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Core Curriculum in Nephrology

Continuous Dialysis Therapies: Core Curriculum 2016

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Over the past 2 decades, the development of new renal replacement therapy (RRT) techniques, including continuous RRT (CRRT), has allowed the therapy to be offered to sicker and hemodynamically unstable patients in the intensive care unit (ICU) setting. However, studies designed to compare continuous versus intermittent therapies have not shown a beneficial effect on mortality. Several inherent characteristics of CRRT, including the longer duration of therapy, have been associated with greater hemodynamic stability and a higher likelihood of kidney recovery compared to standard intermittent hemodialysis (IHD). There still exists considerable variation in the application of CRRT in the ICU due to a lack of standardization in this field. To some extent, this reflects the lack of consensus on several aspects of RRT (eg, timing of initiation, dose, session length, and standards for monitoring). Additionally, there is wide variation in how the techniques are prescribed, delivered, and optimized to improve patient outcomes. In this Core Curriculum, we focus on the key concepts to guide nephrologists to prescribe and deliver CRRT and utilize its therapeutic potential.

CRRT PRINCIPLES

The term CRRT describes blood purification techniques that harness the inherent principles of support of kidney function for achieving solute and fluid homeostasis continuously and are intended to be applied for 24 hours or longer. As with other dialysis techniques, CRRT requires a well-functioning access, a permeable membrane, pumps to circulate blood and various solutions across the membrane with accurate fluid balancing, and pressure monitoring systems. Anticoagulation is generally required to achieve a functional circuit over an extended period. Although the basic components of CRRT are similar to those of IHD, there are significant differences in how these are used to achieve solute and fluid homeostasis. Several techniques are grouped in CRRT and are distinguished by different mechanisms of solute transport, fluid management, type of membrane, and use of dialysate and substitution solution.

Solute Transport

By removing solutes through convection, diffusion, and adsorption and replenishing depleted solutes selectively by varying the composition of the solutions used in the process, CRRT can be used to achieve solute balance to any desired level. CRRT techniques vary in which primary mechanism is used and these features distinguish the terminology of the therapy. Continuous venovenous hemofiltration (CVVH) relies solely on convection; continuous venovenous hemodialysis (CVVHD), on diffusion; and continuous venovenous hemodiafiltration (CVVHDF), on a combination of both techniques (Table 1). These mechanisms can be manipulated by the type of membrane and blood and fluid flow rates to selectively influence solute clearances of molecules of different size. Adsorption of solutes occurs to varying degrees in all CRRT circuits and can be a contributor for large-molecule removal, depending on membrane characteristics. This may be limited by saturation of the membrane binding sites that can occur within a few hours.

The long duration in CRRT is used to optimize solute transport across the membrane. The effluent flow rate (Q_{ef}) is the final result of the filtration process and is composed of the net ultrafiltration (Q_{net}) plus substitution fluid rate (Q_s) in CVVH and CVVHDF plus dialysate flow rate in CVVHD and CVVHDF. (Fig 1). Filter clearances for small-sized solutes (eg, urea nitrogen, creatinine, and phosphates) can be estimated by the effluent volume in convective or diffusive techniques as soon as membrane permeability is maintained. Filter clearance for most CRRT circuits is equal to the product of Q_{ef} and the sieving coefficient (S), which is the ratio of solute concentration in the ultrafiltrate (C_{uf}) to solute concentration in plasma (C_p), and is regulated by the reflection coefficient of the membrane ($S = 1 - \sigma$). A solute with S of 1 can pass freely through a filter; if S is 0, the solute cannot pass through the filter. In contrast, for middle molecules, clearance is dependent on membrane permeability characteristics and amount of ultrafiltration volume. For solutes that are adsorbed by membranes (eg, tumor necrosis factor α), overall blood clearance can be greater than filter clearance, even when S is low. Thus, if absorptive clearance is present, blood-side clearances will not

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Table 1. Transport and Operational Characteristics of CRRT Modalities

