

## REVIEW

# Clinical review: Use of renal replacement therapies in special groups of ICU patients

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## Abstract

Acute kidney injury (AKI) in ICU patients is typically associated with other severe conditions that require special attention when renal replacement therapy (RRT) is performed. RRT includes a wide range of techniques, each with specific characteristics and implications for use in ICU patients. In the present review we discuss a wide range of conditions that can occur in ICU patients who have AKI, and the implications this has for RRT. Patients at increased risk for bleeding should be treated without anticoagulation or with regional citrate anticoagulation. In patients who are haemodynamically unstable, continuous therapies are most often employed. These therapies allow slow removal of volume and guarantee a stable blood pH. In patients with cerebral oedema, continuous therapy is recommended in order to prevent decreased cerebral blood flow, which will lead to cerebral ischemia. Continuous therapy will also prevent sudden change in serum osmolality with aggravation of cerebral oedema. Patients with hyponatraemia, as in liver failure or decompensated heart failure, require extra attention because a rapid increase of serum sodium concentration can lead to irreversible brain damage through osmotic myelinolysis. Finally, in patients with severe lactic acidosis, RRT can be used as a bridging therapy, awaiting correction of the underlying cause. Especially in ICU patients who have severe AKI, treatment with RRT requires balancing the pros and cons of different options and modalities. Exact and specific guidelines for RRT in these patients are not available for most clinical situations. In the present article we provide an update on the existing evidence.

## Introduction

The use of renal replacement therapy (RRT) in ICU patients is increasing over the years [1-3]. This increase may be explained by a higher number of ICU patients with older age and increased comorbidity, as well as by a decrease of exclusion criteria for RRT, such as in special groups of ICU patients – for example, those with haemodynamic instability and bleeding.

RRT encompasses a broad range of techniques (Table 1). A distinction can be made based on duration (intermittent, continuous), membrane permeability (high flux, low flux), diffusion (haemodialysis) or convection (haemofiltration) or a combination of these (haemodiafiltration), and equipment used (machine for regular haemodialysis, single-pass batch system or machines that are specifically developed for continuous renal replacement therapy (CRRT)).

Examples of continuous techniques include continuous haemodialysis, continuous venovenous haemofiltration (CVVH) and continuous venovenous haemodiafiltration (CVVHDF). Intermittent therapies include haemodialysis (HD) with varying duration, ranging from short (2 to 4 hours) to long (6 to 12 hours) as in sustained low-efficiency daily dialysis (or hybrid therapy, as it alternatively named). This form of intermittent RRT can be performed with a classic dialysis machine, and its dialysis characteristics are intermediate between classic HD and CRRT. Blood flow and dialysate flows are decreased and the treatment time is increased up to 6 to 12 hours per day. This treatment allows better haemodynamic tolerance and some hours per day off-machine, while the dialysis dose is maintained [4]. Intermittent haemodiafiltration can be applied as well, at least if online ultrapure water is available in the ICU.

Peritoneal dialysis (PD) is very seldom used for the treatment of acute kidney injury (AKI) in ICU patients. Data on the use of this modality are scarce (only 240 adult patients were studied in three randomised studies) and come from developing countries. An initial report on PD demonstrated increased mortality of patients randomised to this RRT modality in the setting of AKI [5]. However, two other studies (one of which was published twice) found that the outcome of high-volume

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**Table 1. Renal replacement therapy treatment modality options**

Basis	Modalities
Duration of therapy	Intermittent versus continuous
Membrane permeability	High flux versus low flux
Treatment technique	Diffusion or haemodialysis versus convection or haemofiltration versus a combination or haemodiafiltration
Equipment	Single-pass batch system versus regular haemodialysis machine versus continuous renal replacement therapy machine
Anticoagulation used	No anticoagulation versus heparin (low molecular weight or unfractionated) versus citrate versus less frequently used strategies (for example, prostacyclin or argatroban)

and continuous PD was comparable with daily HD or CVVHDF in AKI [6-8]. An important limitation of these last studies is that they excluded patients who died on day 1 after randomisation, thereby rendering a more favourable outcome.

