IL-10, myocardial depressant factors, chemokines), and uraemic toxins. The effectiveness of solute clearance is independent of concentration gradient, but is determined by the magnitude of pressure gradient, as well as membrane pore size, surface area, and water permeability (20). Increasing the transmembrane pressure gradient will produce a larger amount of ultrafiltrate and consequently will enhance the solute clearance (20). This can be achieved by increasing the flow rates in the circuit on the patient side or by increasing the negative pressure on the effluent line (20). This process creates 10 - 50 L of ultrafiltrate per day, which should be replaced with a balanced solution (filter replacement fluid) to prevent electrolyte and acid-base imbalance, as well as large fluid shifts (20, 28). Depending on the size of pores in the membrane, low to middle molecular weight molecules pass through it, but suspended solids, high molecular weight substances, blood cells and proteins are retained (20). Small molecules (< 500-1,500 Daltons) are better cleared by diffusion (haemodialysis), whereas convection (haemofiltration) is more effective for clearance of middle and larger size substances (1,000 to 20,000 Daltons) (10, 20, 27). Examples of molecular weight of some of the important molecules related to haemodialysis are summarised in Table 4.

Diffusion and convection may be used separately, but are frequently used in combination, in which case it is known as haemodiafiltration.

Classification	Molecule	Molecular weight (Daltons)
Small (<500 Da)	Sodium	23
	Magnesium	24
	Phosphorus	31
	Potassium	35
	Calcium	40
	Urea	60
	Phosphate	80
	Creatinine	113
	Uric acid	168
	Glucose	180
	Gentamycin	470
Middle (500 – 15 000 Da)	Vitamin B12	1355
	Vancomycin	1488
	Endothelin	4238
	Endotoxin fragments	1000 – 15 000
	Cytokines	15 000 – 30 000
Large (>15 000 Da)	Inulin	5200
	Beta-2 microglobulin	11 800
	Myoglobin	17 000
	Albumin	55 000-60 000
	Globulin	150 000

Table 4. Molecular weight of common substances relevant to haemodialysis.

MODALITIES

Multiple modalities of renal replacement therapy can be employed in the treatment of patients with renal failure, which include (3, 27):

1. Haemodialysis
    a. Intermittent haemodialysis (IHD).
    b. Prolonged intermittent renal replacement therapy (PIRRT):
        - Sustained low-efficiency dialysis (SLED)
        - Extended daily dialysis (EDD)
    c. Continuous renal replacement therapy (CRRT):
        - Slow continuous ultrafiltration (SCUF)
        - Continuous veno-venous haemofiltration (CVVH)
        - Continuous veno-venous haemodialysis (CVVHD)
        - Continuous veno-venous haemodiafiltration (CVVHDF)
2. Peritoneal dialysis:
        - Automated peritoneal dialysis (APD)
        - Continuous ambulatory peritoneal dialysis (CAPD)

Intermittent haemodialysis

Intermittent haemodialysis was invented by Dr Kolff in 1945 and remains one of the most commonly used modalities of renal support worldwide (28-30). The solute removal is achieved by diffusion, while water clearance occurs by ultrafiltration (6). The duration of the dialysis session is generally 2 – 6 hours (10). It provides rapid and effective removal of solute and water (6). The main limitation of this modality of renal replacement therapy is the risk of systemic hypotension, precluding its use in haemodynamically unstable patients (6, 28).

Continuous renal replacement therapy

Continuous renal replacement therapy was first introduced by Peter Kramer from Germany in 1977 for the treatment of haemodynamically unstable critically ill patients who could not tolerate intermittent haemodialysis (6, 28). This technique includes a spectrum of modalities that are applied for 24 hours per day, but differ by the mechanism of solute removal (3). The main advantages of CRRT are haemodynamic stability, better metabolic control, improved fluid management and potential clearance of pro-inflammatory cytokines (19, 20, 28). Most commonly used modalities of CRRT are continuous veno-venous haemofiltration (CVVH), continuous veno-venous haemodialysis (CVVHD), continuous veno-venous haemodiafiltration (CVVHDF) and slow continuous ultrafiltration (SCUF).

Initially CRRT was developed in a form of continuous arterio-venous haemofiltration (CAVH) (28). It represented a simple arterio-venous circuit, where blood was driven through the extracorporeal tubing using patient's own cardiac output (10, 28). However, in view of complications related to catheterisation of femoral artery with a large-bore catheter, other techniques using veno-venous circuits were consequently devised, which are used in current practice (28).

Modern system comprises a large bore double-lumen central venous catheter, extracorporeal tubing, blood pump, haemofilter, effluent pump, pressure monitors, air detectors, dedicated port for heparin or citrate/calcium infusion and multiple safety alarms (2, 20). The circuit also includes dialysate, replacement fluid pump or both, depending on the modality used (Figure 2) (6).

Blood is moved from "arterial" (red) lumen of the venous catheter by roller peristaltic pumps to a semi-permeable membrane and then returned to the patient via the ''venous'' (blue) lumen of catheter (4, 6). Incorporated blood pumps create a pressure gradient across the membrane, causing ultrafiltration of the plasma water leading to volume removal (6). Solutes are cleared by convection (continuous veno-venous haemofiltration), diffusion (continuous veno-venous haemodialysis) or both mechanisms (continuous veno-venous haemodiafiltration) (Figure 3) (6).

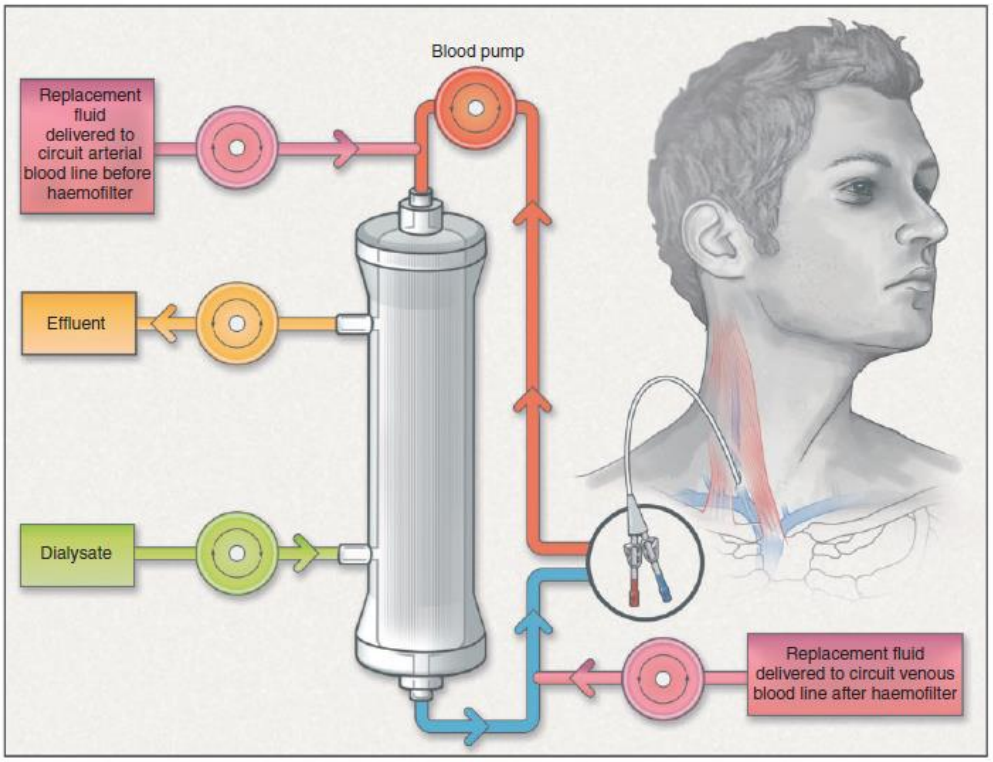
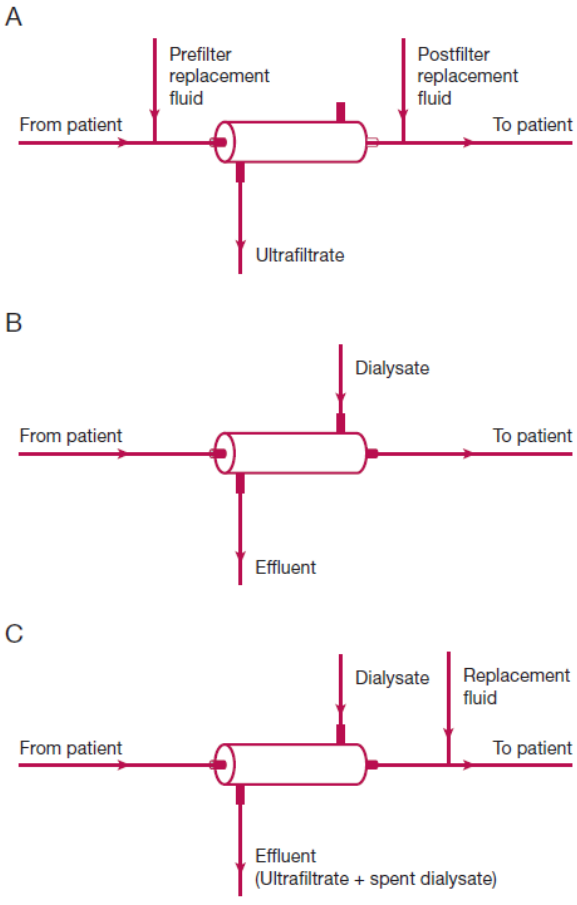


Figure 2. Circuit components (6).



A – Continuous haemofiltration. B – Continuous haemodialysis. C - Continuous haemofiltration.

Figure 3. Schematic diagrams of modalities of CRRT (3).

In convective methods (CVVH and CVVHDF), high rates of ultrafiltration are necessary to provide an effective solute clearance, potentially leading to excessive water removal, haemoconcentration and increased risk of filter clotting (6). To prevent that, a replacement fluid is infused either before or after filter (4). Pre-filter reinfusion leads to the dilution of blood reducing the risk of clotting, however the decreased solute concentration makes its clearance less effective (3). This can be counteracted by maximising the blood flow and ultrafiltration rate (2, 4). When fluid is added after the filter, solute clearance is improved and is linearly proportional to the effluent rate (2). On the other hand, the process of concentration polarisation is enhanced, where protein particles and cells deposit on the filter, reducing membrane permeability and increasing the risk of clotting (2). This can be offset by keeping the filtration fraction percentage, which is a ratio of ultrafiltration to blood flow, below 20% (2). There is no strong evidence to suggest a preference for pre- or post-filter reinfusion, so the choice usually depends on local practice (2).
The type of replacement fluid depends on the acid-base status of the patient (4). For example, normal saline or bicarbonate containing solution can be infused in case of metabolic alkalosis or metabolic acidosis respectively (4).

In CVVHD dialysate is instilled in the opposite direction to the blood flow and solutes are cleared by diffusion (4). This mode does not require replacement fluids as the ultrafiltration rates are minimal and there is no significant fluid removal (3, 4).
CVVHDF combines haemodialysis and haemofiltration techniques, using both dialysate and replacement fluid in view of high ultrafiltration rates (4, 6).
Slow continuous ultrafiltration (SCUF) is mostly used in patients with isolated fluid overload, such as diuretic-resistant cardiac failure, capillary leak syndrome, malnutrition and hepatic failure (4, 20). Its main effect is plasma water removal without correction of electrolytes (4).
Table 5 summarises modalities of CRRT (1, 4, 6, 31, 32).

	CVVH	CVVHD	CVVHDF	SCUF
Primary mechanism	Convection	Diffusion	Diffusion and convection	Ultrafiltration
Treatment time	Continuous	Continuous	Continuous	Continuous
Blood flow rate	100-250 ml/min	100-250 ml/min	50-200 ml/min	100-250 ml/min
Dialysate	No	15-60 ml/min	15-30 ml/min	No
Replacement fluid	15-60 ml/min	No	10-30 ml/min	No

CVVH - Continuous veno-venous haemofiltration, CVVHD - Continuous veno-venous haemodialysis, CVVHDF - Continuous veno-venous haemodia filtration, SCUF - Slow continuous ultrafiltration

Table 5. Summary of CRRT modalities (1, 4, 6, 31, 32).

Choice of CRRT modality

The choice of CRRT modality is influenced by several factors, including patient's volume status, electrolyte and acid-base abnormalities, and the medical centre's preference (4). As mentioned above, fluid overloaded patients can be managed with SCUF (4). CVVHD can be considered in patients with isolated electrolyte abnormalities (4). Clearance of small molecules, such as urea, creatinine and electrolytes, is excellent and similar with CVVHD, post-dilution CVVH and CVVHDF (6). With pre-dilution CVVH small solute removal is slightly less efficient than with CVVHD. However, removal of middle size substances, such as inflammatory cytokines and uremic toxins, is far superior with CVVH. Also, many critically ill patients receive large volume of fluid during resuscitation and drug administration (4). Thus, apart from normalisation of their electrolyte and acid-base dysbalances, they require management of their fluid balance (4). This can be achieved with the use of either CVVH or CVVHDF (4). There is no objective outcome data

to guide clinicians on which modality of CRRT should be used, so the choice usually depends on physician preference and expertise (4, 6).

