40 Renal Replacement Therapy

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Acute kidney injury (AKI) is a common complication in critically ill patients admitted to the intensive care unit (ICU).[1-3] Recent epidemiologic data suggest that over 50% of ICU patients suffer from AKI and that up to 13.5% will be treated with renal replacement therapy (RRT).[1-3] Changes in patient characteristics, with admission of older patients with more comorbidities such as diabetes, cardiovascular disease, and hypertension, have resulted in a marked increase in the proportion of patients treated with RRT in the past decade.[4,5] RRT has, therefore, become an essential and commonly used treatment option for ICU patients.

TECHNICAL ASPECTS OF RRT

RRT is most often delivered via extracorporeal techniques. Alternatively, the peritoneum of the patient can be used as a semipermeable exchange membrane. This latter technique is primarily used in resource-poor areas and seldom in developed countries.

Extracorporeal techniques can be done with different modalities (Table 40-1). These are named according to the duration of RRT and the technique used to exchange solutes and water (either diffusion or convection).

Diffusion and Convection

Exchange of waste products over a semipermeable membrane can occur via diffusion (hemodialysis [HD]) or convection (hemofiltration) (Fig. 40-1).

In diffusion, blood and dialysate flow countercurrent on both sides of the semipermeable membrane of the hemofilter. The driving force that moves solutes across the semipermeable membrane is the solute concentration gradient. Uremic toxins, such as blood urea nitrogen and creatinine, will have high blood concentrations and are absent in the dialysate. Other factors that determine the movement of solutes from the blood to dialysate are the diffusion coefficient of the membrane, its thickness, and its surface area. Diffusion is very efficient in removing small molecules, such as potassium, ammonium, and creatinine (<20 kDa); it is less efficient in removing larger solutes and water.

In hemofiltration, solutes and water are transported over the membrane by a difference in pressure between both sides of the membrane. Pressure forces the water and solutes from the blood compartment to the so-called effluent. The permeability coefficient of the membrane and the difference in pressure between both sides of the membrane determine the amount of fluid and solutes transported across the membrane via convection. The effluent rate is controlled by a pump. Hemofiltration is more efficient for removal of water and larger molecules (<60 kDa). In hemodiafiltration, both convection and diffusion are combined.

There are currently no data to suggest the superiority of diffusion over convection.

Duration of RRT

Intermittent hemodialysis (IHD) is a very efficient dialysis technique, performed during a 3- to 4-h period. Continuous renal replacement therapy (CRRT) is less efficient; it is conducted 24 h per day. Hybrid techniques, alternatively termed *sustained low-efficiency daily dialysis* (SLEDD) or *extended daily dialysis* (EDD), have intermediate efficacy and are used 6 to 12 h per day.[6,7]

Intermittent and hybrid therapies are performed with dialysis machines that are also used for chronic dialysis patients. These machines typically have more complicated interfaces and are, therefore, often managed by dialysis nurses. CRRT is most often performed with specially designed machines with a relatively simple interface, which are managed by ICU nurses.

Specific Aspects of a CRRT Circuit

Figure 40-2 illustrates the different aspects of CRRT, performed as continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF).

The dose of CRRT is by convention expressed as the clearance of urea, a small molecule that is not retained by the membrane in either HD or hemofiltration. The effluent rate, which is the volume of fluid produced by hemofiltration and/or HD, therefore equals the clearance of urea and, when corrected for body weight, can be used to express the dose of CRRT: dose of CRRT = effluent rate per hour per kg body weight (mL/kg/h). For a desired dose of 25 mL/kg/h in a 60-kg patient, the effluent rate will be $25 \times 60 = 1500$ mL/h. This effluent needs to be partly or completely replaced by another fluid; otherwise body fluid losses will be too high. The amount of effluent that is replaced will determine the fluid balance of the patient. This replacement fluid can be given prefilter (predilution), postfilter (postdilution), or as a combination of both. When the fluid is given by the postdilution mode, blood will concentrate while passing through the capillaries of the hemofilter. This may lead to clogging (partial clotting) and clotting of the capillaries, leading to decreased efficacy because fewer capillaries are available. To prevent this, a filtration fraction (the ratio of effluent flow over plasma flow) of <25% is advised. The filtration fraction is indicated on the dashboard of present-day CRRT machines. On the other hand, predilution administration will dilute the blood in capillary filters, leading to a decreased risk for clotting but also decreased clearance and efficacy.