Parameters	SCUF	CVVH	CVVHD	CVVHDF
Solute transport mechanism	Convection	Convection	Diffusion	Diffusion and convection
Blood flow rate (Q_b), mL/min	100-200	100-250	100-250	100-250
Dialysate flow rate (Q_d), mL/h[a]	0	0	1,000-2,000	1,000-2,000
Substitution fluid rate (Q_s), mL/h	0	1,000-2,000	0	1,000-2,000
Ultrafiltration rate (Q_{uf}), mL/min[a]	2-8	16-33	2-8[b]	33-66
Net ultrafiltration rate (Q_{net}), mL/h	Q_{uf}	$Q_{ef} - Q_s$[c]	Q_{uf}[b]	$Q_{ef} - Q_s$[c]
Effluent flow rate (Q_{ef}), L/d	2-8	24-48	24-48	48-96
Components of Q_{ef}	Q_{uf}	$Q_{uf} = Q_s + Q_{net}$	$Q_d \pm Q_{net}$	$Q_{uf} + Q_d$
Sieving coefficient (S)	C_{uf}/C_p	C_{uf}/C_p	C_{ef}/C_p	C_{ef}/C_p

Abbreviations and definitions: CRRT, continuous renal replacement therapy; C_{ef}, solute concentration in effluent; C_p, solute concentration in plasma; C_{uf}, solute concentration in ultrafiltrate; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; SCUF, slow continuous ultrafiltration; Q_d, amount of fluid instilled into filter countercurrent to flow of blood; Q_s, fluid instilled pre- or postfilter to replace ultrafiltrate volume; Q_{uf}, plasma water removed from circulating blood into the effluent bag, it is driven by the machine settings to include the quantity of pre- and postdilution substitution fluids (Q_s) plus the desired net fluid removal (Q_{net}); S, ability of substance to pass through filter.

[a]Other units may be used; those listed are the usual units.

[b]The fluid removed reflects Q_{net} and adds additional solute clearance.

[c]Variable to achieve CRRT balance.

match filter clearances. Table 1 describes the terminology for CRRT techniques.

Techniques

The various CRRT techniques differ mainly in their driving force for solute removal and the membrane used.

Continuous Venovenous Hemofiltration

CVVH uses convection, whereby the ultrafiltrate passes through the membrane driven by a transmembrane pressure gradient (TMP). As shown by Cerdá and Ronco, this process can be represented by the following equation:

$$U_f = K_f \times TMP$$

where K_f is the coefficient of hydraulic permeability and $TMP = (P_b - P_{uf}) - \pi$. In the latter equation, P_b is hydrostatic pressure of blood, P_{uf} is the hydrostatic pressure of the ultrafiltrate or dialysate, and π is the oncotic pressure of plasma proteins.

The convective clearance (C_x) of a solute can be estimated by the following formula:

$$C_x = Q_{uf} \times S$$

where S (the sieving characteristics of membrane) = C_{uf}/C_p, with C_p being the concentration of solute in plasma, and C_{uf}, the concentration of solute in the ultrafiltrate.

This technique requires the use of a substitution fluid to replace part or all of the removed fluid. The composition of the substitution fluid can vary, and the solution can be infused pre- or postfilter. Net ultrafiltration (Q_{net}) is the difference from ultrafiltration volume minus substitution fluid infusion.

Continuous Venovenous Hemodialysis

CVVHD uses diffusive clearance, in which the movement of solutes is enabled by the concentration gradient across the dialysis membrane. Solute diffusion (S_d) can be estimated as follows:

$$S_d = (C_g/M_t) \times D \times T \times A$$

where C_g is the concentration gradient, M_t is the thickness of membrane, D is the diffusion coefficient of the solute, T is the temperature of solution, and A is the surface area of membrane.

The gradient across the membranes is affected by Q_d and blood flow rate (Q_b). The Q_d are much slower than Q_b, so there is complete saturation of the dialysate. Q_d is the rate-limiting factor for solute removal. It is effective for small-molecular-weight solutes such as potassium, urea, and creatinine. Q_d can vary from 0.5 to 3 L/h (8-50 mL/min), and Q_b can vary from 100 to 200 mL/min.

Continuous Venovenous Hemodiafiltration

CVVHDF combines diffusion and convective technique. In hemodiafiltration, both dialysate and substitution ("hemofiltration") solutions are used, and small and middle molecules can both be efficiently removed.

Slow Continuous Ultrafiltration

Slow continuous ultrafiltration (SCUF) uses exclusively the principle of ultrafiltration without fluid substitution. The ultrafiltrate allows removal of excess fluid and is used to safely treat fluid overload. It can remove up to 8L of fluid a day, but solute removal is minimal because it is limited by total ultrafiltrate volume.