Each of these RRT modalities has specific characteristics with implications for their use in specific ICU patient groups.

### Patients with increased risk for haemorrhage

Most modalities of RRT, with the exception of PD, need anticoagulation to prevent clotting in the extracorporeal circuit, thereby increasing the circuit life and dose of RRT and containing the cost for replacement of a new filter and tubin. The downside of the use of anticoagulants is the increased risk for haemorrhage. The most frequently used anticoagulant in ICU patients is unfractionated heparin, followed by low molecular weight heparin and regional citrate anticoagulation [9].

### No anticoagulation

In most patients, a 2-hour dialysis session can be performed without anticoagulation; but in patients with thrombocytopenia and coagulation disorders, even longer sessions up to CRRT can be performed without clotting. The use of heparin-coated membranes facilitates this session extension. Intermittent flushing with saline can also postpone clotting. If haemofiltration is applied, predilution is preferred to prevent haemoconcentration in the circuit. In addition, in postdilution mode, the filtration fraction – calculated as effluent rate/plasma flow rate – should be below 20 to 25%.

If no anticoagulation is allowed, catheter locks used to fill up dialysis catheters between dialysis session should be heparin-free as leakage of heparin through the side holes is demonstrated. For that purpose, citrate-containing solutions can be used as a catheter lock.

In the absence of contraindications, such as diverticulitis or recent abdominal surgery, PD in theory can be an alternative RRT modality in patients at high risk for bleeding.

### Regional anticoagulation with citrate or with heparin/protamine

Regional anticoagulation with citrate is based on its binding with calcium. Citrate, infused into the afferent

bloodline, binds ionised calcium and hence blocks coagulation [10-12]. The removal of citrate is dependent on the dialysate flow and/or ultrafiltration rate. Citrate may enter the systemic circulation and can induce hypocalcaemia, resulting in cardiac problems. Calcium substitution with a systemic calcium infusion is therefore nearly always necessary, especially in CRRT. The removal of citrate per minute is greater in dialysis compared with CVVH. Citrate anticoagulation is therefore theoretically safer in intermittent haemodialysis compared with CVVH, whereby less citrate is removed. Many different citrate schemes are used for predilution and postdilution CVVH, continuous venovenous haemodialysis (CVVHD) and CVVHDF, and we would like the reader to refer to specific texts on this topic [11,12]. Haemodialysis with citrate can be performed with calcium-containing dialysate or with calcium-free dialysate, preferred for short and long sessions, respectively. In continuous modalities, and when using calcium-free dialysate, ionised calcium must be measured rigorously and calcium needs to be re-infused to prevent hypocalcaemia. Citrate accumulation can be monitored by the total to ionised calcium ratio. When this is above 2.5, the citrate dose should be decreased and calcium reinfused. In patients with reduced citrate metabolism, such as in liver failure and in patients with pre-existing hypocalcaemia and/or hypomagnesaemia, extra caution is warranted.

Regional citrate anticoagulation is increasingly used, and is currently recommended by the Kidney Disease: Improving Global Outcomes consensus group as the preferred anticoagulant for CRRT both in patients with and without increased bleeding risk (level of evidence 2B and 2C, indicating a suggestion based on low quality of evidence) (data not yet published; M Schetz, personal communication). Several studies have demonstrated the feasibility of this technique with different protocols. Regional citrate anticoagulation resulted in an increased filter life in some studies, less bleeding complications, and in one study was even associated with increased survival when compared with low molecular weight heparin, although this could not be confirmed in another study where unfractionated heparin was the comparator [13-17].

Although regional anticoagulation was originally described with unfractionated heparin and protamine

[18,19], its use has decreased in parallel with the increasing popularity of citrate. Protamine has several side effects such as anaphylaxis, hypotension, cardiac depression, leukopaenia and thrombocytopenia. Further, there is risk for a rebound anticoagulant effect, due to the shorter half-life of protamine compared with heparin. Regional anticoagulation with heparin-protamine is therefore no longer recommended [20].