Dose of RRT

In CRRT, the delivered dose should be 20 to 25 mL/kg/h of effluent. Two large prospective randomized studies compared this dose to a higher dose and found that outcomes were similar.[8,9]

In intermittent RRT, the minimum delivered dose of dialysis should be 3 sessions per week lasting at least 4 h, with a blood flow of >200 mL/min and a dialysate flow of >500 mL/min or a Kt/V index of >3.9 per week, or maintenance of the predialysis urea concentration of 20 to 25 mmol/L.[9,10]

Anticoagulation

Coagulation is one of the major barriers to effective extracorporeal therapies. When blood leaves the body, the coagulation cascade becomes activated, which can lead to thrombocyte activation, partial clogging (which lowers the effectiveness of dialysis), and even complete clotting/blockage of the dialysis/extracorporeal circuit (resulting in

TABLE 40-1 Renal Replacement Therapy Modalities

MODALITY	ABBREVIATION	TREATMENT DURATION (per day)	BLOOD FLOW (mL/h)	DIALYSATE FLOW (mL/min)
Intermittent hemodialysis	IHD	2-4 h	150-450	300-600
Hybrid techniques		6-12 h	100-200	250-500
• Slow low-efficiency daily dialysis	SLEDD			
• Extended Daily Dialysis	EDD			
• Prolonged Intermittent Renal Replacement Therapy	PIRRT			
Continuous Renal Replacement Therapy	CRRT	24 h	100-250	15-60
• Continuous venovenous Hemodialysis	CVVHD			
• Continuous venovenous Hemofiltration	CVVH			
• Continuous venovenous Hemodiafiltration	CVVHDF			
Peritoneal dialysis	PD	6 × 2-4 h		

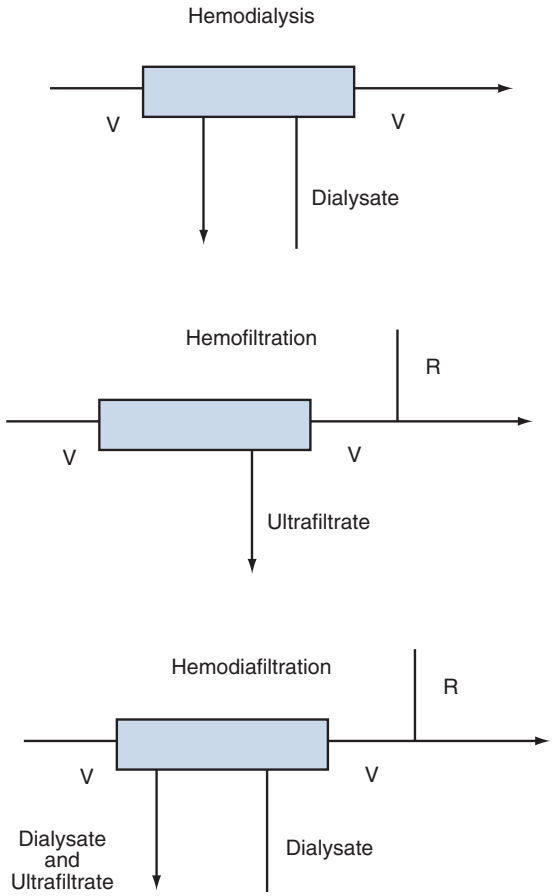

FIGURE 40-1 ■ Diffusion (as in hemodialysis) and convection (as in hemofiltration). V, venous blood prefilter and postfilter; R, replacement fluid.

loss of extracorporeal blood). Anticoagulation for RRT should be tailored according to the patient's characteristics and the modality chosen. The risk for coagulation rises with low blood flow or when the vascular access is not functioning well. Special attention is required for non-anticoagulant strategies to avoid coagulation of the circuit. Patients with a high hematocrit are at higher risk for clotting of the extracorporeal/dialysis circuit because of the higher viscosity of their blood. The local hematocrit in the filter rises when ultrafiltration is applied. Therefore, the filtration fraction (ratio of ultrafiltrate flow to blood flow) may not exceed 25% in postdilution RRT. In predilution mode, hemoconcentration is reduced by diluting the blood with replacement fluids before the blood enters the filter. Blood products should be administered separately from RRT as much as possible. Prompt reaction to pump alarms is important to avoid interruption of blood flow. Careful circuit priming is fundamental. Circuits with a lot of blood-air contact due to the use of drip chambers are especially prone to clotting and require extra attention. There is no evidence pointing toward the efficacy of intermittently rinsing the circuit with saline flushes to prevent clotting.[11]