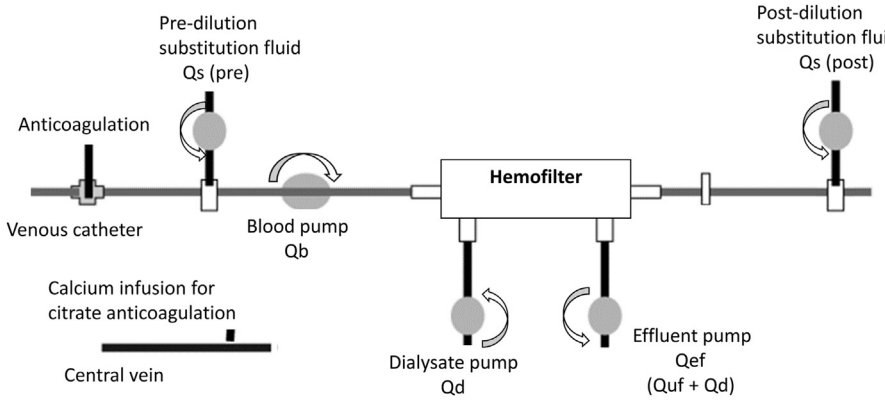

Figure 1. Continuous renal replacement therapy circuit represents pumps and sites of entry of dialysate and predilution and postdilution substitution fluid. Abbreviations and definitions: Q_d, dialysate flow rate; Q_{ef}, effluent flow rate (equivalent to ultrafiltration rate [Q_{uf}] in slow continuous ultrafiltration and continuous venovenous hemofiltration, Q_d in continuous venovenous hemodialysis, and $Q_{uf} + Q_d$ in continuous venovenous hemodiafiltration); Q_s (pre), substitution fluid rate infused prefilter; Q_s (post), substitution fluid rate infused postfilter.

Fluid Management

Fluid management in CRRT offers the opportunity to adjust plasma composition and the amount of fluid in the body. These 2 processes can be dissociated, thereby permitting any level of fluid balance to be coupled with a specific level of the target solute (eg, a sodium level can be kept high, normal, or low while fluid balance is kept even, negative, or positive) and maintained over time. This flexibility in therapy is achieved by manipulating the composition of the dialysate and substitution fluids and varying the amount of net ultrafiltration over a specific time. Commercially prepared sterile fluids are now available as premixed dialysis and substitution solutions for CRRT. However, most of these solutions (Table 2) require adjustments in potassium and magnesium levels to accommodate varying patient needs. Fluid can also be manufactured at the pharmacy or hospital level. Manufacturing or customizations are prone to human error, and mistakes can lead to significant electrolyte derangements. Premixed bicarbonate-based solutions are difficult to store because bacterial contamination and microprecipitation of calcium carbonate crystals can occur.

Adjusting Plasma Composition

A major advantage of CRRT is the possibility to adjust substitution fluid and dialysate fluid composition to achieve a desirable change in plasma composition. The substitution fluid and/or dialysate should contain electrolytes in concentrations aiming for correction of a patient's metabolic derangements and taking into account pre-existing deficits or excesses and all inputs and losses.

The choice of alkali for CRRT buffer in the dialysate and substitution fluid depends on the clinical situation and availability. Lactic acidosis is a common cause of metabolic acidosis and a possible complication of CRRT when lactate-buffered solutions are used. Lactate is metabolized to bicarbonate by the liver, and with hypotension and multiorgan failure, the metabolic rate for conversion to bicarbonate can be decreased, resulting in lactate accumulation. A serum lactate increase $>$ 5 mmol/L during CRRT should indicate lactate intolerance. The KDIGO (Kidney Disease: Improving Global Outcomes) guideline suggests using bicarbonate instead of lactate as a buffer in dialysate and substitution fluid for RRT in patients with acute kidney injury (AKI; evidence level, *2C*), in patients with AKI and circulatory shock (*1B*), and in patients with AKI and liver failure and/or lactic acidemia (*2B*). In ICU patients, bicarbonate buffer in dialysate or substitution solution results in

Table 2. Examples of Available Substitution Fluid and Dialysate Solutions Available in the United States for CRRT by Manufacturer

	Gambro (Baxter)		NxStage	B. Braun
	[a]PrismaSol BGK/B22K/ BK	[b]PrismaSATE BGK/B22K/ BK	[b]RFP 400-456	[b]Duosol 4551-4556
Na^+, mEq/L	140	140	130-140	140-136
K^+, mEq/L	0-4	0-2-4	0-4	0-4
Cl^-, mEq/L	108-113	108-120.5	108.5-120.5	109-117
Lactate, mEq/L	3	3	0	0
Bicarbonate, mEq/L	22-32	22-32	25-35	35-25
Ca^{2+}, mEq/L	0-2.5-3.5	0-2.5-3.5	0-3	3-0
Mg^+, mEq/L	1.0-1.2-1.5	1.0-1.2-1.5	1-1.5	1-1.5
Dextrose, g/dL	0-1	0-1.1	1	1-0

Abbreviation: CRRT, continuous renal replacement therapy.
[a]Substitution fluid.
[b]Dialysate solutions.

better acidosis correction, reduced lactate levels, and better hemodynamic improvement.