IHD versus CRRT

When choosing between IHD and CRRT, the main considerations are availability, experience of the team, cost, haemodynamic stability of the patient, need for anticoagulation and indication for renal replacement therapy (10, 19). Despite numerous studies trying to determine the safety and survival benefit of CRRT versus IHD, no evidence has proven the superiority of one technique over another (33-36). Also, the data on renal recovery has been controversial (37). Observational studies suggest that haemodynamic instability during IHD may impede the recovery of renal function, however randomised studies didn't confirm the difference between IHD and CRRT (33, 35, 38). Both treatment techniques, if used correctly, can provide similar metabolic control (2, 33).

However, it is generally accepted that CRRT is an optimal modality for haemodynamically unstable patients (KDIGO) (2, 39). Prolonged treatment time allows for slow and gentle volume and electrolyte clearance, allowing better mobilisation of solutes from the extra-plasmatic space and enhancing haemodynamic stability (19, 28, 30, 34). CRRT was shown to better maintain cerebral perfusion, which is particularly important in the treatment of patients with acute brain injury and hepatorenal failure with cerebral oedema (3, 20, 40, 41). Also, this technique is more effective in correction of fluid overload and establishing a negative balance (3, 42). The enhanced clearance of pro-inflammatory cytokines with convective dialysis may be beneficial in septic patients with AKI, however its clinical significance has not yet been proven (20). Certain limitations of CRRT should be kept in mind, such as extended patient immobilisation, need for trained staff and specialised equipment, frequent filter clotting and changing, increased anticoagulation requirements and increased cost (19, 43).
High rates of water and solute clearance during IHD may lead to episodes of severe hypotension, compromising renal and cerebral perfusion, delaying recovery of renal function and increasing the risk of chronic dialysis dependence (19, 33). Drug pharmacokinetics are affected by higher intensity of clearance, potentially resulting in subtherapeutic dosage (19). Also, rapid fluid shifts may cause osmotic variations, exacerbating cerebral oedema (37, 44). Certain measures can, however, be implemented during intermittent haemodialysis to enhance haemodynamic stability, such as higher sodium concentration and cooling of dialysate, increased duration of dialysis session and use of vasopressors (20, 38, 41). Higher blood and dialysate flows that can be achieved during IHD allow faster correction of metabolic abnormalities, which is particularly relevant in the management of life-threatening hyperkalaemia, rhabdomyolysis, tumour lysis syndrome and poisoning (19, 30, 37). Due to lower (or absent) anticoagulation requirements, IHD may be favoured in situations with active bleeding or elevated bleeding risk, for example trauma, recent surgery and coagulopathy (30, 38). Additional advantages include user-friendliness, reduced expenses, patient mobilisation and flexibility of application (30, 43).

Prolonged intermittent renal replacement therapy

Prolonged intermittent renal replacement therapy (PIRRT) represents a hybrid of IHD and CRRT, combining benefits of both modalities, with the duration of dialysis between 8 and 12 hours (2, 20). It includes sustained low-efficiency (daily) dialysis (SLE(D)D) and extended daily dialysis (EDD) (10). Most commonly, conventional IHD equipment is used for this technique, with lower blood and dialysate flow rates, leading to more gradual fluid removal, slower rate of solute clearance and prolonged treatment time (2, 3, 10). Duration and intensity of therapy are personalised to the needs of each patient (19, 30). The advantages of this technique are haemodynamic stability that is quite similar to CRRT, faster mobilisation of patients, flexibility, lower cost compared to CRRT and possibility of low-dose or absent anticoagulation (2, 30, 45). Studies comparing SLEDD with CRRT showed similar haemodynamic profiles and solute clearance (30, 45, 46), however bigger trials are required to confirm the superiority of one of the methods (19, 30). Peritoneal dialysis is out of scope of this document. Table 6 compares different modalities of RRT (19).

Characteristics	IHD	CRRT	SLEDD
Mechanism	Diffusion	CVVH: filtration CVVHD: diffusion CVVHDF: both SCUF: ultrafiltration	Diffusion
Solute removal	Small solutes	CVVH: larger solutes CVVHD: small solutes CVVHDF: small & larger solutes SCUF: minimal	Small solutes
Fluid removal	Yes	CVVH: yes, replaced CVVHD: yes CVVHDF: yes, replaced SCUF: yes (up to 8 L/d)	Yes
Duration	3-6 hours/day	hours/day	6-12 hours/day
Blood flow rate	350-500 ml/min	<200 ml/min	200 ml/min
Dialysate flow rate	500–800 ml/min	17-34 ml/min	300 ml/min
Haemodynamic stability	Poor	Good	Fair-good
Efficiency	High	Low-moderate	Moderate
Cost	Low	High	High
Anticoagulation	Not needed	Important	Usually not needed
Patient clinical conditions used in	In ambulatory CRF patients, hyperkalaemia	Unstable and non-ambulatory critically ill patients, hsepsis, uraemia, patients with raised intracranial pressure	Critically ill patients
Advantages	Rapid solute correction and toxin removal Decreased anticoagulation requirements Cost effective	Improved haemodynamics Can target fluid removal specifically (SCUF)	Improved haemodynamics Can be times around procedures/studies Decreased anticoagulation requirements
Disadvantages	Large and rapid fluid shifts can cause haemodynamic instability Dialysis disequilibrium syndrome Vascular access required	Slower solute correction Anticoagulation required Risk of hypothermia	Slower solute clearance Technically more complex Some level of anticoagulation may be required Access site complications

RRT - Renal Replacement Therapy, IHD - Intermittent Hemodialysis, CRRT - Continuous Renal Replacement Therapy, SLEDD - Sustained Low Efficiency Daily Dialysis, CRF - Chronic Renal Failure

Table 6. Comparison between different modes of RRT (19).

INDICATIONS FOR RENAL SUPPORT

The optimal time to initiate renal replacement therapy (RRT) in critically ill patients with acute kidney injury (AKI) remains controversial (39). It is clear that in the presence of life-threatening complications directly related to renal failure, such as severe hyperkalaemia, severe metabolic acidosis, diuretic-resistant fluid overload, overt uraemic symptoms, and dialyzable drug intoxications (called the "conventional" criteria), RRT should be started immediately (see Table 7) (6, 10, 22, 47, 48). However, in patients with severe AKI but without such indications, the timing of RRT initiation remains a subject of debate (49).

Absolute indications for initiation of renal replacement therapy in AKI
Severe metabolic acidosis
Fluid overload
Electrolyte abnormalities • Hyperkalaemia • Hyperphosphataemia • Hypermagnesaemia • Dysnatraemia
Uremic complications • Encephalopathy • Pericarditis
Dialysable drug intoxications

Table 7. "Conventional" or "absolute" indications for initiation of renal replacement therapy (6, 10, 22, 47, 48).

At present, there is no universally accepted consensus on exact definitions of "life-threatening complications of renal failure", and no precise thresholds of these physiological parameters, triggering initiation of RRT, exist (48, 50).

The KDIGO guideline recommends that, when making decision to start RRT, clinicians should consider the overall clinical state of the patient, the severity of renal dysfunction, the presence of complications and other organ dysfunctions, fluid and acid-base status, and trends of serum potassium, urea, creatinine, rather than single thresholds (6, 22, 25).

Due to predominantly renal homeostasis, hyperkalaemia is very common in AKI, and, if left untreated, may lead to cardiotoxicity and fatal arrhythmias (3, 21). Hyperkalaemia can be treated medically, using enteric potassium-binding resins, diuretics and agents promoting intracellular shift of potassium, such as insulin/dextrose infusions, beta-2 adrenergic agonists and bicarbonate (21, 22). Renal replacement therapy is indicated when severe hyperkalaemia persists despite medical management (3). There is no clearly defined threshold for RRT initiation, and decision depends on the acuity of the potassium level change and clinical manifestations of hyperkalaemia, however RRT is generally considered in patients with potassium concentration greater than 6.5 mmol/L (21, 22). Intermittent haemodialysis is the most effective and commonly used modality of RRT for management of life-threatening hyperkalaemia, whereas CVVHDF is slower and may be preferred in non-life-threatening hyperkalaemia (21, 22).

Less frequent, but possible indications for RRT include other electrolyte disturbances, such as hyperphosphataemia, hypercalcaemia, hypermagnesaemia and dysnatraemia (21, 51).

Metabolic acidosis is a common complication of kidney failure (3, 21). No clear guidance exist delineating pH and bicarbonate levels that should prompt initiation of dialysis (22, 50). However, intractable metabolic acidosis with pH ≤ 7.15 or serum bicarbonate ≤ 12-15 mmol/L is generally considered as indication for RRT (3, 21, 50). Both IHD and CRRT are effective in correcting this acid-base abnormality (3).

Volume overload occurs frequently in AKI, due to kidney's inability to regulate fluid balance, aggravated by administration of intravenous fluids and medications during resuscitation and ongoing treatment of critically ill patients (3, 21). Several studies have shown an association between severity of fluid overload at RRT initiation and increased mortality (42, 52). There is no specific threshold, but RRT is generally indicated in volume overloaded patients with pulmonary oedema that is resistant to diuretic therapy (3, 21, 50).

RRT is indicated in case of poisoning and drug intoxication with such drugs, as salicylates, methanol, ethylene glycol, metformin, lithium and valproic acid, among others (see Table 8) (3, 22). It is possible to clear these substances by dialysis due to their small size, low volume of distribution of less than 1 L/kg body weight, and low degree of protein binding (22).

Cleared by RRT	Not cleared by RRT
Lithium	Digoxin
Methanol	Tricyclics
Ethylene glycol	Phenytoin
Salicylates	Gliclazide
Barbiturates	Beta-blockers (except atenolol)
Metformin	Benzodiazepines
Aminoglycosides, metronidazole, carbapenems, cephalosporins and most penicillins	Warfarin Macrolide and quinolone antibiotics

Table 8. "Examples of drugs/toxins cleared or not cleared by RRT" (53).

Overt uraemic symptoms, such as encephalopathy and pericarditis, are established indications for initiating RRT (3, 21). However, the early manifestations of uraemia are non-specific and may be difficult to differentiate from other causes in critically ill patients (3, 21). Therefore, progressive azotaemia with serum urea levels of more than 30 mmol/L and serum creatinine concentrations of more than 300 mmol/L, are frequently suggested as the indications to start RRT prior to the development of uraemic complications (3, 21). Serum urea is, however, not a perfect marker of kidney function, as its volume of distribution, production rate and tubular reabsorption vary greatly in critically ill patients (21, 50). There is no conclusive evidence on the exact thresholds of urea level that should prompt dialysis.

INITIATION

Despite subject of initiation of RRT being investigated in multiple studies, there is no consensus on optimal timing of dialysis outside life-threatening indications (37).

It has been proposed that early/immediate initiation of RRT might be beneficial by allowing for more rapid establishment of acid-base homeostasis, easier control of fluid balance, elimination of uremic toxins (54), and therefore prevention of the major complications of AKI (55).

On the other hand, RRT is associated with several risks and burdens. Hemodynamic instability during dialysis may lead to further renal impairment, as well as to cardiac and neurologic complications. In addition, in some patients spontaneous recovery of renal function may occur with conservative treatment alone. The strategy of early initiation of RRT might needlessly expose these patients to iatrogenic complications of vascular access (for example, infection, haemorrhage, thrombosis, vascular injury), as well as side-effects of RRT itself (for example,

intradialytic hypotension, fluid shifts, altered drug metabolism) (50, 55). Also, there is increased nursing workload, resource utilisation and significant cost (20).

Previously, the evidence on optimal RRT timing was derived mostly from retrospective and observational studies published between 2000 and 2010 (49).The meta-analyses of this data suggested reduced mortality and better renal recovery with earlier RRT (56, 57). However, the major pitfall of these older studies is that the patients who did not undergo RRT were not included. Exclusion of these patients who recovered renal function spontaneously and had an excellent prognosis, penalised the outcome of the delayed initiation group and represented a major selection bias (3, 49). Furthermore, the definitions of "early" and "late" initiation varied between the studies (2).

Recently, several randomised controlled trials have expanded the evidence on RRT initiation strategies but yielded conflicting results. The largest of them are ELAIN, AKIKI, IDEAL-ICU and STARRT-AKI. In contrast to the older studies, they included in their analyses those patients that were randomised but didn't undergo dialysis. The ELAIN trial (2016) showed a remarkable reduction in 90-day mortality in critically ill patients with early RRT, whereas AKIKI (2016), IDEAL-ICU (2018) and STARRT-AKI (2020) did not find a survival difference between early and delayed strategies (49).

It should be noted that there have been differences in inclusion criteria, patient's characteristics and dialysis techniques between these studies, which might explain the discrepancies in the results.