- No anticoagulation strategy
  Several authors described large series of patients treated without any form of anticoagulation during RRT for AKI (in up to 50%-60%).[8,9] Especially in patients with a preexisting coagulopathy, an acceptable length of treatment can be reached, even without anticoagulant administration.[12] Risking circuit clotting, in the worst case leading to the loss of approximately 200 mL of extracorporeal blood and eventually also the venous access, may be defensible in patients with a high bleeding risk. Neither the effect of clogging on filter performance nor the consumption of coagulation factors in RRT without anticoagulation is well studied.
- Unfractionated heparin
  Unfractionated heparin (UFH), the most widely used anticoagulant, has a half-life between 0.5 and 3.0 h in patients receiving dialysis.[13] It has a rapid onset of action of approximately 3 to 5 min. Heparin acts by potentiating thrombin and inhibiting activated coagulation factor X (FXa). It is mostly administered as a prefilter infusion, by a variety of regimens, including single-dose, repeated-bolus, or constant-infusion methods. A possible administration scheme is to start with a bolus of 500 to 1000 units, followed by 500 to 750 units/h. Other authors suggest adapting the dose to the body weight, starting with a bolus of 10 to 20 units/kg/h, followed by a rate of 10 to 20 units/kg/h. This maintenance infusion would typically be stopped 30 min before the end of treatment. The dose must be altered for patients exhibiting coagulopathy or an increased bleeding risk. UFH can be easily monitored with routine laboratory tests, such as the activated partial thromboplastin time (aPTT) or activated coagulation time (ACT). Since heparin causes systemic anticoagulation, moderate anticoagulation targets are recommended for ICU patients (1.5-2 times prolongation of the aPTT, or baseline ACT plus 40%). If needed, heparin can be reversed with protamine. Heparin failure, resulting in clotting of the circuit, can be due to antithrombin deficiency or heparin neutralization by binding to plasma proteins. During heparin treatment, the thrombocyte count should be monitored, allowing timely detection of heparin-induced thrombocytopenia (HIT). Current guidelines suggest using heparin for intermittent RRT in patients without an increased bleeding risk, and in the presence of contraindications to citrate, which is used in continuous RRT.
- Low-molecular-weight heparins
  Several studies have shown that low-molecular-weight heparins (LMWH) are effective and can be safely used for anticoagulation