#### **Other anticoagulation strategies**

Prostaglandins and the synthetic protease inhibitor nafamostat mesilate inhibit platelet aggregation and adhesion. In CRRT, prostaglandin I<sub>2</sub> and prostaglandin E<sub>1</sub> administered in a fixed dose resulted in less filter clotting and less bleeding complications in a small prospective randomised study ( $n = 50$  patients) [21]. Prostaglandin I<sub>2</sub> has also been successfully used in patients with combined AKI and acute liver failure, who were at increased risk for bleeding [22]. Prostaglandin induces vasodilation and therefore hypotension, however, and may also lead to increased intracranial hypertension and decreased cerebral perfusion pressure [23]. These side effects and the cost of this anticoagulation strategy hindered its widespread introduction and use.

#### **Patients with heparin-induced thrombocytopenia type II**

When heparin-induced thrombocytopenia type II is suspected or confirmed, the administration of unfractionated heparin and low molecular weight heparin is contraindicated. In that respect, catheter locks, rinsing solutions, dialyser membranes, catheters, and so forth, must also be heparin free. Besides regional citrate anticoagulation (or prostacyclin), the following anticoagulants could be used in patients with heparin-induced thrombocytopenia type II.

Argatroban, a direct thrombin inhibitor, is mainly hepatically metabolised with a short half-life of 35 minutes in patients with end-stage kidney disease (ESKD). The activated clotting time and the activated partial thromboplastin time can be used for monitoring. Only minor extracorporeal clearance with high-flux membranes is demonstrated. Argatroban, due to its short half-life, is a safe anticoagulant in patients with renal failure without hepatic impairment. In patients with multiple organ failure, however, one-tenth of the usual dose without an initial bolus is recommended, depending on hepatic function [24].

Different argatroban dosing regimens have been described for different RRT modalities. A proposed dose in chronic haemodialysis patients is a 250 µg/kg bolus followed by continuous infusion of 2 µg/kg/minute [25]. In ICU patients treated with CRRT, it is recommended to administer a loading dose of 100 µg/kg argatroban followed by a maintenance infusion rate (µg/kg/minute)

that is adjusted for severity of illness (measured by either  $2.15 - 0.06 \times$  Acute Physiology and Chronic Health Evaluation II score, or by  $2.06 - 0.03 \times$  Simplified Acute Physiology Score II) and liver function, assessed by the indocyanine green disappearance rate ( $-0.35 + 0.08 \times$  indocyanine green disappearance rate) [26]. For ICU patients treated with predilution intermittent venovenous haemodialysis, recommendations are a loading dose of 75 µg/kg followed by a continuous infusion of 0.4 to 0.6 µg/kg/minute until 20 minutes before termination of RRT [27].

Despite clinical use of argatroban in RRT, it should be mentioned that this is an off-label use for this drug.

Fondaparinux is a synthetic heparin analogue that can be used in patients with heparin-induced thrombocytopenia type II. In the absence of renal function, a single intravenous dose of 2.5 mg can maintain dialysis circuit patency provided that low-flux membranes are used [28]. Owing to its renal clearance, therapeutic anti-factor Xa activity is still demonstrated 48 hours after administration of 2.5 mg fondaparinux. Removal of fondaparinux is enhanced by the use of high-flux membranes. In ICU patients, caution is recommended for this anticoagulant considering its long half-life and the high bleeding risk, and/or the frequent need for surgical intervention or invasive procedures. Also, heparin-induced thrombocytopenia is an off-label indication for fondaparinux.