The most prominent difference between these studies is the stage of AKI upon inclusion in the study (58). In ELAIN trial the inclusion criteria were stage 2 KDIGO, whereas in both AKIKI and IDEAL-ICU trials, patients had to reach stage 3 KDIGO to be enrolled in the study (50, 58). Also, the definitions of "early" and "late" initiation varies greatly between the studies. In the "early" arm of ELAIN trial, RRT was initiated within 12 hours of stage 2 KDIGO, while in AKIKI and IDEAL-ICU renal support was started when patient developed stage 3 AKI (58-60). In the "delayed" group in ELAIN study RRT was initiated when patients either reached stage 3 KDIGO or developed absolute indications for dialysis (58, 59). In "delayed" arm of other two trials, RRT was started in patients with stage 3 AKI either when they developed life-threatening complications, or if renal failure persisted for more than 72 hours in AKIKI study or 48 hours in IDEAL-ICU study (54, 60). Therefore, patients with less severe AKI composed the "early" arm of ELAIN trial, and not surprisingly their outcome was better (58). Moreover, it should be noted that delayed strategy eliminated the need for dialysis in 49 % and 38 % of patients in AKIKI and IDEAL-ICU trials respectively, versus only 9 % in ELAIN study (50, 58). Table 9 summarises most recent randomised controlled trials on initiation of RRT (54, 55, 59, 60).

Trial	ELAIN	AKIKI	IDEAL-ICU	STARRT-AKI
Author	Zarbock et al.	Gaudry et al.	Barbar et al.	Wald et al.
Year	2016	2016	2018	2020
Country	Germany	France	France	15 countries
Number of hospitals	1 ICU	31 ICU	29 ICU	168 ICU
Population	Surgical, 231	Mixed, 619 (80% medical)	Medical, 488 (septic shock)	Mixed, 3019
Inclusion criteria	Stage 2 KDIGO and NGAL >150ng/ mL	Stage 3 KDIGO And Mechanical ventilation	RIFLE-F stage (equivalent to stage 3 KDIGO)	Stage 2 or 3 KDIGO

	and at least one of the following: -severe sepsis -use of vasopressors -refractory fluid overload -non-renal organ failure, SOFA ≥ 2	And/or Catecholamine infusion	and septic shock within 48 hours	
Early RRT criteria	Within 8 hours of diagnosis	Within 6 hours of diagnosis	Within 12 hours of diagnosis	Within 12 hours of diagnosis
Late RRT criteria (apart from conventional indications)	Within 12 hours of stage 3 KDIGO	Oliguria/ anuria for more than 72 hours	No renal recovery for more than 48 hours	No renal recovery for more than 72 hours
Modality	CVVHDF	IHD, CRRT	IHD, CRRT	IHD, SLED, CRRT
Primary outcome	90-day mortality	60-day mortality	90-day mortality	90-day mortality
Early vs Late mortality	39.3% vs 54.7%	48.5% vs 49.7%	58% vs 54%	43.9% vs 43.7%
Time difference between RRT strategies	25 hours	57 hours	51 hours	31 hours
% of patients in "late" arm not requiring RRT	9.2 %	49%	38%	38%

Table 9. Summary of ELAIN, AKIKI, IDEAL-ICU and STARRT-AKI randomised controlled trials (54, 55, 59, 60).

Recent systematic review and individual patient data meta-analysis by Gaudry et al. (2020) showed that "there is no statistically significant difference in 28-day mortality between early and delayed strategies of RRT initiation in critically ill patients with an acute kidney injury" (49).
The result of further trial investigating the optimal timing of RRT initiation (AKIKI-2) is still awaited (61).
In conclusion, in the presence of the absolute indications for dialysis, such as significant fluid overload refractory to diuretic therapy, refractory severe hyperkalaemia and refractory severe metabolic acidosis, RRT should not be deferred. In the absence of these criteria, the initiation of dialysis can be deliberately delayed (50). Appropriate care and close monitoring should be undertaken to timeously identify patients with emerging life-threatening complications of renal failure. This "wait and see" approach could lead to a reduced use of RRT, with the potential for health resource savings (49).

DOSING
The topic of optimal RRT dosing and the best method of measuring dialysis performance remains controversial despite extensive research (22).

Initially, dialysis adequacy was assessed using static parameters, such as pre-dialysis concentrations of urea or creatinine, however low correlation was shown between these static values and outcomes (62). Therefore, a dynamic assessment of dialysis dose was developed, based on urea kinetic modelling (UKM), which considers both generation rates and plasma clearance of urea (10, 62).

The most commonly used method for calculation of dialysis dose is called Kt/V (63). It is defined as “dialyser clearance of urea (K, in ml/min) multiplied by the duration of dialysis treatment (t, in minutes) divided by the volume of distribution of urea in the body (V, in ml), which is approximately equal to the total body water, corrected for volume lost during ultrafiltration” (63).

Another method is also based on urea clearance and is called urea reduction ratio (URR). It is related to Kt/V and defined as “ a fractional reduction of urea (blood urea nitrogen (BUN)) during a single dialysis” (63). The formula for its calculation is: URR = (1 - [postdialysis BUN ÷ predialysis BUN]) (63).

Although urea kinetic modeling is widely used for RRT evaluation in end-stage renal disease, there are several limitations of its application in acute kidney injury (22, 64). Urea kinetic models require relatively steady state of pre-dialysis volume status and nitrogen balance during repetitive cycles of haemodialysis (1, 64). However, critically ill patients with AKI are frequently unstable, often volume overloaded, have increased catabolism,have variable rates of urea generation and volumes of distribution (10, 64, 65). Additionally, changes in regional blood flow during episodes of hypotension in unstable patients affect the distribution of urea between compartments (64). In spite of these constraints, and in view of absence of better techniques, Kt/V and URR are commonly used for dose measurement of RRT in AKI (64). It is suggested, that Kt/V > 1 and URR > 58% per treatment are associated with improved survival in patients with intermediate severity of disease (64).

Certain measures can be undertaken to improve the efficacy of dialysis. As V value (volume of distribution) is fixed, the dose can be manipulated by increasing either K or t (63). Dialysate clearance of urea (K) may be augmented either by increasing blood flow through the dialyser, or by using membrane with larger surface area and with larger pores (63). Another way to improve Kt/V is to increase dialysis time, achieved by extending the time per treatment, or by increasing the frequency of sessions, or both (63).

Dialysis dosing for intermittent haemodialysis in AKI is assessed in relationship to frequency and duration of sessions as it has been extrapolated from patients with end-stage renal disease (1, 20). KDIGO recommends “delivering thrice-weekly Kt/V of 1.3 or a weekly Kt/V of 3.9 for intermittent and extended RRT in AKI” (22).

For continuous techniques, clearance is measured as hourly volume of effluent fluid, which is the total of the ultrafiltration volume obtained by convective clearance and the volume of dialysate obtained by diffusive clearance (10, 37). The CRRT dose is expressed as the ml/kg/h of effluent (10).

Many studies have investigated the impact of CRRT dose on outcomes. Older single-centre studies suggested that higher dose CRRT may be beneficial, although their results were inconsistent (3). Ronco et al. (2000) reported a greater survival of patients treated with high-dose RRT (35 ml/kg/h) compare to lower intensity (20 ml/kg/h) (66). However, recent large randomised controlled studies failed to show any such benefit, providing evidence that there is no decrease in mortality with effluent rates above 25 ml/kg/h (20).

“The Randomised Evaluation of Normal versus Augmented Level of renal replacement therapy in ICU (RENAL) study randomised 1508 critically ill patients with AKI to intensive (40 ml/kg/h) or non-intensive (25ml/kg/h) CRRT and no difference in 90-days mortality was seen in the two groups” (17). The VA/NIH Acute Renal Failure Trial Network (ATN) study randomised 1124 critically ill patients to more-intensive dosing (CVVHDF at 35 ml/kg/h, or IHD or PIRRT six times per week) or less-intensive strategy (CVVHDF at 20 ml/kg/h, or IHD or PIRRT three times per week) (18). Survival at 90 days and renal recovery were similar between two groups, and rate of complications was higher in the higher intensity group (37).

Based on these findings, the KDIGO Clinical Practice Guidelines recommend “a target dose for CRRT of 20 to 25 mL/kg per hour” (3, 22). When prescribing RRT, it should be remembered that the actual delivered dose of RRT is frequently substantially lower than the prescribed dose (22, 37). This happens due to various reasons leading to treatment interruptions, including machine malfunction, vascular access problems, filter clotting, surgical procedures and medical imaging (1, 4, 22, 37). KDIGO recommends “to increase effluent dosing by 25% to ensure delivery of the target dose” (22).

It is believed, that high circulating levels of proinflammatory markers in sepsis may lead to organ damage and dysfunction. As these substances are cleared during haemofiltration, it was suggested, that patient with septic shock could benefit from higher doses of RRT. However, the “High-Volume Versus Standard-Volume Haemofiltration for Septic Shock Patients With Acute Kidney Injury (IVOIRE) trial” compared CVVH at 35 ml/kg/h with CVVH at 70 mL/kg/h in patients with septic AKI, and showed no mortality benefit with the higher dose of hemofiltration (67). Thus, CRRT is not recommended as an adjuvant therapy in patients with sepsis (3).

DISCONTINUATION

The decision to discontinue RRT is complex and requires consideration of patient’s clinical condition, degree of kidney function recovery and ongoing need for dialysis (16, 22). Many patients with AKI will improve enough to avoid long-term RRT, but still 13-29 % will be dependent on dialysis at hospital discharge (11, 12).

The KDIGO guideline recommends cessation of renal replacement therapy when it is no longer required, either in case of sufficient improvement in native kidney function, or in case of futility in view of the overall prognosis and goals of care (2, 3, 22). The condition that prompted dialysis, for example electrolyte imbalance, fluid overload or uraemic complications, should be corrected prior to discontinuation of therapy (8, 16, 22).

There are no standardised recommendations on optimal timing, or precise criteria for discontinuation, of RRT due to lack of strong evidence (3, 8, 16). The strategy of weaning from renal support should thus be individualized in each patient (16, 22). Daily assessment of the patient’s clinical condition, such as haemodynamic status, respiratory function, fluid balance, as well as daily monitoring of renal function, including urine output, serum urea and creatinine, urine biochemistry, and calculation of creatinine clearance, may be used to assist with decision-making on weaning of RRT (2, 16, 22).

The process of weaning from CRRT in patients no longer requiring vasopressor/inotropic support, may involve transition to another RRT modality, such as PIRRT or directly to IHD, allowing better mobilisation and earlier discharge from ICU (3, 6, 22).

Increase in urine output is usually the first symptom of renal improvement and is one of the main predictors of successful termination of RRT (2, 3, 16, 20, 22). In a large prospective observational Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study, Uchino et al. identified urine output > 400 mL/d without concomitant diuretics and urine output > 2000 mL/d with diuretic therapy as the most significant predictors of successful CRRT discontinuation (3, 16, 22, 68). “Those patients, who were successfully weaned from RRT and did not require re-initiation of renal support, had significantly lower in-hospital mortality than those who needed repeated sessions” (28.5 vs. 42. 7%) (3, 16, 68).

In a randomized controlled Acute Renal Failure Trial Network (ATN) study by Palevsky et al., creatinine clearance was measured (urine was collected over 6 hours) in patients with urine flow of more than 30 ml/h or with spontaneous decrease in serum creatinine level (2, 3, 20, 69). “Renal support was terminated if creatinine clearance was more than 20 ml/min, was continued if

creatinine clearance was less than 12 ml/min, and was left to discretion of treating team if measurements were between 12 and 20 ml/min" (2, 3, 20, 69). Wheeler and Tolwani retrospectively analysed 24-h creatinine clearance and determined that values of more than 15 ml/min were predictive of successful RRT termination (16).

A retrospective observational study by Wu et al. determined independent predictors for early re-dialysis after initial weaning from RRT, such as prolonged duration of dialysis, low urine output on Day 1 after discontinuation, higher disease severity score and age over 65 years (16, 22, 70). In several studies mortality rate was shown to be higher in patients requiring re-initiation of RRT, either reflecting the severity of underlying disease or harmful effect of early weaning itself (2, 16, 22). The effects of RRT re-institution on patient outcomes have not been properly investigated (16, 22).

The role of furosemide in renal recovery was evaluated in a randomized controlled study by van der Voort et al., which showed increase in urine output and sodium excretion, but no effect on kidney function recovery or duration of renal failure (2, 22). Wu et al. found no influence of diuretic use on successful discontinuation of RRT (22, 70).

Other markers of kidney function that could suggest renal recovery were investigated, such as daily urinary urea and creatinine excretions, serum neutrophil gelatinase-associated lipocalin (NGAL) and plasma NT-pro-BNP, however studies reported conflicting results and stronger evidence is required to establish a proper protocol for RRT discontinuation (2, 16).

At present, increasing urine output, creatinine clearance of more than 15-20 ml/min and a progressive decline in serum creatinine in the context of steady-state RRT and stable general condition of the patient, are considered significant predictors of renal recovery (16, 20) (Figure 4).