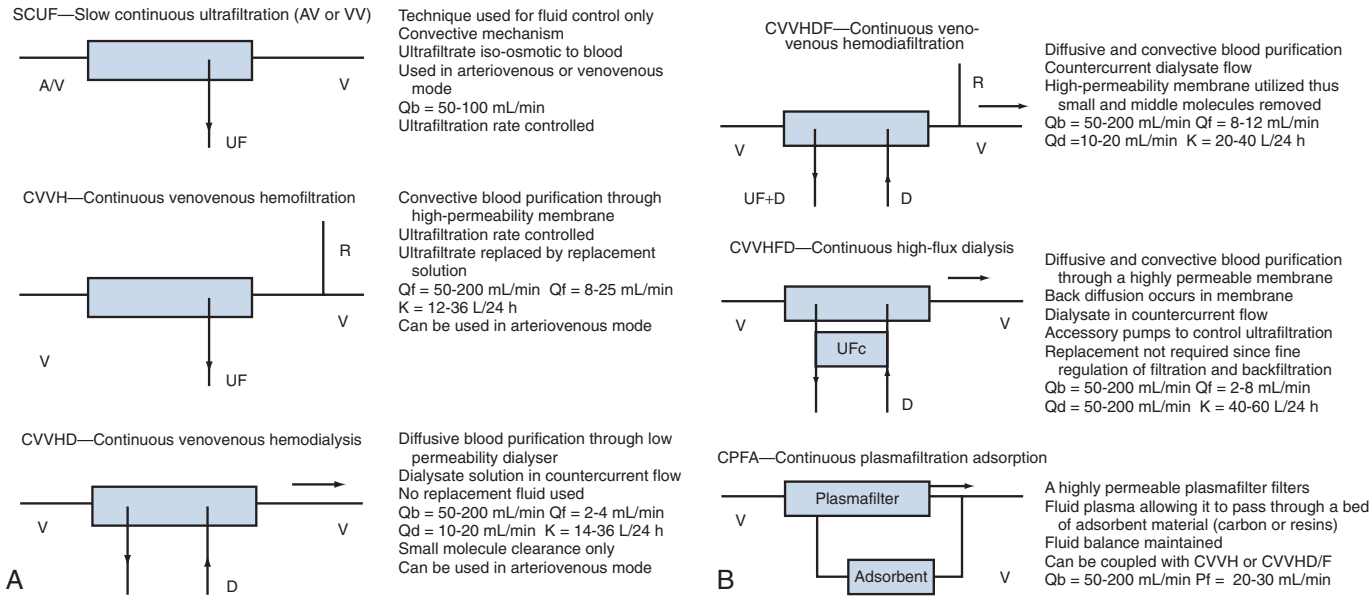

FIGURE 40-2 ■ Schematic representation and definitions of the different continuous renal replacement therapies according to standard nomenclature. Functional capabilities are described. A, artery; D, dialysate; K, clearance; Pf, plasma filtration rate; Qb, arterial flow; Qd, dialysate flow; Qf, ultrafiltration rate; UF, ultrafiltrate; UFc, ultrafiltrate control pump; V, vein.

during chronic HD. LMWH are administered as a single bolus at the beginning of dialysis: immediately after the start of dialysis with postfilter administration or 5 min after the start with prefilter administration.[14] They have a weight-based dosing, require no monitoring when used in short sessions, and have a reduced risk for HIT. The use of LMWH for IHD in AKI is increasing. LMWH are partially cleared during HD (especially with high-flux membranes), but periodic measurement of anti-Factor Xa levels may be useful with prolonged daily use.

- Citrate

  The 2012 Kidney Disease Improving Global Outcomes Clinical Practice Guidelines for Acute Kidney Injury have recommended regional citrate anticoagulation as the preferred anticoagulation modality for continuous RRT in critically ill patients for whom it is not contraindicated.[15] Citrate chelates calcium, an essential cofactor for many steps of the coagulation cascade. A whole range of protocols exist, using different dialysate/replacement fluids for the different RRT modalities. Prefilter infusion of citrate, either as a separate trisodium citrate solution or added to calcium-free predilution replacement fluid, lowers ionized calcium levels in the extracorporeal circuit to a level that achieves full blood anticoagulation (i.e., 0.3-0.4 mmol/L). In most protocols, the citrate dose is adapted according to the resulting postfilter circuit ionized calcium measurements, although recently, there has been some concern about the reliability of measurements obtained from point-of-care devices used for this purpose. Citrate and citrate complexes are partially removed in the effluent because of their low molecular weights (198 and 258, respectively) and high sieving coefficients. Citrate clearance is higher with dialysis than with CVVH, with extraction ratios from 20% to 60%, depending on the modality and dose of RRT. Calcium infusion is needed to replace calcium losses and maintain systemic ionized calcium levels within the normal range. The remaining citrate is metabolized in the liver, muscle, and kidney, producing bicarbonate and eventually leading to metabolic alkalosis. Most of the protocols compensate for this by administering a lower concentration of bicarbonate in the replacement fluid. In contrast, in patients with impaired citrate metabolism, acidosis can ensue. Other potential metabolic derangements include hypernatremia (due to metabolization of trisodium citrate), hypomagnesemia (due to effluent losses in the form of citrate complexes), and hypocalcemia. Citrate accumulation can occur in patients with profound shock or severe liver failure, although recent studies have argued that citrate can be used safely in the latter.[16] During citrate accumulation, there is a simultaneous increase of the total calcium and fall of the ionized calcium. The total calcium to ionized calcium ratio is the best marker for citrate intoxication. When this ratio exceeds 2.5, citrate administration must be stopped. Unintended rapid infusion of a hypertonic citrate solution, causing life-threatening hypocalcemia, is the main risk of citrate anticoagulation. In this situation, it is recommended that the citrate infusion be stopped, while continuing dialysis with a calcium-containing dialysate. In experienced hands, severe hypocalcemia-related complications seldom occur, and regional citrate anticoagulation has been shown to be safe. Treatment protocols should describe how to adjust flows under different conditions to prevent metabolic derangements. Compared with heparin, citrate is associated with lower risk of circuit loss, a lower incidence of filter failure, less bleeding, and lower transfusion rates. Furthermore, citrate is a source of energy and has potential anti-inflammatory effects.
- UFH and protamine