Lepirudin, or recombinant hirudin, is a direct thrombin inhibitor and can also be used in patients with heparin-induced thrombocytopenia type II. In dialysis patients, a single intravenous dose of 0.08 mg/kg is recommended [29]. Because of its renal clearance, this dose results in sustained anticoagulation. Dialyser clearance depends on the membrane characteristics. High-flux membranes allow filtration of lepirudin, with the highest sieving coefficient for polysulfone (0.97) and lesser sieving coefficients for polymethylmethacrylate and polyarylethersulfone (0.75 and 0.73, respectively). Low-flux membranes do not filter lepirudin [30]. Dependent on the dialysis frequency, the dialysis membrane, and the activated partial thromboplastin time, measured before the start of the dialysis session, a reduced dose should be used from the second dialysis. Because of its prolonged half-life (52 hours), lepirudin is not an anticoagulant of choice in the intensive care patient with AKI.

#### **Patients with severe haemodynamic instability**

Haemodynamically unstable patients should be treated carefully, which can be achieved either by CVVH(D), sustained low-efficiency daily dialysis or continuous HD. In many haemodynamically unstable patients, HD can be performed when specific precautions are taken [31,32]. These precautions include: less aggressive ultrafiltration, increasing the treatment time in CRRT and daily

treatment in intermittent HD, eventually using blood volume measurements to guide ultrafiltration; increasing dialysate sodium and calcium concentrations to respectively 145 mmol/l and 1.5 mmol/l; adapting the dialysate temperature to obtain isothermic dialysis; connecting afferent and efferent bloodlines simultaneously at the start of the procedure; using low blood flow (<150 ml/minute) and low dialysate flows; using biocompatible membranes; and using (ultra)pure water [31].

An argument in favour of CRRT in haemodynamically unstable patients is that solute control is more constant. This factor may be of particular benefit in patients with severe lactic acidosis, where RRT may help to stabilise the haemodynamic status by correction of blood pH. In patients with severe lactic acidosis, intermittent therapy will only offer a temporal improvement of blood pH – between treatments there will be recurrent acidosis, with its untoward haemodynamic consequences.

In summary, patients with severe haemodynamic instability are best treated with CRRT in order to allow removal of extravascular fluid and to maintain a stable blood pH.

A more elaborate discussion on the choice between CRRT and HD is presented in another publication in this topic series [33].

### **Patients with intracranial hypertension or cerebral oedema**

Patients with cerebral oedema or intracranial hypertension have decreased or absent autoregulation of cerebral blood flow. A decrease in systemic blood pressure, as may occur during RRT, will therefore lead to decreased cerebral blood flow and to cerebral ischaemia, which will consequently lead to more oedema [34]. Continuous arteriovenous haemofiltration has been proven to better maintain cerebral blood flow in patients with acute liver failure and cerebral oedema compared with intermittent dialysis [35,36]. These findings have been extrapolated to treatment recommendations for patients with other causes of cerebral oedema and to newer modalities of CRRT such as CVVH or CVVHD [37,38].

Another argument in favour of a low efficient CRRT is that this therapy will seldom be complicated with acute and important tonicity changes of the systemic circulation. Because intermittent HD is a very efficient RRT modality, these changes may occur after a session of HD. A decrease in serum osmolality will subsequently lead to water uptake by the cells, and to development of cellular oedema [39]. Intracranial pressure may therefore increase after HD.

If a patient is also at increased risk for intracranial haemorrhage, such as after traumatic brain injury, RRT should be administered without anticoagulation or with regional citrate anticoagulation. Theoretically, PD can be

considered as an alternative. Concerns on this modality are the efficacy and the effects on intra-abdominal pressure. The intra-abdominal pressure may increase secondary to infusion of PD fluid in the abdominal cavity, which may have diverse effects on intracranial pressure and cerebral perfusion [40,41]. Increased abdominal pressure may translate into increased intracranial pressure. Further, intra-abdominal hypertension may also decrease systemic preload and increase afterload, leading to lower blood pressure and decreased cerebral perfusion pressure.