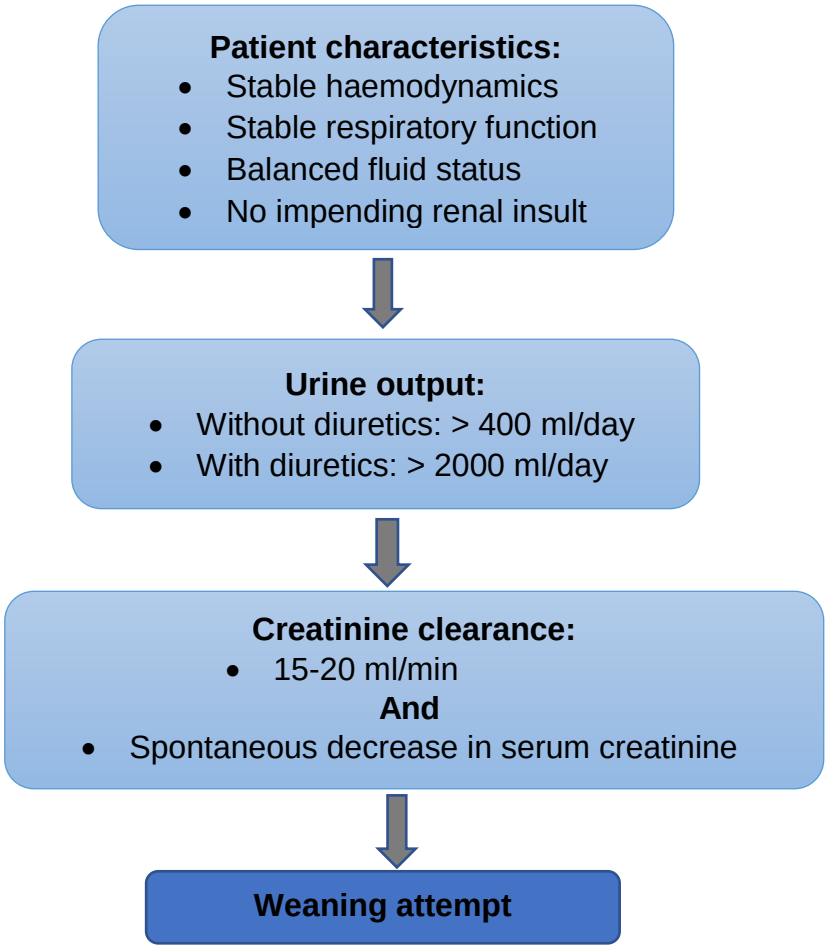


Figure 4. Suggested "algorithm for weaning a critically ill patient with AKI from renal replacement therapy" (16).

PHYSICAL ASPECTS

Dialysis membrane

The renal replacement therapy membrane is a semi-permeable hollow-fibre filter that can be made from cellulose, substituted cellulose or synthetic non-cellulose polymers (4, 22, 71, 72). They differ by degree of biocompatibility, which is defined as a degree of inflammatory response triggered by interaction between blood and dialysis membrane (22, 28, 71).

The previously used cuprophane (cellulose-based) membranes are regarded as bio – incompatible, as their use leads to the activation of complement system, adhesion and activation of the platelets and leucocytes, release of mediators of inflammation and oxidative stress (22, 28, 37, 71). Clinically it may present as acute hypotension, fever, hypoxaemia and may result in long-term sequelae, such as neutrophilic infiltration of kidneys, lungs and other organs, delayed recovery of renal function, increased protein catabolism and susceptibility to infection (20, 22, 28, 72).

Synthetic non-cellulose membranes, composed of polyacrylonitrile (PAN), polysulfone, or polymethylmethacrylate (PMMA) are considered biocompatible (22, 72). Although there is lack of definitive conclusions on effect of biocompatibility on patient's outcome, it is recommended to use the most biocompatible synthetic membranes for the renal replacement therapy (1, 10, 20). Biocompatibility of substituted cellulose membranes ranges from incompatible to highly compatible (72).

Another important characteristic of the membrane is its permeability to water and large solutes, referred to as flux (4, 10). Depending on number and size of the pores, membranes are divided into low-flux and high-flux (22).

In convective dialysis, the use of high-flux membranes with high hydraulic permeability is preferred, as it allows the clearance of larger solutes and more efficient ultrafiltration without the need for excessive transmembrane pressure (37, 71). The standard membrane for haemofiltration has a cut-off, or permeability limit, of 30-35 kDa, allowing clearance of small to middle molecules (71). The superpermeable (super high-flux) membranes with a permeability limit of 40-100 kDa were designed to promote the passage of larger molecules, such as cytokines, immunoglobulins and myoglobin, that could be theoretically beneficial in the treatment of sepsis and rhabdomyolysis (1, 5, 37). However, it's use leads to an increased albumin loss, and clinical or survival benefit has not yet been established (1, 37, 71). In diffusive techniques, low-flux membranes with a cut-off of approximately 5 kDa and low water permeability are used (37, 71).

Frequency of filter changing depends on the anticoagulation used and is guided by transmembrane pressure (71). With unfractionated heparin anticoagulation it should be changed every 24 to 48 h, and every 72 to 96 h with regional citrate anticoagulation (71). Increased transmembrane pressure of more than 300 mmHg is indicative of membrane clotting (71).

Vascular access

RRT requires a dedicated vascular access that provides an adequate and regular blood flow (4, 22). For this purpose, a specially designed large-bore dual lumen dialysis catheter made of polyurethane or silicone, is inserted percutaneously into a large vein using the Seldinger technique (3, 4, 28). KDIGO Clinical Practice Guideline for AKI recommends using central veins in the following order: right internal jugular vein, either femoral vein, left internal jugular vein, subclavian vein with preference for the dominant side (3, 22, 73).

The aspects that should be considered when choosing the insertion site of dialysis catheter are risks of venous thrombosis and stenosis, infection, catheter dysfunction and recirculation (22).

Contrary to popular belief, femoral vein cannulation is not associated with highest risk of catheter-related blood stream infection (22, 73, 74). Recent large prospective trial showed similar incidence of catheter colonisation with internal jugular and femoral venous accesses, except from obese patients, where the risk of infection was higher with the femoral site (37, 74). Also, femoral cannulation restricts patient's mobilisation (22).

Rate of catheter dysfunction is lower with right internal jugular catheter compare to femoral catheter (75), which in turn has less malfunctioning and better survival than left internal jugular (22, 76). When comparing right to left jugular catheters, the latter has higher rate of dysfunction and risk of venous thrombosis/stenosis, that could be related to its tortuous course with several angulations (73, 76-78).

Despite the lowest rate of infection (79), the subclavian vein cannulation is the least desired option due to the high risk of subclavian and axillary veins thrombosis and stenosis, compromising subsequent arterio-venous fistula placement if chronic haemodialysis is required (2, 4, 20, 22).

Proper positioning of catheter tip is crucial for obtaining optimal flow rates and reducing the risk recirculation (3, 20). The tip of jugular catheter should be placed at the junction of superior vena cava and right atrium (3, 22, 80). Positioning of the catheter in the right atrium may lead to cardiac arrhythmias, atrial wall perforation, and cardiac tamponade (22). To achieve correct position, the length of left jugular catheter should be longer than that of the right (15-20 cm vs 12-15 cm respectively) (3). For femoral access, 19-25 cm long catheters should be used to achieve tip placement close to or within inferior vena cava(3, 10, 20, 81). The recirculation of blood can be as high as 23% with the use of short femoral catheters, leading to catheter malfunctioning, lower blood flows and increased risk of filter clotting (3, 10, 22, 82). The outer diameter of catheter should be around one third of the vein diameter, and usually varies between 11 and 14 French (2, 22).

Ultrasound-guided cannulation is recommended to improve the success rate and to avoid iatrogenic complications related to catheter insertion (2, 22, 37).

ANTICOAGULATION

Clotting of the dialysis circuit is a major concern during renal replacement therapy (3, 4, 28). It leads to membrane dysfunction, reduced solute clearance, circuit downtime and ineffective treatment (4, 6, 28). The benefit of maintaining filter patency needs to be balanced against the risk of bleeding with anticoagulation on a case-to-case basis (28).

Anticoagulation-free RRT is possible, but very challenging (28). There are several technical strategies that may help to prevent filter clotting (3, 6). These include adequately functioning vascular access, higher blood flows, frequent flushing of the circuit with saline, reduced filtration fraction, pre-filter administration of replacement fluids in convective modes of dialysis, prompt response to machine alarms to minimise interruptions in the blood flow and avoidance of blood transfusions through the circuit (3, 6, 22, 28).

Anticoagulation strategies can be either systemic, or regional (4). Systemic anticoagulation includes unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), thrombin inhibitors, factor Xa inhibitors and alternative anticoagulation, such as protease inhibitors or platelet inhibitors (3, 22). Regional methods are regional citrate anticoagulation and regional heparinisation (2, 22).

Figure 5 provides schematical representation of coagulation cascade and mechanism of action of most common anticoagulants used in RRT.

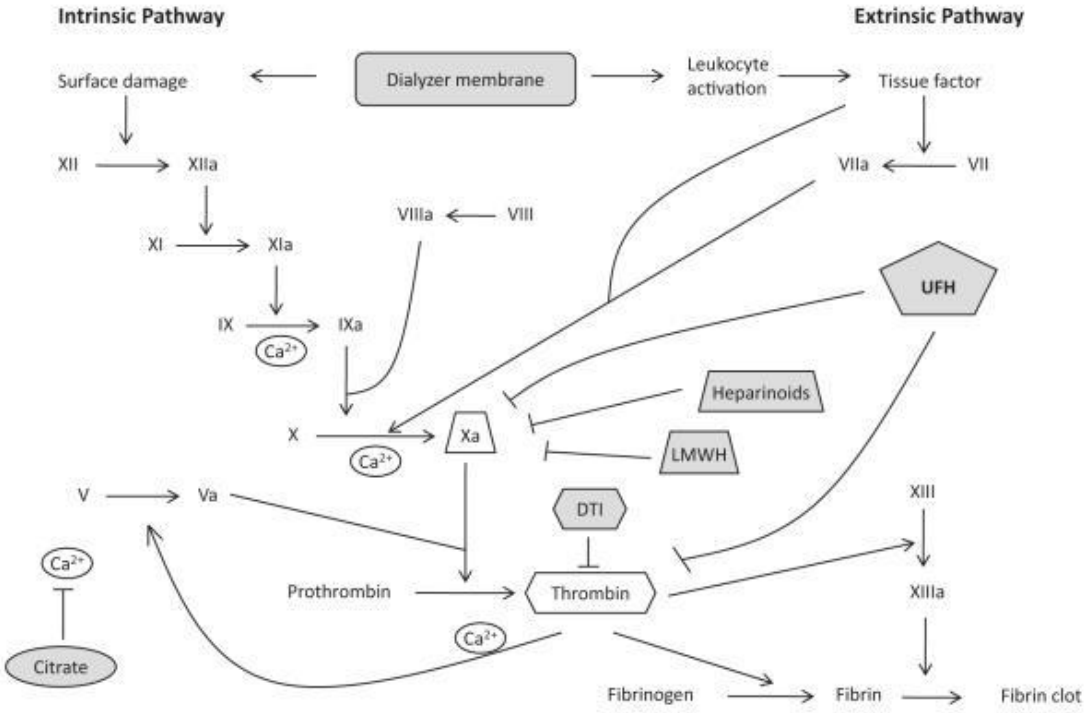


Figure 5. Coagulation cascade and mechanism of action of most common anticoagulants used in renal replacement therapy (83).

Advantages, disadvantages and monitoring of different anticoagulation methods are summarised in Table 10.

Anticoagulant	Advantage	Disadvantage	Monitoring
UFH	Wide availability Low cost Ease of administration Simple monitoring Availability of reversal agent Short half-life	Risk of bleeding Heparin-induced thrombocytopenia Hypertriglyceridaemia Osteoporosis Hypoaldosteronism Hyperkalaemia Heparin resistance in critically ill patients Unpredictable kinetics	aPTT1.5-2.0 times upper limit of normal Platelet count
LMWH	Lower incidence of HIT No metabolic SE More reliable anticoagulant response	Long half-life Risk of accumulation in renal failure Incomplete reversal by protamine Cost Monitoring requires non-routine test	Anti-Factor Xa activity essay 0.25-0.35 U/ml
Direct thrombin inhibitors			
Argatroban	Can be used in HIT Short half-life Fewer bleeding complications	Not safe in liver impairment No reversal agent Expensive	aPTT target 1.5-2.5 upper limit of normal

	Hepatic metabolism		
Bilivarudin	Can be used in HIT Extra-hepatic metabolism Safe to use in hepatic failure	No reversal agent Higher risk of bleeding Prolonged half-life Expensive	Requires specialised tests Inaccurate monitoring with aPTT
Factor Xa inhibitors			
Danaparoid	Can be used in HIT	No reversal agent Prolonged half-life Cross-reactivity with HIT antibodies	Anti-Factor Xa activity essay
Fondaparinux	Can be used in HIT	No reversal agent Prolonged half-life Accumulation in renal failure	Anti-Factor Xa activity essay
Regional citrate anticoagulation	Avoidance of systemic anticoagulation Lower bleeding risk Improved filter patency Can be used in HIT Anti-inflammatory effect	Citrate toxicity Hypocalcaemia Hypernatraemia Hypomagnesaemia Metabolic alkalosis Metabolic acidosis Contraindicated in liver failure and shock states Complexity Requires strict protocol	Ionized calcium in extracorporeal circuit Systemic total and ionized calcium Electrolytes Blood pH
Regional heparin-protamine anticoagulation	Avoidance of systemic anticoagulation	Heparin-induced thrombocytopenia Anaphylaxis Hypotension Pulmonary vasoconstriction Right ventricular failure	Circuit aPTT
Alternative anticoagulants			
Nafamostate	Very short half-life Lower risk of bleeding	Not widely available Anaphylaxis Hyperkalaemia Bone marrow suppression Absence of antidote	aPTT
Prostacyclin	Short half-life Lower bleeding risk Usually used in liver failure	Systemic hypotension Absence of antidote Cost	No monitoring available aPTT if used with heparin

		May need low-dose heparin addition	

Table 10. Overview of the advantages, disadvantages and monitoring of different anticoagulants (2, 3, 6, 22, 37, 83, 84).