When citrate is used as an anticoagulant, it also provides a buffer base because each citrate molecule is metabolized in the liver and muscle to 3 molecules of bicarbonate. However, citrate metabolism may be impaired in severe liver failure and markedly hypotensive patients.

A key feature of CRRT is the flexibility in maintaining a specific level of any electrolyte and calibrating the rate of correction to accommodate the clinical need. For instance, patients with severe hypo- or hypernatremia (sodium $<$ 115 or $>$160 mEq/L) can be managed with CRRT and the rate of correction can be adjusted by varying sodium composition in the substitution fluid and dialysate.

Achieving Fluid Balance

Fluid removal in RRT is achieved through varying amounts of net ultrafiltration rate (Q_{net}) that can be tailored to individual need. The net ultrafiltrate is the difference between total ultrafiltrate (the plasma water removed) and total substitution (the fluid given to the patient) through the CRRT machine. CRRT machines offer the precision to balance all the fluids removed and replaced across the dialysis circuit in order to generate a net amount of fluid removal over a time. However, the CRRT machine balance does not represent the actual patient fluid balance, which includes all intakes and outputs including the CRRT machine balance (itself determined by Q_{net}). Consequently, achieving patient fluid balance with CRRT requires knowledge of other intakes and outputs that need to be integrated in the prescription and delivery. We describe 3 techniques for achieving fluid balance with CRRT.

The most common technique is to vary Q_{net} to meet the anticipated fluid balance needs over 8 to 24 hours. Net ultrafiltration can be adjusted at different intervals ranging from hourly to every 6 to 12 hours. Inherent to this method is that effluent volume and hence solute clearance will vary with each adjustment in net ultrafiltration. A second method of maintaining fluid balance is to keep a fixed rate of ultrafiltration that exceeds the hourly intake from all sources and to vary the amount of postdilution substitution fluid administered. This method ensures a constant effluent volume and solute clearance level. The postdilution fluid can be given outside the CRRT circuit through a peripheral intravenous line, thereby minimizing interactions with the machine. The third method is similar to the second, but fluid balance is tailored to achieve a targeted hemodynamic parameter every hour. Predefined targets are set for parameters, such as central venous pressure, mean arterial pressure (MAP), or pulmonary arterial wedge pressure, and scales are prescribed to achieve these targets.

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MAINTAINING THE CRRT CIRCUIT

Several features of the CRRT circuit need to function properly in order to keep the therapy running for patient solute, electrolyte, acid-base, and fluid control. The first determinant of an efficacious therapy is the access.

Access

An essential requirement for successful CRRT is a well-functioning vascular access. Temporary or tunneled cuffed hemodialysis catheters are currently used as vascular access for CRRT. The KDIGO guideline recommends the use of ultrasound guidance for catheter placement because its use has been reported to reduce the failure and complication rates of central venous catheter insertion (evidence level 1A). For patients requiring more than a week of acute dialysis therapy, tunneled, cuffed, double-lumen, polymeric silicone catheters are recommended. Because these catheters have a larger diameter than nontunneled catheters, higher blood flows can be maintained.

The optimal site for catheter location is determined by the risks of the catheter placement procedure, possibility of thrombosis, stenosis, and infection. The right internal jugular vein is preferred for temporary catheters because it allows for a more direct route to the superior vena cava as compared to the left jugular vein, which can cause reduced blood flow in patients with head movements. With the exception of obese patients, the femoral veins should be considered as the second choice for CRRT. Observational trials have shown that the femoral access can be associated with higher frequency of malfunction and decreased survival compared with jugular catheters. Subclavian vein cannulation is discouraged because it may lead

to stenosis of the vessel, which may interfere with arteriovenous graft or fistula functioning in the future.