### **Patients with hyponatraemia**

When chronic hyponatraemia is corrected rapidly, patients may develop osmotic demyelination syndrome [42,43], a condition with most irreversible brain damage. Therefore, in asymptomatic patients with chronic hyponatraemia, the sodium concentration should be increased slowly, with a maximum increase of 10 to 12 mmol/l during the first 24 hours and of 18 mmol/l during the first 48 hours of treatment [44]. High serum urea concentration may protect the brain against the development of osmotic demyelination [45,46]. An explanation for this may be the slow diffusion of urea over the blood–brain barrier. Dialysis will decrease serum urea rapidly, but urea that has accumulated in brain cells will decrease only slowly. This difference will create a blood–brain gradient of urea, and will lead to accumulation of water in brain cells and a slower decline of cell volume, which is the mechanism that leads to osmotic demyelination. Low-efficiency RRT such as CVVH is recommended in these patients.

Some authors have recommended the use of replacement fluid with reduced sodium concentration. This can be established by adding sterile water to the replacement fluid bag [47]. Diluting replacement fluid will also result in decreased potassium and bicarbonate concentrations, and therefore may induce hypokalaemia and acidosis. These patients therefore need frequent follow-up of sodium and potassium concentrations and blood pH. During treatment, increasing plasma sodium concentrations may require less diluted replacement fluid; patients may also have need for additional potassium or bicarbonate infusion. Because this procedure is potentially error prone, and may lead to contamination of sterile replacement fluid, an alternative strategy is intravenous infusion of hypotonic fluid (for example, 5% glucose).

### **Patients with high serum urea concentration**

When serum urea is high (typically >175 mg/dl) patients are at risk for developing dialysis disequilibrium syndrome, a neurological condition characterised by nausea and headache. The exact mechanism of dialysis disequilibrium is uncertain. A sudden decrease of serum



osmolality and slower decrease of (brain) cell osmolality with resultant increase of cellular water content is the most probable cause. A change in intracellular pH and accumulation of organic osmolites are also mentioned as a possible cause for this condition. Preventive measures include initiation RRT with ultrafiltration followed by dialysis, which will increase plasma osmolality and so prevent development of cerebral oedema and dialysis disequilibrium. Decreasing the dose of dialysis will also prevent important changes of urea concentration, and so prevent dialysis disequilibrium. This can be achieved by shortening the first RRT session when intermittent modalities are used (2 hours), decreasing blood flow (<200 ml/minute), using a small less efficient dialyser, or using low-dose CVVH (for example, ultrafiltration rate <20 ml/kg/hour). A urea reduction ratio of 0.4 to 0.45 or a urea clearance over time of the dialysis session corrected for volume of distribution (Kt/V) of 0.6 to 0.7 has been proposed. Administration of osmotic agents such as mannitol (1 g/kg intravenously per dialysis session) may also be of help. Finally, an increased dialysate sodium concentration (143 to 146 mmol/l) is also recommended in patients at risk [48-50].

#### **Patients with acute or acute on chronic liver failure**

There are several aspects that deserve special attention in patients with liver failure and AKI.

#### **Encephalopathy and cerebral oedema**

Patients with acute liver failure and encephalopathy are very likely to have cerebral oedema, especially when the time between occurrence of jaundice and encephalopathy is short; for example, as in fulminant liver failure, defined by a time delay between icterus and encephalopathy of less than 2 weeks [37,51]. These patients are at increased risk for increased intracranial pressure and brain stem herniation. One should therefore apply the principles for prevention of deterioration of intracranial pressure as described above. In summary, CRRT with special attention for haemodynamic stability and maintenance of cerebral perfusion pressure is warranted.

#### **Hyponatraemia**

Patients with liver failure often experience chronic hyponatraemia. Hence, special attention should be given to a slow increase of serum sodium, as discussed above.

#### **Hepatorenal syndrome**

Patients with acute and acute on chronic liver failure may develop AKI as a consequence of hepatorenal syndrome. Especially in patients with acute on chronic liver failure this is an end stage of the process of water retention and increased catecholamine stress, characterised by hyponatraemia and ascites [52].