  Regional anticoagulation can also be accomplished by the combination of UFH and protamine. Use of this strategy has decreased in parallel with the increasing popularity of citrate. Protamine has several side effects, such as anaphylaxis, hypotension, cardiac depression, leukopenia, and thrombocytopenia. Further, there may be the possibility of a rebound anticoagulant effect because of the shorter half-life of protamine compared with heparin. Regional anticoagulation with heparin-protamine is, therefore, no longer recommended.[10,15,17]
- Platelet-inhibiting agents

  Prostacyclin (PGI_2) and its analogue (nafamostat) inhibit platelet aggregation and adhesion. They have been used alone or in combination with heparin to improve filter survival. There is neither a great amount of data nor a lot of clinical experience with these medications for this purpose, and several guidance documents do not recommend their use in RRT. In addition to these drugs being expensive, there are safety concerns about hemodynamic stability

with the use of PGI_2, and about anaphylaxis, agranulocytosis, and hyperkalemia with the use of nafamostat.

Vascular Access

Vascular access is with a double-lumen catheter, preferably in the right jugular vein or a femoral vein. It is recommended that the subclavian approach not be used for vascular access of a catheter for RRT. Contact of the catheter with the vessel wall may lead to thrombosis and ensuing stenosis, and it may jeopardize the possibility for an arteriovenous fistula in case there is no recovery of kidney function and the patient remains dialysis-dependent. Thrombosis will be more likely to occur when the catheter has a trajectory with angulations, such as when it is inserted into the left jugular vein or subclavian veins.

For optimal blood flow rates, the tip of the catheter should be located in a large vein—that is, the inferior or superior vena cava. Therefore, for an adult, the optimal length of a catheter is 12 to 15 cm for the right jugular vein, 15 to 20 cm for the left jugular vein, and 19 to 24 cm for the femoral veins. There are several different designs of dialysis catheters. At present it is not clear which design is preferable. The outer diameter of catheters varies between 11F and 14F; larger catheter diameters will result in better blood flow rates.

INITIATION OF RRT

At present, the available evidence does not permit the proposal of strict guidelines for the timing of initiating RRT. If exposure to RRT were without risks, we would not wait until the development of absolute criteria. But very early initiation of RRT will expose the patient to potential hazards associated with insertion of the catheter (e.g., blood loss, thrombosis, catheter infection) and exposure to the extracorporeal circuit (e.g., air embolism, hypotension).[18] If RRT offers support in patients with only mild or moderate AKI, early initiation may be beneficial. However, available data suggest no benefit in, for instance, modulation of the inflammatory response,[19-21] and one study even showed harm when RRT was started very early in patients with severe sepsis or septic shock.[22]

Cohort studies on the timing of RRT have shown a benefit from early initiation of RRT.[23] However, the few small prospective, randomized trials that evaluated early initiation of RRT did not show a benefit from early initiation.[24-26] On the other hand, cohort studies also showed that late initiation is associated with worse outcomes.[27-29]

Knowledge regarding the deterioration or recovery of kidney function within a certain time period would help us in determining the timing of RRT, especially when there are only relative criteria for initiating RRT (Table 40-2). A clinical risk assessment may identify patients at greater risk for further deterioration of kidney function. This may take into account such risk factors as age, chronic kidney disease, and severity of illness of the patient. Other tools that have been explored are measurements of specific kidney biomarkers and the furosemide stress test.[30-36]

The kidneys are crucial for the removal of water and homeostasis of electrolytes and acid-base. Volume overload in an anuric patient and severe electrolyte and acid-base abnormalities are, therefore, absolute criteria for the initiation of RRT (Table 40-2).[37]