Systemic anticoagulation

Unfractionated heparin (UFH)

Unfractionated heparin remains most widely used method (4, 6, 22). It is a polysaccharide, composed of glycoasaminoglycan chains of different molecular weight, ranging from 3000 to 30 000 daltons (32). Higher molecular weight components bind predominantly to antithrombin, while smaller fragments inhibit factor Xa (32, 85). Among advantages of UFH are wide availability, ease of use, low cost, short half-life (0.5 – 3 hours), monitoring with routine tests such as activated partial thromboplastin time (aPTT) and reversibility with protamine (2, 4, 22). Side effects of UFH include increased bleeding risk, heparin-induced thrombocytopenia (HIT), pro-inflammatory effect, osteoporosis, hypertriglyceridaemia, hypoaldosteronism and heparin resistance (2, 4, 22, 83).

UFH is usually administered in an "arterial" bloodline of the circuit as an initial bolus of 30 IU/kg, followed by a continuous infusion of 5-10 IU/kg/hr, titrated to target systemic aPTT of 45-60 sec or 1.5-2.0 times the upper limit of normal, although the dosing protocol should be adjusted according to the mode of RRT, patient's coagulation status and bleeding risk (2, 3, 22, 28). Monitoring of platelet count is also required to detect HIT (22).

Low molecular weight heparin (LMWH)

Low molecular weight heparins are produced from UFH by cleavage, and due to the smaller size (approximately 5000 dalton), they have less ability to bind antithrombin and have predominantly anti-factor Xa activity (3, 4, 84). LMWH have several advantages over UFH, such as less non-specific endothelium, protein and cell binding, reduced risk of HIT, more predictable pharmacokinetics, more reliable anticoagulant effect and fewer metabolic side effects (2-4, 22, 84, 86). However, it is more expensive, only partially reversible with protamine, and requires non-routine test for monitoring (anti-Xa activity essay), which is not widely available and time-consuming (2, 4, 22). Also, there is a risk of accumulation in renal failure, as LMWH is cleared primarily by kidneys and has a long half-life (22, 37). The dose of LMWH varies depending on the mode of RRT, bleeding risk of the patient and the individual pharmacokinetics of LMWH. LMWH may be given as a fixed dose or dose-adjusted to achieve a target of anti-Xa activity of 0.25 – 0.35 U/ml (2, 84, 86).

UFH vs LMWH

In a meta-analysis of randomised controlled studies comparing safety and efficacy of UFH and LMWH in IHD, no statistically significant difference was found (37, 87). During CRRT, randomised controlled studies showed similar or longer filter patency with LMWH, as well as lower risk of bleeding complication (84, 85, 88).

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (type II) is a syndrome caused by formation of antibodies against heparin-platelet-4-factor complex, leading to both bleeding and thromboembolism (83). It can be suspected in patients with repeated filter clotting and the likelihood can be estimated by using "4-T scoring", which includes the severity of thrombocytopenia, timing of decrease in platelet count, clinical manifestations of thromboembolism, and absence of other potential causes of thrombocytopenia (22, 83).

If heparin-induced thrombocytopenia is diagnosed or strongly suspected, all forms of heparin should be stopped and alternative anticoagulation started either with direct thrombin inhibitors

(such as argatroban or bivalirudin) or factor Xa inhibitors (such as danaparoid or fondaparinux) (2, 3, 22).

Direct thrombin inhibitors

The most common option is argatroban, a direct thrombin inhibitor with short half-life, hepatic metabolism, routine monitoring with aPTT, but with risk of accumulation in liver impairment (22). Bivalirudin is preferred in patients with liver failure in view of its extra-hepatic metabolism, however it has prolonged half-life, requires specialised tests for monitoring as aPTT is unreliable due to non-linear drug-response curve, and has higher risk of bleeding compare to argatroban (3, 83, 84).

Factor Xa inhibitors

Factor Xa inhibitors are alternative treatment of HIT. Danaparoid is heparin derivative, it has long half-life, can be monitored with anti-Xa activity essay, but may have cross-reactivity with HIT antibodies (83, 84). Fondaparinux is a synthetic pentasaccharide with long half-life, risk of accumulation in renal failure and slightly less efficacy in maintaining filter patency compare to UFH (83, 89).

Alternative anticoagulation

Alternative anticoagulants, such as protease inhibitors (nafamostate) and platelet inhibitors (eg. Prostacyclin), are thought to provide benefit of reduced bleeding risk due to their short half-life and low molecular weight, and sometimes considered as regional anticoagulants (22). However, they are expensive, have limited availability and have been shown to have reduced efficacy (22, 85). Serious side effects were reported with their use, including anaphylaxis, bone marrow suppression and hyperkalaemia with nafamostate, and systemic hypotension due to vasodilatation with prostacyclin (22, 32, 84). Currently, due to lack of evidence on safety and efficacy of alternative anticoagulants, their routine use is not recommended (22, 85).

Regional anticoagulation

Regional Citrate Anticoagulation (RCA)

The mechanism of action of citrate relies on its ability to chelate the ionised calcium in the extracorporeal circuit, preventing calcium participation in both extrinsic and intrinsic pathways of coagulation cascade (3, 86). Sodium citrate is administered in the pre-filter line proximally to patient's blood entering the circuit, in a dose of approximately 4-6 mmol/l blood titrated to achieve a post-filter ionised calcium concentration of less than 0.4 mmol/l (2, 3, 86). Most of the formed citrate-calcium complex is eliminated via filter as effluent, whereas the remaining part enters the systemic circulation and undergoes metabolism in liver, muscles and kidneys, producing bicarbonate (2, 22). Systemic concentration of ionised calcium is maintained in the physiological range by separate infusion of calcium (3, 22).

Main advantages of RCA are strictly regional nature of anticoagulation and therefore reduced risk of bleeding, prolonged filter survival, potential anti-inflammatory effect, and avoidance of heparin-induced thrombocytopenia, as well as other complications of systemic anticoagulants (2, 3).

However, RCA may lead to multiple electrolyte and acid-base abnormalities (3). Metabolic conversion of citrate to bicarbonate may cause metabolic alkalosis and use of hypertonic sodium citrate may result in hypernatraemia (3). In patients with hepatic failure and severe shock states, citrate accumulates, leading to citrate toxicity (2, 3). It may be indicated by profound hypocalcaemia despite increasing calcium supplementation, raised systemic total to ionised calcium ratio of more than 2.5 and increasing high anion gap metabolic acidosis (3). Clinically citrate accumulation presents as coagulopathy, tetany, seizures, hypotension, decreased cardiac contractility and prolonged QT syndrome (4, 83). Management includes immediate discontinuation of citrate infusion and calcium replacement (90).

Because of the risk of serious complications, citrate anticoagulation requires strict adherence to protocols, indicating rates of citrate and calcium infusions, electrolyte content of dialysate and replacement fluids, and frequency of blood tests (22). Usually, calcium-free and low sodium dialysate/replacement fluids are used (4, 86). Circuit ionised calcium, systemic total and ionised calcium, sodium, magnesium, and blood pH should be monitored at least every 6 hours (3, 22).

Many randomised controlled studies compared regional citrate anticoagulation to systemic heparin during CRRT, with results showing longer filter lifetime, fewer bleeding complications and less transfusion requirements with citrate use (22, 90-93). In patients with high bleeding risk, several observational studies reported lower incidence of haemorrhage with regional citrate anticoagulation (37, 94).

It is recommended by KDIGO to employ RCA as a first choice of anticoagulation for CRRT in patients without contraindications to citrate, such as liver failure and shock (22). However, due to complexity of the procedure and monitoring, it should be used only in centres with established protocols and sufficient experience (22). Systemic heparin remains one of the most common anticoagulation techniques in many countries (22).

Regional heparin-protamine anticoagulation

Another method of regional anticoagulation is a pre-filter infusion of heparin with a post-filter administration of the heparin reversal agent, protamine (22). However, this technique is not widely recommended due to major drawbacks of simultaneously exposing patient to the side effects of heparin, such as heparin-induced thrombocytopenia, and the risks of anaphylaxis, severe hypotension, pulmonary vasospasm and right heart failure with protamine (22, 37). In addition, there is a risk of rebound effect due to longer half-life of heparin compare to its antidote (22, 37).

Choice of anticoagulation in RRT

The decision about the choice of anticoagulation is based on the patient's coagulation status and bleeding risk, mode of renal replacement therapy and local practice (22). The following are the recommendations issued by KDIGO Clinical Practice Guideline for Acute Kidney Injury, 2012 (see Figure 6) (22).

Heparin includes low-molecular-weight or unfractionated heparin. CRRT, continuous renal replacement therapy; RRT, renal replacement therapy.

In patients with low bleeding risk, no coagulation abnormalities and no indications for systemic anticoagulation, unfractionated or low molecular weight heparin is recommended for IHD, regional citrate anticoagulation for CRRT, and in the presence of contraindications to citrate, UFH is preferred for CRRT (22, 37).

In patients at high risk of bleeding or with impaired coagulation, systemic anticoagulation should be avoided in both IHD and CRRT (22, 37). Regional citrate anticoagulation may be used during CRRT if there is no contraindication to its use (22, 37). Table 11 summarises clinical conditions representing high risk of bleeding (22, 86).

Active bleeding
History of bleeding within last 7 days
Major surgery within 7 days
Intracranial surgery within 14 days
Biopsy of the visceral organ within 72 hours
Recent trauma
Recent stroke

Intracranial arterio-venous malformation or aneurysm
Retinal haemorrhage
Uncontrolled hypertension
Presence of an epidural catheter

Table 11."Clinical conditions representing high risk of bleeding" (22, 86).

In patients requiring systemic anticoagulation for their underlying disease, systemic heparin should be preferred and no additional anticoagulation for RRT is usually required (37).

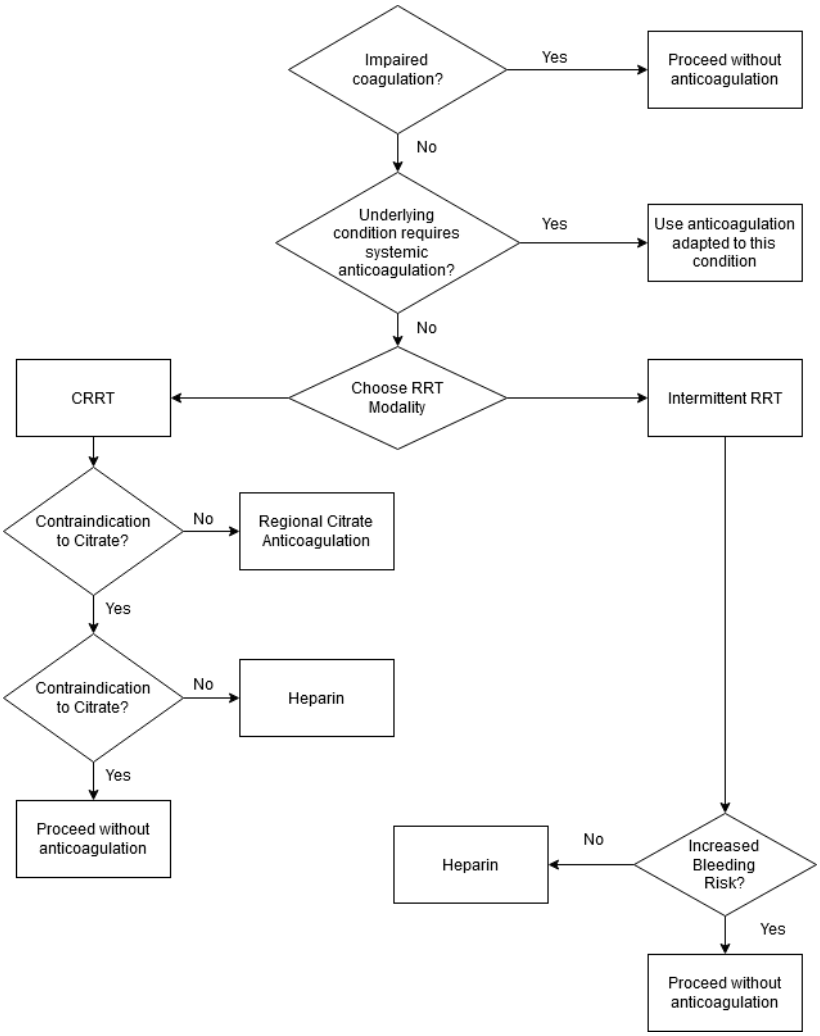


Figure 6. Flow chart summary of recommendations by KDIGO (22).