A small prospective randomised study suggests that treatment with artificial liver support may improve survival in these patients [53]. This study was underpowered ( $n = 13$  patients), however, and the control population was not treated with vasopressin analogues, which is currently the standard of care. A large prospective randomised study comparing the standard of care for liver dialysis with that of the Prometheus liver dialysis system (Fresenius Medical Care, Bad Homburg, Germany) in patients with acute on chronic liver failure recently found in subanalysis that patients with hepatorenal syndrome treated with Prometheus liver dialysis had better survival [54]. This study is currently only presented as an abstract, so we can only discuss preliminary results.

There are no data that support the use of one specific RRT modality above another for hepatorenal syndrome, although generally less aggressive modalities such as sustained low-efficiency daily dialysis or CRRT will be used most.

#### **Coagulation abnormalities**

Patients with liver failure have decreased production of coagulation factors II, V, VII, IX, X and XI, thrombocytopenia and decreased thrombocyte function [55,56]. This will lead to decreased coagulation. Many patients with severe liver failure can therefore undergo RRT without anticoagulation. However, decreased production of protein C, protein S and antithrombin III, increased concentrations of factor VIII, von Willebrand factor and heparin cofactor II, and a decreased concentration of plasminogen will lead to increased coagulation, despite abnormal coagulation tests. Coagulation tests can therefore be misleading and, despite abnormal tests, filter clotting may occur. Monitoring the coagulation status with functional haemostasis monitoring devices such as thromboelastography or Sonoclot (Sienco Inc., Arvada, Colorado, USA), which measure the individual contribution of coagulation by platelets and coagulation factors, and fibrinolysis may be of help to better understand the coagulation status of these patients.

#### **Patients with severe lactic acidosis**

The treatment for lactic acidosis should be aimed at correcting the cause. However, as severe acidosis may in itself lead to profound systemic hypotension, RRT is sometimes used as a bridge until correction of the underlying cause, especially in patients who also have AKI [57]. RRT may correct blood pH, by removing lactic acid and through administration of bicarbonate from the dialysate. Continuous modalities are preferred to prevent intradialytic rebound, and dialysis is more efficient in removing small molecules as lactate [58,59].

### **Patients with congestive heart failure**

Patients with decompensated heart failure and diuretic resistance, without AKI, can benefit from isolated ultrafiltration [60,61]. When these patients are haemodynamically unstable, the ultrafiltration rate should be limited by increasing the treatment time. This limitation can be achieved by CRRT or hybrid therapy. PD is also used for fluid removal in patients with congestive heart failure and ESKD. However, fluid removal is less predictable compared with extracorporeal ultrafiltration [62,63].

Special attention should be given to patients with congestive heart failure and (chronic) hyponatraemia (see the discussion on hyponatraemia above).

### **Patients with burn injury**

On average, 3% of patients with severe burn injury are treated with RRT for AKI [64]. Patients with burn injury and AKI often have large wounds and repetitive surgical interventions with increased risk for bleeding.

Another issue in burn patients is accumulation of iodine. Burn patients treated with topical povidone-iodine may have elevated iodine concentrations, secondary to increased absorption in combination with hampered renal excretion. This can lead to metabolic acidosis, AKI, and heart conduction abnormalities, eventually leading to heart block. The molecular weight of iodine is 253; hence the dialyser clearance during high-flux dialysis is comparable with that of small solutes such as urea. Intercompartmental clearance is low, however, so long treatment times are mandatory [65]. Protracted high-flux haemodialysis or haemodiafiltration, with high blood and dialysate flow, is therefore the treatment of choice to remove iodine.

### **Patients with accidental hypothermia**

Consensus exists about cardiopulmonary bypass as the treatment of choice in cases of severe accidental hypothermia with cardiac arrest. In settings where cardiopulmonary bypass is not available, or in haemodynamically stable patients, HD is a valuable alternative [66]. Setting dialysate flow and temperature to their maximum optimises the efficiency of warming. Blood flow and the membrane surface should also be optimised. HD can be started without exogenous anticoagulation because hypothermia is associated with coagulopathy.