CHOICE OF MODALITY OF RRT

Since the introduction of CRRT in the mid-1980s, there has been debate regarding the optimal modality of RRT. Several relatively small studies and meta-analyses showed that CRRT and IHD are associated with similar patient outcomes.[38,39] However, the number of patients included in individual studies was relatively low, the baseline characteristics of the patients were different, and the techniques used (e.g., modalities, dose, initiation criteria) varied among studies, making comparisons difficult. Renal outcomes may, however, be better when CRRT is used. Cohort studies, as well as a comparison of the large prospective, randomized studies regarding dose, the ATN and RENAL studies, suggest that CRRT is associated with better renal recovery and less end-stage kidney disease in survivors.[8,9,40-42]

TABLE 40-2 Criteria for Initiation of RRT

INDICATION	CHARACTERISTIC
ABSOLUTE CRITERIA	
Metabolic abnormality	BUN > 100 mg/dL (35.7 mmol/L)
	Hyperkalemia > 6 mmol/L with ECG abnormalities
	Hypermagnesemia > 8 meq/L (4 mmol/L) with anuria and absence of deep tendon reflexes
Acidosis	pH < 7.15
	Lactic acidosis related to metformin use
Fluid overload	Diuretic-resistant
RELATIVE CRITERIA	
Metabolic abnormality	BUN > 76 mg/dL (27 mmol/L)
	Hyperkalemia > 6 mmol/L
	Dysnatremia
	Hypermagnesemia > 8 meq/L (4 mmol/L)
Acidosis	pH > 7.15
Anuria/oligura	AKI stage 1
	AKI stage 2
	AKI stage 3
Fluid overload	Diuretic-sensitive

AKI, acute kidney injury; BUN, blood urea nitrogen; ECG, electrocardiogram.
Modified from Gibney N, Hoste E, Burdmann EA, et al. Timing of initiation and discontinuation of renal replacement therapy in AKI: unanswered key questions. Clin J Am Soc Nephrol. 2008;3:876–880. Tab 1.

CRRT is performed with a lower extracorporeal blood flow and allows removal of fluid over a longer time period and a lower ultrafiltration rate, characteristics that enhance the hemodynamic tolerability of this technique. Hence, CRRT is often recommended for hemodynamically unstable patients,[15] although studies in specialized centers could not demonstrate that CRRT was better tolerated than IHD in shock patients.[43]

Intermittent techniques, however, use fewer resources since they allow for several treatments with one machine per day, and the dialysate and replacement fluid are produced by the dialysis machines, in contrast to the need to buy these special solutions for CRRT. Whether the cost of CRRT is greater than that of IHD or vice versa will depend on the specific setting.[44,45] An important argument in favor of IHD and hybrid therapy is that these modalities will allow for mobilization of the patient during the off period. A recent meta-analysis suggests that hybrid therapies are associated with the same outcomes as CRRT, suggesting that increasing the length of intermittent treatment may combine the best of IHD and CRRT.[46] However, these data were compiled from a limited number of patients in primarily cohort studies, making this conclusion prone to bias.

SPECIAL INDICATIONS

Heparin-Induced Thrombocytopenia

Up to 3% of heparin-exposed patients develop antibodies directed against the complex of heparin and platelet factor 4, resulting in thrombocytopenia with or without thrombosis. If HIT is likely, all heparin administration, including LMWH, heparin-coated dialyzer membranes, and catheter locks containing heparin, must be stopped. Guidance documents recommend various options for anticoagulation during RRT in this circumstance: regional citrate anticoagulation or the use of direct thrombin inhibitors (such as argatroban or bivalirudin) or factor Xa inhibitors (such as danaparoid or fondaparinux).[10,15,47]

Patients with High Serum Urea Concentration

When using acute RRT in a highly uremic patient (typically >175 mg/dL), precautions should be taken to prevent disequilibrium syndrome.