DRUG DOSING

Patients with AKI usually require multiple medications. Currently available recommendations provide only general guidance on drug dosing in AKI patients undergoing RRT, and care should be taken to avoid both underdosing and overdosing of treatment (3, 20).

The pharmacokinetics of drugs in critically ill patients are very complex, affected by multiple factors, such as clearance by renal replacement therapy, patient's residual GFR and the effects of acute kidney injury and critical illness, leading to an increased volume of distribution, alteration in protein binding, and changes in renal and non-renal clearance, among others (3, 20, 95).
Molecular weight and protein binding of drugs affect their ability to cross the RRT membrane (96). Drugs with high molecular weight, high protein binding and large volumes of distribution will remain in blood and will not cross the membrane (3, 96). The dosing of these drugs that are poorly cleared by RRT does not require adjusting (3). Low molecular weight drugs that are non-protein-bound will be eliminated by RRT more readily, and their clearance usually equals the effluent flow

(3, 20). The clearance of protein-bound low molecular weight drugs will depend on their unbound fraction (3).

Technical parameters of the dialysis machine also influence drug removal (96). Clearance of molecules is directly proportional to the size of membrane pores (20, 95). Blood, dialysate and ultrafiltration flow rates can be adjusted, and the faster the effluent rate, the higher the drug clearance (96). Mode of RRT and frequency of dialysis influence drug removal as well (96).

Therapeutic drug monitoring should be done for all medications with measurable blood levels (96). Drugs such as vasopressors, analgesics and sedatives, can be titrated to the desired clinical effect (3, 96). Appropriate dosing of antibacterial agents is of extreme importance in the management of septic patients (3). Underdosing of antibiotics may lead to a treatment failure, whereas too high doses may lead to systemic exposure and toxicity (3, 97). Details of antibiotic dosing in renal replacement therapy can be found in articles by Blot et al.(2014) and Jamal et al.(2015) (98, 99).

COMPLICATIONS

Renal replacement therapy is associated with several potential complications, which are summarized in Table 12 (6). Close monitoring of dialysis machine performance and the patient's haemodynamics, fluid, acid-base and electrolyte status, are crucial in preventing complications (6).

Complications that may happen during insertion of the dialysis catheter are haemorrhage, haematoma, haemothorax, haemomediastinum, atrial perforation, cardiac tamponade, retroperitoneal haemorrhage, air embolism and arrhythmias (3, 6, 100, 101). Many of these problems can be prevented by using ultrasound guidance during catheter placement (22, 101). It is recommended to obtain a chest radiograph after the insertion and prior to the initial use of internal jugular or subclavian catheters, in order to confirm the appropriate placement and to exclude iatrogenic complications (22).

Air embolism is a potentially life-threatening complication (86). Air may enter the circulation during insertion or removal of catheter, or at any time during the procedure in case of loose connections or residual air left after inadequate priming the circuit (3, 86). Longer term complications may arise during vascular access use, such as infection, venous and/or catheter thrombosis, venous stenosis, catheter dysfunction, arterio-venous fistula and aneurysm formations (3, 6, 100, 101).

Electrolyte imbalance happens frequently during RRT (3, 100). The most common abnormalities are hypophosphataemia and hypomagnesaemia, as they are cleared during CRRT and dialysate/replacement fluids typically do not contain these electrolytes (100). Hypophosphataemia can lead to cardiac depression, immune dysfunction, respiratory failure and difficult weaning from ventilation (2, 102). Other derangements may also occur, such as hypo- or hypercalcaemia, hypokalaemia, hypo- or hypernatraemia (3, 100). Regular monitoring of electrolyte concentrations and timeous replacement are crucial (100).

Thermal loss occurs during continuous renal replacement therapy because of extracorporeal radiant heat exchange and use of non-heated dialysate/replacement fluids (3, 100). Hypothermia causes peripheral vascular constriction which may enhance haemodynamic stability, however it increases patient's energy requirements and may lead to delayed recognition of infection due to the absence of fever (3, 100). In case of significant hypothermia, patient should be actively warmed (3).

Interaction between blood and extracorporeal circuit surface may trigger an inflammatory response, resulting in anaphylaxis or delayed immunological reactions (3, 100). Use of synthetic polyacrylonitrile AN-69 membranes was reported to cause bradykinin release syndrome, clinically

presenting as severe hypotension and pulmonary vascular congestion (4, 22). This anaphylactoid reaction is self-limited and noted to be more pronounced in patients on treatment with angiotensin converting enzyme inhibitors (ACE-I) and in severely acidotic patients (4, 22).

Intradialytic hypotension is a common complication of intermittent haemodialysis, but even with continuous techniques, it may occur in up to a third of patients (3). It has been defined by KDOQI guidelines as a symptomatic decrease in systolic blood pressure of 20 mmHg or more, or a decrease in mean arterial pressure of 10 mmHg or more (103). Hypotension has been linked to increased mortality, as well as to development of subclinical ischaemia of such vital organs, as brain, heart and kidneys, resulting in chronic organ dysfunction (104). Hypotension during haemodialysis may be due to the patient's underlying critical illness, may be from a new non-dialysis related complication or may be related to the haemodialysis (3). With regard to hypotension from the dialysis itself, the most common mechanism of intradialytic hypotension is high ultrafiltration rates, leading to reduction in circulating blood volume that exceeds vascular refilling rate (100, 104). In this case, intravenous fluids should be administered and ultrafiltration rate adjusted (3). It is recommended to keep ultrafiltration rates below 13 ml/kg per hour (86). Vasopressor support may be required if the hypotension is severe, and/or non-responsive to the aforementioned strategies. Acetate- and lactate-based buffers in dialysis fluid may cause vasodilatation and decreased cardiac contractility, leading to hypotension (3). Currently, bicarbonate-based solutions are preferred as they don't contribute to haemodynamic instability (3).

One of the commonly used strategies to prevent intradialytic hypotension, is a cooling of dialysate (86). This leads to the activation of sympathetic nervous system and therefore increases peripheral vascular resistance and cardiac contractility, enhancing haemodynamic stability (86). The temperature of dialysate is decreased by 0.5° to 1°C below body temperature, keeping it above 35°C, and patient is monitored for hypothermia-induced symptoms and complications (86).

Another technique proposed to reduce intradialytic hypotension is sodium profiling (104). Due to solute diffusion during dialysis, the osmolarity of plasma decreases, reducing the osmotic drive for vascular refilling, which may result in hypotension (86, 104). To counteract this fast reduction in plasma osmolarity, concentration of sodium in the dialysate can be increased to more than 140 mEq/L (86, 104). However, it may result in sodium gain, hypertension, thirst, interdialytic weight gain, and is currently not recommended (86, 104).

In case of persistent hypotension, more serious causes should be considered, such as myocardial ischaemia, heart failure or pericardial disease (86).
Anticoagulation has its own spectrum of side-effects, which are explained in detail in the chapter on anticoagulation.

Haemolysis may occur due to mechanical damage of erythrocytes by roller pumps or defective tubing (86). Also, it may be induced by hyperosmolar dialysate or electrolyte abnormalities, such as hypophosphataemia, hyponatraemia and hypokalaemia (86, 100). If left untreated, this may itself lead to "pigment-induced" renal injury (100).

Many water-soluble vitamins and essential minerals, including zinc, selenium, manganese, vitamin C and vitamin E, among others, are lost during RRT (100). Replacement is required to prevent severe depletion (100). Hypoalbuminaemia and malnutrition may result from filtration of amino acids, albumin and other key nutrients (100).

Drug pharmacokinetics are altered due to both renal insufficiency and renal replacement therapy (100). Close monitoring of drug levels and dose adjustments are necessary to prevent underdosing or toxic accumulation (6, 100).

Dialysis disequilibrium syndrome (DDS) is a complication of intermittent haemodialysis, which has become less common due to increased awareness (86). It progresses from mild symptoms, like nausea and vomiting, tiredness, and headache, to severe presentations with confusion, seizures and coma (86). Typically, it is more pronounced with a first dialysis session, in the elderly and in patients with very high urea levels and with severe acidosis (86). The main cause of DDS is a rapid shift in electrolyte concentration and osmolality, with serum osmolality dropping more rapidly than brain osmolality, leading to cerebral oedema (86). Certain measures can be undertaken to prevent its development, for example shortening initial dialysis sessions, using dialysate with higher sodium concentrations, reducing blood and dialysate flow rates, and administration of mannitol (86).

Recovery of renal function may be delayed by periods of intra-dialytic hypotension, catheter-related infections and blood-membrane interactions, resulting in ongoing kidney injury (100). It is thus imperative to attempt to prevent these complications and to treat them early and aggressively if they do occur.

Catheter-related complications
Haemorrhage
Haematoma
Haemothorax
Pneumothorax
Haemomediastinum
Atrial perforation
Pericardial tamponade
Retroperitoneal haemorrhage
Air embolism
Arrhythmias
Aneurysm formation
Arterio-venous fistula formation
Infection
Venous Thrombosis
Venous Stenosis
Catheter disconnection
Catheter dysfunction (kinking, thrombosis, recirculation)
Extracorporeal circuit-related complications
Reactions to membrane or tubing (bioincompatibility, bradykinin release, immunologic activation, anaphylaxis)
Hypothermia
Circuit/filter clotting
Air embolism
Haemolysis
Anticoagulation-related complications
Heparin-associated:
Heparin-induced thrombocytopenia
Bleeding
Hypertriglyceridaemia
Hypoaldosteronism
Osteoporosis
Citrate-associated:
Citrate toxicity
Hypocalcaemia
Hypernatraemia

Metabolic acidosis and alkalosis
Hypotension
Cardiac events
Electrolyte disturbances
Hypophosphataemia
Hypomagnesaemia
Hypocalcaemia
Hyponatraemia
Hypernatraemia
Hypokalaemia
Acid-base disturbances
Metabolic acidosis
Metabolic alkalosis
Dialysis disequilibrium syndrome
Nutritional losses
Amino acids and proteins
Vitamins
Trace elements
Poor glycaemic control
Volume management errors
Altered drug pharmacokinetics
Delayed renal recovery

Table 12. Complications associated with renal replacement therapy (3, 100).

ANAESTHETIC IMPLICATIONS

Patients with acute kidney injury are usually critically ill. Many of them are haemodynamically unstable and require multiple organ support, such as mechanical ventilation, renal replacement therapy and inotropic infusions (105).

Their complex medical condition places them at increased risk of peri-operative morbidity and mortality (106). Therefore, a thorough pre-operative assessment and anaesthetic planning are pivotal in management of these patients (31).

Pre-operative considerations

It is vital to assess cardiac and respiratory functions, intravascular volume status and fluid balance, laboratory parameters of the patient, and to establish the cause of AKI and indication for renal replacement therapy (31, 105).

Volume assessment is imperative. Both hypovolaemia or hypervolaemia can occur and are associated with negative outcomes (31). Hypovolaemia is a common reason for intra-operative hypotension and organ hypoperfusion, whereas fluid overload may lead to pulmonary oedema and hypoxia (31, 106). Apart from clinical examination looking for signs and symptoms of volume overload or hypovolaemia (peripheral oedema, pulmonary crackles, skin turgor, thirst, jugular venous pressure, vital parameters, weight changes etc.), such investigations as chest radiography, cardiac and lung ultrasound, arterial blood gas and cardiac natriuretic peptide, could be useful (31, 107, 108).

Patients with renal impairment are prone to multiple metabolic abnormalities. Serum potassium, sodium, calcium, magnesium, phosphorus, urea and creatinine, pH status should be checked pre-operatively (106-108).

Assessment of coagulation status is important, as it may be affected both by uraemic effects of kidney failure and by anticoagulation used for RRT. The method of anticoagulation used should

be known, and peri-operative strategies should be discussed (105). Coagulation tests may include haemoglobin and haematocrit, platelet count, prothrombin time and partial prothrombin time, as well as thromboelastogram (105).

After complete assessment, a decision should be taken on the appropriate timing of surgery (105). In case of minor and short surgical procedures, renal support can usually be safely discontinued for the duration of the surgery (105). However, it may be safer to continue RRT intra-operatively when the patient is scheduled for major long-duration surgery that is associated with major fluid shifts and haemodynamic instability (105). This strategy is quite common in cardiac and liver transplant surgeries, but it requires trained anaesthesiologists and operation theatre staff familiar with dialysis equipment (105). The other option is to delay the surgery till patient becomes more stable (31). It should be noted, that if RRT is discontinued intra-operatively, the metabolic abnormalities can recur during surgery and should be monitored for (31, 105).

Patients with chronic kidney disease (CKD) also represent a challenge to anaesthetists and are at substantial risk of peri-operative complications (106). They usually have "multiple co-morbidities, such as hypertension, ischaemic heart disease, peripheral vascular disease and diabetes mellitus", which should be investigated and optimized prior to surgery (107). Their volume status is difficult to estimate despite them being on regular haemodialysis, as period of euvolaemia after dialysis session is short and it is uncertain whether treatment goals were achieved (106).