### **Patients with intoxications**

The use of RRT in the treatment of intoxicated patients has decreased over recent years. Reasons for this decline are diverse. Some intoxications, such as with paraquat and theophyllin, are nowadays less frequent in the western world. Other intoxications, such as with methanol and ethylene glycol, are often treated with

fomepizole. At present, the most frequently encountered intoxications treated with RRT are caused by lithium, methanol, ethylene glycol and iodine. Rare intoxications that should in special indications be treated with haemodialysis include valproic acid, isoniazid and metformin [67]. The mainstay for treatment of salicylate intoxication remains alkalinisation of blood and urine. In patients with severe salicylate intoxication and in patients presenting with severe fluid overload and/or pulmonary or cerebral oedema, however, HD should be used to effectively remove salicylate from blood [68,69].

With the introduction of high-flux membranes and haemodiafiltration, haemoperfusion with charcoal cartridges has lost importance.

The lack of residual endogenous clearance, sometimes caused by the intoxication itself, will accelerate the decision to start dialysis. Examples include AKI in patients with lithium, iodine or ethylene glycol intoxications. If the molecular weight of a toxin is low and protein binding is limited, dialyser clearance is expected to be high. This is a prerequisite for efficient removal. The body clearance depends on the compartmental behaviour. If the distribution is multicompartmental, with slow equilibration between the different compartments, rebound can ensue. In these cases, long dialysis times are necessary. Because of this latter reason and because of the availability of alternative treatment (digoxin-specific Fab fragments), digoxin intoxications are seldom treated by haemodialysis.

Our preference is to apply haemodialysis (mostly high flux) with high blood flow (250 to 300 ml/minute) and high dialysate flow (500 ml/minute) and a long treatment time or even continuously in order to optimise both dialyser and body clearance. For larger solutes, protracted or continuous online haemodiafiltration is more efficient. CVVH or CVVHD results in much less dialyser clearance because of absent or limited dialysate flow. Patients with lithium intoxication without renal failure should preferably not be treated with a single-pass batch system, as premature mixing of dialysate has been documented in the absence of uraemic solutes [70]. In these patients, haemodialysis with a conventional haemodialysis machine is recommended.

### **Chronic haemodialysis patients admitted to the ICU**

Chronic haemodialysis patients represent a minority of ICU patients. In a tertiary care centre in the USA, 3.7% of ICU patients were chronic haemodialysis patients [71]. Other studies found that 11 to 12% of all patients treated with RRT in the ICU are chronic dialysis patients [72,73]. The main reasons for ICU admission are sepsis and cardiovascular complications, which are comparable with AKI patients [72,73]. Instead of the regular outpatient

dialysis schedule of 4 hours of dialysis three times weekly, RRT during the ICU stay should be adapted towards the current needs of the patient. Daily, protracted dialysis can easily be performed through the arteriovenous fistula. Staff should be extremely vigilant in keeping this arteriovenous fistula patent. They should therefore be advised against using the arm with the arteriovenous fistula for blood sampling, arterial line insertion or non-invasive blood pressure measurement. Needling of this arteriovenous fistula should only be performed by an experienced dialysis nurse. A temporary dialysis catheter is preferred when a continuous technique is applied.

### **Renal replacement therapy during surgery**

Occasionally, haemodialysis is performed during surgery. Because liver transplantation in patients with renal impairment can be associated with severe hyperkalaemia, especially during reperfusion, intraoperative dialysis should be considered. Unstable patients with acidosis and persistent electrolyte disturbances may also benefit from a continuation of the dialysis in the operation room. Special attention should be paid to the temperature of the dialysate, to avoid cooling of the patient. If no water treatment is available in the operation room, haemodialysis can be performed with a single-pass batch system. Anticoagulation is mostly contraindicated, or in the case of liver transplantation is not needed. If necessary, a heparin-coated membrane can be used [74]. During liver transplantation, citrate may accumulate when regional citrate anticoagulation is used. The citrate load is often already elevated in these patients due to the administration of fresh frozen plasma and packed cells. We therefore do not recommend citrate anticoagulation in these patients.