This rare neurologic condition is characterized by nausea, vomiting, restlessness, and headache. Some patients, however, may progress to seizures, coma, or death. The syndrome is believed to be primarily related to the decreased osmolarity of the blood after the initiation of RRT, creating an osmotic gradient between the blood and the brain, which is compensated for by an influx of water into the brain compartment. To avoid brain edema caused by large variations in osmolality, several preventive measures can be taken, targeting a reduction in the plasma urea nitrogen of at most 40%. The dialysis dose can be reduced by lowering blood flow and dialysate flow, using a small dialyzer, and limiting the length of the treatment. The use of a sodium-enriched dialysate may further reduce the risk.[48]

Patients with Intracranial Hypertension or Cerebral Edema

In patients with acute brain injury, AKI requiring RRT may worsen the neurologic status in several ways. The accumulated urea and solutes diffuse from the blood compartment to the brain cells, thereby increasing water uptake by the brain cells. Dysfunction in the blood-brain barrier reinforces this process. The shift of water into brain tissue, as a result of lowered tonicity of plasma with respect to the brain cells (as described in disequilibrium syndrome), may result in increased intracranial pressure causing cerebral hypoperfusion. This is exacerbated by decreased or absent autoregulation of cerebral blood flow due to the brain injury and eventual hypotension during RRT. Both hypotension and disequilibrium can be avoided by the slow progressive removal of fluids and solutes during CRRT, which is in this setting preferred over intermittent RRT. If the patient is also at increased risk for intracranial bleeding, locoregional citrate anticoagulation is recommended.[17]

Patients with Hyponatremia

If patients with severe chronic hyponatremia are treated with conventional RRT, the serum sodium concentration can be expected to increase rapidly, exposing patients to the risk of developing osmotic demyelination. High serum urea concentration may protect the brain against this.[49,50] To avoid osmotic demyelination in patients with chronic hyponatremia, the treatment during a single dialysis session has to be adjusted to provide a rate of correction that does not exceed the generally recommended rate. The easiest way to do this is by choosing a low-efficiency RRT such as CVVH and to maintain the sodium concentration of the replacement fluid slightly higher than the serum sodium concentration. In the routinely available dialysate/replacement solutions, the variability in sodium content is limited. Adapting the sodium concentration can be established by adding sterile water to the replacement fluid bag. Diluting replacement fluid will also result in decreased potassium and bicarbonate concentrations and, therefore, may induce hypokalemia and acidosis. If only HD is available, one can use the lowest available concentration (130 mmol/L), reduce the blood flow rate markedly (to 2 mL/kg/min), and shorten the dialysis time.[51]

Prevention of Contrast-Induced Nephropathy

A single dialysis session removes 60% to 90% of contrast media from the blood,[52,53] and one study argued that periprocedural CRRT may be beneficial in patients with chronic kidney disease.[54] However, meta-analyses including studies in patients without severe chronic kidney disease could not show a benefit for this strategy.[52,55] Considering the possible complications, cost, logistical difficulties, and uncertain benefit, several guidelines do not recommend RRT for the prevention of contrast-induced nephropathy.[15,56]

Patients with Severe Hemodynamic Instability

CVVHD, SLEDD, and continuous HD seem to be equivalent treatment strategies with regard to mortality, kidney recovery, and fluid removal for hemodynamically unstable patients.[17,46,57-60] Treating those patients requires some precautions: less aggressive ultrafiltration; increasing dialysate sodium and calcium concentrations to 145 mmol/L and 1.5 mmol/L, respectively; adapting the dialysate temperature to obtain isothermal dialysis; connecting afferent and efferent blood lines simultaneously at the start of the procedure; raising the blood flow slowly; and using biocompatible membranes.[17]

Patients with Severe Lactate Acidosis

The key issue in the management of lactic acidosis is to treat the underlying cause. Continuous RRT can be performed in critically ill patients with severe lactic acidosis and AKI.[61] Using continuous HD with bicarbonate dialysate, lactate concentrations can be lowered and the pH can be corrected. However, no adequately powered randomized, controlled trial with clinical outcome endpoints has yet evaluated RRT in this setting.[62]

KEY POINTS

1. Uremia is the accumulation of uremic toxins of different molecular weights associated with pathogenicity secondary to kidney dysfunction.
2. Acute kidney injury (AKI) is a separate syndrome from chronic renal failure and should be approached in a distinct manner.
3. Specific indications exist for the initiation of renal replacement therapy (RRT) in AKI. Early initiation has been shown to be beneficial in cohort studies. The optimal timing of early is at present unclear and may differ in patient groups.
4. Multiple therapeutic modalities of RRT exist to treat AKI. No modality is clearly superior to another. Treatments should be tailored depending on the clinical scenario.
5. Knowledge of prescribed drug pharmacokinetics is important when dosing patients on RRT.

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