Patients with CKD are usually anaemic due to deficient erythropoietin synthesis. Iron supplementation, erythropoetin and blood transfusions are used for treatment of anemia, however conservative approach is recommended with regards to blood transfusions (31). They are also at high risk of bleeding due to dysfunctional von Willebrand factor, impaired platelet adhesion and aggregation, and anemia (31, 106). Management of uraemic coagulopathy includes desmopressin, cryoprecipitate, erythropoietin, oestrogen and dialysis (106). Patients with renal failure frequently have delayed gastric emptying, thus aspiration prophylaxis should be given pre-operatively (107, 108).

There is no clear guidance on the timing of haemodialysis in relationship to surgery (31). Commonly the dialysis is performed on the previous day or on the day of operation (106, 108).

Intra-operative management

The goals of intra-operative management of patients with AKI are to maintain haemodynamic stability and perfusion to vital organs, to optimize volume status, and to prevent further injury to kidneys (106).

Monitoring

For minor surgeries in stable patients standard monitoring should be sufficient (106). Conversely, in unstable patients undergoing major procedures, invasive monitoring may be required (106). Arterial line will allow beat-to-beat blood pressure monitoring and frequent blood sampling for assessment of electrolytes and acid-base status (106). Radial artery is preferred site of insertion (107). Transoesophageal echocardiography may assist in assessment of cardiac function and volume status, as well as other novel tools for haemodynamic monitoring (106).

Venous access

Venous access requires special consideration. Due to progression of their disease, patients may develop chronic renal failure and may require future placement of an arterio-venous fistula for chronic dialysis. It is advised to place the peripheral venous cannula in the dorsum of the hand, avoiding the forearm and antecubital fossa (31). In presence of arterio-venous fistula in patients with end-stage renal disease, the contralateral hand should be used for venous/arterial lines and non-invasive blood pressure monitoring to avoid damage to the shunt (31, 107, 108).

Establishment of a central venous access may be challenging due to the presence of a dialysis catheter, or the possibility of central venous thrombosis developing after previous venous catheters (106).

Intravenous fluids

Special attention to fluid administration is required (31). For minor procedures, infusion of intravenous fluids should be minimized and limited to replacement of insensible losses only (106, 108). For major surgeries, euvolaemia should be maintained to preserve cardiac preload and organ perfusion (106). Fluid resuscitation and vasopressors should be used if required to treat hypotension (108). During procedures with major fluid shifts, isotonic crystalloids, colloids, or both can be used (108). There is no data proving superiority of one type of fluid over another (31). Some studies have shown, that liberal use of 0,9% isotonic saline may lead to hyperkalaemia more frequently than Ringer's lactate solution, due to development of hyperchloraemic metabolic acidosis (106).

Mechanical ventilation

Controlled ventilation is preferred to spontaneous (108). Inadequate spontaneous breathing may lead to hypercarbia and worsening of pre-existing metabolic acidosis (108). Controlled modes with hyperventilation may assist in respiratory compensation of acidosis (106).

Infection control

Strict asepsis is required for all invasive procedures as immunity is suppressed by uraemia and critical illness (107).

Patients on renal replacement therapy are particularly susceptible to Methicillin-Resistant Staphylococcus Aureus (MRSA) infection, which can lead to high mortality (109). Hepatitis B and C are also common in dialysis patients, therefore universal precautions are important (107).

Drugs

Due to renal impairment, dosage of drugs with renal excretion may need to be modified in order to avoid drug accumulation and overdosing (108). Pharmacokinetics of drugs might also be affected by kidney injury and critical illness (108).

Induction agents

Dose of induction agents should be reduced in critically patients and in those who recently undergone dialysis due to relative hypovolaemia (108). Propofol, etomidate and ketamine can be safely used as their pharmacokinetics are minimally affected by renal impairment (108). Patients with kidney failure have increased sensitivity to barbiturates (106).

Inhalational agents

Most commonly used volatiles (isoflurane, sevoflurane and desflurane) are considered safe in patients with renal failure (31). Some studies recommend avoiding sevoflurane in prolonged procedures with low gas flows due to potential of inorganic fluoride production (107, 108). Nephrotoxicity of compound A (a product of sevoflurane) has not been confirmed in humans (31). Nitrous oxide is avoided in end-stage renal disease patients with very low haemoglobin levels (108).

Muscle relaxants and reversal

Succinylcholine is known to cause a transient rise in serum potassium concentration by 0.5 to 1.0 mmol/L, but it can be safely used in chronic kidney disease patients with normal levels of potassium (31, 108). It is, howe,ver contraindicated in hyperkalaemic patients, and better avoided in patients with unknown potassium concentration and in patients with acute kidney injury (31, 106).

Cisatracurium and atracurium are safe in renal failure as they are metabolized by Hoffmann hydrolysis and do not depend on the kidneys for their elimination (106). Rocuronium and vecuronium undergo primarily hepatic clearance, but their elimination is partly dependent on the kidney, therefore their duration of action can be prolonged in renal failure (31). These agents,

however, can be used with appropriate monitoring of neuromuscular function (108). Pancuronium should be avoided as it is eliminated primarily by the kidneys (108).
The half-life of neostigmine is extended in renal impairment, and the dose of antimuscarinic agent should be matched to it (31). Sugammadex is ”currently not recommended in patients with severe renal impairment” (31).

Opioids

Metabolites of morphine (morphine 6-glucuronide) and pethidine (normeperidine) accumulate in renal failure and may lead to respiratory depression and seizures respectively (31, 107, 108). Fentanyl and sufentanil can be used, but their dose should be adjusted (31). Remifentanil is safe to use due to its metabolism by ester hydrolysis in blood (108).

NSAIDs

NSAIDs are contraindicated in kidney failure due to nephrotoxicity (106).

Benzodiazepines

Diazepam and Midazolam should be used with caution as their metabolites can accumulate in renal impairment (108).

Antiemetics and aspiration prophylaxis

Doses of histamine H2-receptor antagonists and metoclopramide should be decreased in renal impairment as they are dependent on renal excretion (108).
Proton pump inhibitors and 5-HT3 antagonists don’t require dose adjustment (108).

Post-operative considerations

If renal replacement therapy is recommenced or continued in the post-operative period, close consideration should be given to flows and replacement/dialysate solution composition in order to counteract intra-operative fluids losses and electrolyte imbalances (31).

Patient’s fluid status, electrolytes, coagulation profile and analgesic requirements should be carefully assessed (107) .

CONCLUSION

Acute kidney injury is frequent in the critical care and associated with high morbidity and mortality (31). Renal replacement therapy represents a cmainstay of treatment in severe AKI (31). Despite increased experience and intensive research, many aspects of this therapy remain controversial. Superiority of one of the RRT techniques over another has not been proven (34). Other than for life-threatening complications of renal failure, the perfect time to start dialysis has not been defined (3). It was suggested that biomarkers can play a significant role in predicting which patients may need earlier dialysis, however this needs more research (22). The ideal anticoagulation method has still not been found. In the “recent Acute Dialysis Quality Initiative (ADQI) consensus conference a new approach called “precision CRRT” was introduced, emphasizing that renal support should be adjusted on the individualized basis to the constantly

changing clinical status of the critically ill AKI patient” (23). Since AKI has been shown to be associated with the progression to chronic renal disease, which represents a major social and economic burden, answering all the above questions remains a research and public health priority (25).

REFERENCES

1. Christie E, Pannu N. Dialysis and acute kidney injury: current evidence. Seminars in dialysis. 2014;27(2):154-9.
2. Ronco C, Ricci Z, De Backer D, Kellum JA, Taccone FS, Joannidis M, et al. Renal replacement therapy in acute kidney injury: controversy and consensus. Critical Care. 2015;19(1):146.
3. Tandukar S, Palevsky PM. Continuous Renal Replacement Therapy: Who, When, Why, and How. Chest. 2019;155(3):626-38.
4. Alvarez G, Chrusch C, Hulme T, Posadas-Calleja JG. Renal replacement therapy: a practical update. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 2019;66(5):593-604.
5. Siebeck M, Dimski T, Brandenburger T, Slowinski T, Kindgen-Milles D. Super High-Flux Continuous Venovenous Hemodialysis Using Regional Citrate Anticoagulation: Long-Term Stability of Middle Molecule Clearance. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. 2018;22(4):355-64.
6. Tolwani A. Continuous renal-replacement therapy for acute kidney injury. New England Journal of Medicine. 2012;367(26):2505-14.
7. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive care medicine. 2015;41(8):1411-23.
8. Bouchard J, Weidemann C, Mehta RL. Renal replacement therapy in acute kidney injury: intermittent versus continuous? How much is enough? Advances in chronic kidney disease. 2008;15(3):235-47.
9. Ihara K, Ishigami J, Inoshita S. Predictors of withdrawal from renal replacement therapy among patients with acute kidney injury requiring renal replacement therapy. Clinical and experimental nephrology. 2019;23(6):814-24.
10. Pannu N, Gibney RN. Renal replacement therapy in the intensive care unit. Ther Clin Risk Manag. 2005;1(2):141-50.
11. Bagshaw SM, Laupland KB, Doig CJ, Mortis G, Fick GH, Mucenski M, et al. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Critical care (London, England). 2005;9(6):700-9.
12. Pôncio L, Balbi AL, Rocha É P, Dias DB, Ponce D. The long-term outcome after acute kidney injury: a narrative review. Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia. 2015;37(1):115-20.
13. Sawhney S, Marks A, Fluck N, Levin A, Prescott G, Black CUoBCVC. Intermediate and Long-term Outcomes of Survivors of Acute Kidney Injury Episodes: A Large Population-Based Cohort Study. American Journal of Kidney Diseases. 2017;69(1):18-28.
14. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2009;53(6):961-73.
15. Wald R, Shariff SZ, Adhikari NK, Bagshaw SM, Burns KE, Friedrich JO, et al. The association between renal replacement therapy modality and long-term outcomes among critically ill adults with acute kidney injury: a retrospective cohort study*. Critical care medicine. 2014;42(4):868-77.
16. Schiffl H. Discontinuation of renal replacement therapy in critically ill patients with severe acute kidney injury: predictive factors of renal function recovery. International Urology and Nephrology. 2018;50(10):1845-51.
17. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, et al. Intensity of continuous renal-replacement therapy in critically ill patients. The New England journal of medicine. 2009;361(17):1627-38.
18. Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, et al. Intensity of renal support in critically ill patients with acute kidney injury. The New England journal of medicine. 2008;359(1):7-20.
19. Fathima N, Kashif T, Janapala RN, Jayaraj JS, Qaseem A. Single-best Choice Between Intermittent Versus Continuous Renal Replacement Therapy: A Review. Cureus. 2019;11(9):e5558-e.
20. Gemmell L, Docking R, Black E. Renal replacement therapy in critical care. BJA Education. 2017;17(3):88-93.
21. Joannidis M, Forni LG. Clinical review: timing of renal replacement therapy. Critical care (London, England). 2011;15(3):223-.

22. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. 2012(2):1-138.
23. Clark WR, Neri M, Garzotto F, Ricci Z, Goldstein SL, Ding X, et al. The future of critical care: renal support in 2027. Critical Care [Internet]. 2017; 21(1):[1-9 pp.].
24. Palevsky PM. Definition and staging criteria of acute kidney injury in adults. Waltham, MA: UpToDate; 2020.
25. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet (London, England). 2012;380(9843):756-66.
26. Makris K, Spanou L. Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes. Clin Biochem Rev. 2016;37(2):85-98.
27. Fleming GM. Renal replacement therapy review: past, present and future. Organogenesis. 2011;7(1):2-12.
28. Pascoe MD, Halkett JA. Technology in nephrology2008.
29. Nosé YJAO. Dr. Willem J. Kolff: the godfather of artificial organ technologies (February 14, 1911–February 11, 2009). 2009;33(5):389-402.
30. Vanholder R, Van Biesen W, Hoste E, Lameire N. Pro/con debate: Continuous versus intermittent dialysis for acute kidney injury: a never-ending story yet approaching the finish? Critical Care. 2011;15(1):204.
31. Acho C, Chhina A, Galusca D. Anesthetic Considerations for Patients on Renal Replacement Therapy. Anesthesiology Clinics. 2020;38.
32. Ronco C, Bellomo, R. Critical care nephrology. Philadelphia, PA: elsevier; 2018.
33. Schneider AG, Bellomo R, Bagshaw SM, Glassford NJ, Lo S, Jun M, et al. Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive care medicine. 2013;39(6):987-97.
34. Bagshaw SM, Berthiaume LR, Delaney A, Bellomo RJCcm. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. 2008;36(2):610-7.
35. Mehta RL, McDonald B, Gabbai FB, Pahl M, Pascual MTA, Farkas A, et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. Kidney International. 2001;60(3):1154-63.
36. Schefold JC, Haehling Sv, Pschowski R, Bender TO, Berkmann C, Briegel S, et al. The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): a prospective randomized controlled trial. Critical Care. 2014;18(1):R11.
37. Vinsonneau C, Allain-Launay E, Blayau C, Darmon M, du Cheyron D, Gaillot T, et al. Renal replacement therapy in adult and pediatric intensive care : Recommendations by an expert panel from the French Intensive Care Society (SRLF) with the French Society of Anesthesia Intensive Care (SFAR) French Group for Pediatric Intensive Care Emergencies (GFRUP) the French Dialysis Society (SFD). Annals of intensive care. 2015;5(1):1-19.
38. Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. The Lancet. 2006;368(9533):379-85.
39. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clinical Practice. 2012;120(4):c179-c84.
40. Davenport A, editor THE CLINICAL APPLICATION OF CRRT—CURRENT STATUS: Continuous Renal Replacement Therapies in Patients with Acute Neurological Injury. Seminars in dialysis; 2009: Wiley Online Library.
41. Davenport A. Continuous renal replacement therapies in patients with liver disease. Seminars in dialysis. 2009;22(2):169-72.
42. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney international. 2009;76(4):422-7.
43. Srisawat N, Lawsin L, Uchino S, Bellomo R, Kellum JA. Cost of acute renal replacement therapy in the intensive care unit: results from The Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study. Critical care (London, England). 2010;14(2):R46.
44. Walters R, Fox N, Crum W, Taube D, Thomas DJN. Haemodialysis and cerebral oedema. 2001;87(2):143-7.