### **Extracorporeal therapy in sepsis**

#### **Continuous venovenous haemofiltration**

Two prospective randomised studies evaluated the use of standard CVVH compared with the standard of care in patients with severe sepsis [75,76]. The rationale was that inflammatory mediators were removed at a constant rate in the CVVH intervention group, and that the inflammatory process could therefore be halted. Neither study could demonstrate that CVVH led to decreased serum concentrations of mediators, or to improvement of organ dysfunction. In fact, the most recent study was discontinued after an interim analysis on 76 patients demonstrated more organ dysfunction and more severe organ dysfunction in patients randomised to CVVH compared with the standard of care [76].

#### **High-volume haemofiltration**

Observational data by Ratanarat and colleagues and by Honore and colleagues demonstrated that short-term

high-volume haemofiltration – 6 to 8 hours of CVVH at 85 ml/kg/hour followed by 16 to 18 hours of CVVH at 35 ml/kg/hour [77], and ultrafiltration of 35 l during a 4-hour period followed by conventional CVVH [78] – was associated with better outcomes than compared with historic controls [77,78]. In the High Volume on Intensive Care (IVOIRE) study, septic study patients were randomised to high-volume haemofiltration (70 ml/kg/hour for 96 hours) or to standard-dose CVVH (35 ml/kg/hour). The study was recently stopped after interim analysis, but was not yet published at the time of this review. The results will inform us on the exact place of this technique for treatment of sepsis patients.

#### **Polymyxin-B haemoperfusion**

Polymyxin-B bound to a membrane is a compound that efficiently binds endotoxin, a component released from the cell membrane of Gram-negative bacteria. Endotoxin is a crucial component in the inflammatory cascade following Gram-negative infection. Several smaller studies that were bundled in a meta-analysis and a recent small prospective randomised study in patients with intra-abdominal sepsis demonstrated that binding endotoxin with polymyxin-B haemoperfusion may improve haemodynamics and organ function at 72 hours, and may improve short-term (28-day) mortality in sepsis patients [79,80]. These results are promising, but the dataset is still too small to adopt this therapy in routine practice.

#### **Coupled plasma filtration and absorption combined with haemodialysis.**

Coupled plasma filtration and absorption also targets diminishing the inflammatory process, by removing inflammatory mediators through absorption. For this technique, blood is filtered by a plasma filter. Plasma that is produced by the plasma filter is run through an absorption filter, reinfused into the circuit, and subsequently filtered by a high-permeable polysulfone haemofilter. Results from a small pilot crossover study in 10 patients with severe septic shock demonstrated that this technique improved haemodynamics during the 10-hour plasma filtration and absorption session compared with CVVHDF [81]. Responsiveness of white blood cells to stimulation with lipopolysaccharide was also normalised after treatment with coupled plasma filtration and absorption. A prospective randomised study on this technique was concluded in Italy recently, but the results have not yet been published.

### **Conclusions**

Especially in ICU patients who have severe AKI, treatment with RRT requires balancing the pros and cons of different options and modalities. Special groups of ICU patients that deserve extra consideration are, for

example, patients with coagulation abnormalities or with increased risk for bleeding, such as after surgery, patients with severe haemodynamic instability, liver failure patients and patients with hyponatraemia. Exact and specific guidelines for RRT in these patients are not available for most clinical situations.

#### Abbreviations

AKI, acute kidney injury; CVVH, continuous venovenous haemofiltration; CVVHD, continuous venovenous haemodialysis; CVVHDF, continuous venovenous haemodiafiltration; CRRT, continuous renal replacement therapy; ESKD, end-stage kidney disease; HD, haemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy.

#### Competing interests

AD declares that she has no competing interests. EAJH advised both Gambro and Fresenius in an advisory board, and received a fee for this.

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