45. Kielstein JT, Kretschmer U, Ernst T, Hafer C, Bahr MJ, Haller H, et al. Efficacy and cardiovascular tolerability of extended dialysis in critically ill patients: a randomized controlled study. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2004;43(2):342-9.
46. Kumar VA, Craig M, Depner TA, Yeun JY. Extended daily dialysis: A new approach to renal replacement for acute renal failure in the intensive care unit. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2000;36(2):294-300.
47. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lee J, et al. An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial. Critical care medicine. 2012;40(6):1753-60.
48. Lee J, Cho J-H, Chung BH, Park JT, Lee JP, Chang JH, et al. Classical Indications Are Useful for Initiating Continuous Renal Replacement Therapy in Critically Ill Patients. The Tohoku Journal of Experimental Medicine. 2014;233(4):233-41.
49. Gaudry S, Hajage D, Benichou N, Chaïbi K, Barbar S, Zarbock A, et al. Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. Lancet (London, England). 2020;395(10235):1506-15.
50. Vanmassenhove J, Vanholder R, Van Biesen W, Lameire N, editors. Haste makes waste—Should current guideline recommendations for initiation of renal replacement therapy for acute kidney injury be changed? Seminars in dialysis; 2018: Wiley Online Library.
51. Yessayan L, Yee J, Frinak S, Szamosfalvi B. Continuous renal replacement therapy for the management of acid-base and electrolyte imbalances in acute kidney injury. Advances in chronic kidney disease. 2016;23(3):203-10.
52. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Critical care (London, England). 2008;12(3):R74.
53. Baker A. Renal replacement therapy in critical care. Update in Anaesthesia. 2012;28:215-22.
54. Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R, et al. Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. New England Journal of Medicine. 2018;379(15):1431-42.
55. Wald R, Adhikari NKJ, Smith OM, Weir MA, Pope K, Cohen A, et al. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. Kidney International. 2015;88(4):897-904.
56. Karvellas CJ, Farhat MR, Sajjad I, Mogensen SS, Leung AA, Wald R, et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. Critical care (London, England). 2011;15(1):R72.
57. Seabra VF, Balk EM, Liangos O, Sosa MA, Cendoroglo M, Jaber BL. Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. American Journal of Kidney Diseases. 2008;52(2):272-84.
58. Romagnoli S, Ricci Z. When to start a renal replacement therapy in acute kidney injury (AKI) patients: many irons in the fire. Ann Transl Med. 2016;4(18):355-.
59. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstadt H, et al. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. Jama. 2016;315(20):2190-9.
60. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. New England Journal of Medicine. 2016;375(2):122-33.
61. Gaudry S, Hajage D, Martin-Lefevre L, Louis G, Moschietto S, Titeca-Beauport D, et al. The Artificial Kidney Initiation in Kidney Injury 2 (AKIKI2): study protocol for a randomized controlled trial. Trials. 2019;20(1):726-.
62. Vanholder R, Van Biesen W, Lameire N. A swan song for Kt/Vurea. Seminars in Dialysis. 2019;32(5):424-37.
63. Wajeh Y Qunibi M. Prescribing and assessing adequate hemodialysis. Waltham, MA: UpToDate; 2020.
64. Vijayan A, Palevsky PM. Dosing of renal replacement therapy in acute kidney injury. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2012;59(4):569-76.

65. Liang KV, Zhang JH, Palevsky PM. Urea reduction ratio may be a simpler approach for measurement of adequacy of intermittent hemodialysis in acute kidney injury. BMC Nephrology. 2019;20(1):82.
66. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. The Lancet. 2000;356(9223):26-30.
67. Joannes-Boyau O, Honore PM, Perez P, Bagshaw SM, Grand H, Canivet JL, et al. High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. Intensive care medicine. 2013;39(9):1535-46.
68. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, et al. Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. Critical care medicine. 2009;37(9):2576-82.
69. Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, et al. Intensity of renal support in critically ill patients with acute kidney injury. The New England journal of medicine. 2008;359(1):7-20.
70. Wu VC, Ko WJ, Chang HW, Chen YW, Lin YF, Shiao CC, et al. Risk factors of early redialysis after weaning from postoperative acute renal replacement therapy. Intensive care medicine. 2008;34(1):101-8.
71. Honore PM, Spapen HD. What a Clinician Should Know About a Renal Replacement Membrane? Journal of translational internal medicine. 2018;6(2):62-5.
72. Berns JS. Clinical consequences of hemodialysis membrane incompatibility. 2018. In: UpToDate [Internet]. Waltham, MA: UpToDate.
73. Samaha D, Clark EG. Common errors in temporary hemodialysis catheter insertion. Seminars in Dialysis. 2019;32(5):411-6.
74. Parienti JJ, Thirion M, Megarbane B, Souweine B, Ouchikhe A, Polito A, et al. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. Jama. 2008;299(20):2413-22.
75. Hryszko T, Brzosko S, Mazerska M, Malyszko J, Mysliwiec M. Risk factors of nontunneled noncuffed hemodialysis catheter malfunction. A prospective study. Nephron Clinical practice. 2004;96(2):43-7.
76. Parienti J-J, Mégarbane B, Fischer M-O, Lautrette A, Gazui N, Marin N, et al. Catheter dysfunction and dialysis performance according to vascular access among 736 critically ill adults requiring renal replacement therapy: A randomized controlled study. Read Online: Critical Care Medicine | Society of Critical Care Medicine. 2010;38(4):1118-25.
77. Engstrom BI, Horvath JJ, Stewart JK, Sydnor RH, Miller MJ, Smith TP, et al. Tunneled internal jugular hemodialysis catheters: impact of laterality and tip position on catheter dysfunction and infection rates. Journal of vascular and interventional radiology : JVIR. 2013;24(9):1295-302.
78. Agarwal AK, Patel BM, Haddad NJ. Central vein stenosis: a nephrologist's perspective. Seminars in dialysis. 2007;20(1):53-62.
79. Parienti JJ, Mongardon N, Megarbane B. Intravascular complications of central venous catheterization by insertion site. Journal of Vascular Surgery. 2016;63(3).
80. Schummer W, Sakr Y, Schummer C. Towards Optimal Central Venous Catheter Tip Position. Intensive Care Medicine: Springer New York : New York, NY; 2008. p. 581-90.
81. Morgan D, Ho K, Murray C, Davies H, Louw J. A randomized trial of catheters of different lengths to achieve right atrium versus superior vena cava placement for continuous renal replacement therapy. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2012;60(2):272-9.
82. Little MA, Conlon PJ, Walshe JJDoN, Renal Transplantation BHDI. Access recirculation in temporary hemodialysis catheters as measured by the saline dilution technique. American Journal of Kidney Diseases. 2000;36(6):1135-9.
83. Shen JI, Winkelmayer WC. Use and safety of unfractionated heparin for anticoagulation during maintenance hemodialysis. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2012;60(3):473-86.
84. Nongnuch A, Tangsujaritvijit V, Davenport A. Anticoagulation for renal replacement therapy for patients with Acute Kidney Injury. Minerva urologica e nefrologica = The Italian journal of urology and nephrology. 2015;68.
85. Tolwani AJ, Wille KM. Anticoagulation for Continuous Renal Replacement Therapy. Seminars in Dialysis. 2009;22(2):141-5.
86. Yu A. Brenner & Rector's The Kidney. Philadelphia: Elsevier; 2019.

87. Lim W, Cook DJ, Crowther MA. Safety and efficacy of low molecular weight heparins for hemodialysis in patients with end-stage renal failure: a meta-analysis of randomized trials. Journal of the American Society of Nephrology : JASN. 2004;15(12):3192-206.
88. Joannidis M, Kountchev J, Rauchenzauner M, Schusterschitz N, Ulmer H, Mayr A, et al. Enoxaparin vs. unfractionated heparin for anticoagulation during continuous veno-venous hemofiltration: a randomized controlled crossover study. Intensive care medicine. 2007;33(9):1571-9.
89. Kalicki RM, Aregger F, Alberio L, Lämmle B, Frey FJ, Uehlinger DE. Use of the pentasaccharide fondaparinux as an anticoagulant during haemodialysis. Thrombosis and haemostasis. 2007;98(6):1200-7.
90. Oudemans-van Straaten HM, Kellum JA, Bellomo R. Clinical review: anticoagulation for continuous renal replacement therapy--heparin or citrate? Critical care (London, England). 2011;15(1):202.
91. Hetzel GR, Schmitz M, Wissing H, Ries W, Schott G, Heering PJ, et al. Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2011;26(1):232-9.
92. Oudemans-van Straaten HM, Bosman RJ, Koopmans M, van der Voort PH, Wester JP, van der Spoel JI, et al. Citrate anticoagulation for continuous venovenous hemofiltration. Critical care medicine. 2009;37(2):545-52.
93. Bai M, Zhou M, He L, Ma F, Li Y, Yu Y, et al. Citrate versus heparin anticoagulation for continuous renal replacement therapy: an updated meta-analysis of RCTs. Intensive Care Medicine. 2015;41(12):2098-110.
94. Van der Voort PHJ, Postma SR, Kingma WP, Boerma EC, Van Roon EN. Safety of citrate based hemofiltration in critically ill patients at high risk for bleeding: a comparison with nadroparin. The International journal of artificial organs. 2006;29(6):559-63.
95. Trotman RL, Williamson JC, Shoemaker DM, Salzer WL. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2005;41(8):1159-66.
96. Jang SM, Infante S, Abdi Pour A. Drug Dosing Considerations in Critically Ill Patients Receiving Continuous Renal Replacement Therapy. Pharmacy (Basel). 2020;8(1):18.
97. Schetz M. Drug dosing in continuous renal replacement therapy: general rules. Current opinion in critical care. 2007;13(6):645-51.
98. Blot S, Lipman J, Roberts DM, Roberts JA. The influence of acute kidney injury on antimicrobial dosing in critically ill patients: are dose reductions always necessary? Diagnostic microbiology and infectious disease. 2014;79(1):77-84.
99. Jamal JA, Mueller BA, Choi GY, Lipman J, Roberts JA. How can we ensure effective antibiotic dosing in critically ill patients receiving different types of renal replacement therapy? Diagnostic microbiology and infectious disease. 2015;82(1):92-103.
100. Finkel KW, Podoll AS, editors. THE CLINICAL APPLICATION OF CRRT—CURRENT STATUS: Complications of Continuous Renal Replacement Therapy. Seminars in dialysis; 2009: Wiley Online Library.
101. Vijayan A. Vascular access for continuous renal replacement therapy. Seminars in dialysis. 2009;22(2):133-6.
102. Hiremath S, Slivar S, Magner P. Phosphate balance with continuous renal replacement therapy: a simple solution. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2013;62(3):644.
103. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2005;45(4 Suppl 3):S1-153.
104. Gullapudi VRL, Kazmi I, Selby NM. Techniques to improve intradialytic haemodynamic stability. Current opinion in nephrology and hypertension. 2018;27(6):413-9.
105. Petroni KC, Cohen NH. Continuous Renal Replacement Therapy: Anesthetic Implications. 2002;94(5):1288-97.
106. Gebhard W. Anaesthetic concerns in patients presenting with renal failure. Anaesthesiology Clin. 2010;28:39-54.
107. Oxford handbook of anaesthesia. 4th edition ed. Allman K, editor: Oxford University Press; 2016.
108. Morgan GE, Mikhail M.S. Clinical anesthesiology. 5th edition ed. New York: Lange Medical Books/Mc Graw Hill Medical Pub; 2013.

109. Zacharioudakis IM, Zervou FN, Ziakas PD, Mylonakis E. Meta-analysis of methicillin-resistant Staphylococcus aureus colonization and risk of infection in dialysis patients. Journal of the American Society of Nephrology : JASN. 2014;25(9):2131-41.