A major concern for CRRT is the risk for infections in the vascular access. The main risk factors for the development of catheter-related bloodstream infection are duration of catheter use and number of dialysis sessions. Internal jugular catheters may be left for a prolonged period, up to 3 weeks, because the risk for bacteremia is lower. Femoral catheters have an increased risk for infection in bed-bound and obese patients, and removal should be considered after 1 week. Catheter material and antimicrobial coating or impregnation may also influence infection rates. The use of topical antibiotics at the skin insertion site and use of antibiotic locks are not suggested because they may promote fungal infections and antimicrobial resistance.

Other complications include catheter malfunction due to thrombosis, kinking of the catheter, and formation of a fibrin sheath around the catheter tip. Heparin instillation into both lumens prevents the formation of an intraluminal thrombus. Studies have suggested the safety and superiority of trisodium citrate over heparin for the prevention of catheter-related infections, bleeding complications, and thrombosis. Recombinant tissue plasminogen activator/alteplase can be instilled to reestablish blood flow when a thrombus completely occludes the catheter. Fibrin sheaths that form outside the catheter are resistant to thrombolytic agents and may require mechanical brushing or stripping.

Patients with end-stage renal disease with arteriovenous fistulas or grafts should not use this access for CRRT. The prolonged time and slower Q_b increase the risk for needle dislodgement and bleeding.

Membrane

The type of membrane defines the solute removal capacity and water permeability during CRRT. Molecular weight cutoff, structure, and charge of a membrane affect the ability of a solute to convectively cross a membrane and the adsorption capacity. Inflammatory mediators (interleukin 6 [IL-6], IL-8, IL-1, and tumor necrosis factor α) can be removed by convection according to the molecular weight and degree of plasma protein binding. The ability of removing and adsorbing larger molecular-weight solutes with CVVH and CVVHDF may offer advantages in sepsis or systemic inflammatory response syndrome.

Anticoagulation

During CRRT, blood contact with the extracorporal circuit, tubing, and membrane activates platelets and inflammatory and prothrombotic mediators. The induction of fibrin deposition and filter clotting reduces the surface of the membrane available for diffusion or convection and consequently the efficiency of solute clearance. Several methods of anticoagulation are now available and the key features of the most common methods are summarized in Table 3.

Unfractionated heparin continues to be the most commonly used anticoagulant. It promotes the inactivation of thrombin, factor Xa, and factor IXa by antithrombin, a natural anticoagulant. Despite its frequent use over decades and the widely available test to monitor its effect, heparin resistance due to reduced antithrombin III level with reduced glomerular filtration rate, high incidence of bleeding, and heparin-induced thrombocytopenia are important limitations of its use, especially for continuous therapies. Low-molecular-weight heparins have less protein binding, more predictable pharmacokinetics, and lesser incidence of heparin-induced thrombocytopenia. Disadvantages are increased half-life compared to unfractionated heparin, poor reversibility with protamine, and cost.

An alternative to systemic anticoagulation with heparin-based anticoagulants is citrate regional anticoagulation. Morabito et al discuss how regional

Table 3. Advantages and Disadvantages of Various Anticoagulants During CRRT

Drug	Advantages	Disadvantages
Unfractionated heparin	Widely used, less expensive, shorter half-life, reversible, easy monitoring (aPTT or ACT)	Risk for bleeding, unpredictable action, heparin resistance, HIT
Low-molecular-weight heparin	More reliable anticoagulation, reduced risk for HIT	Cumulative effect, expensive, anti-Xa monitoring needed
Citrate	Regional anticoagulation, low bleeding risk	Metabolic acidosis and hypocalcemia (especially in hepatic failure patients), hypernatremia, metabolic alkalosis
Alternative agents		
Argatroban		
Danaparoid	Safe and effective	Cost
Recombinant hirudin	Lack of experience in most centers	

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; CRRT, continuous renal replacement therapy; HIT, heparin-induced thrombocytopenia.

anticoagulation with citrate is being used more frequently and several different regimens are now available for CVVH and CVVHDF. KDIGO guideline recommendations suggest the use of citrate regional anticoagulation in patients without contraindications for citrate (*2B*). In patients with contraindications for citrate, they suggest using either unfractionated or low-molecular-weight heparin instead of other anticoagulants (*2C*). Citrate is infused continuously in the arterial tubing and chelates free calcium in the circuit, inhibiting the coagulation cascade. Part of the complex, calcium-citrate, is removed by dialysis clearance and part is metabolized in the liver. The citrate infusion rate is adjusted to keep the activated clotting time longer than 160 seconds. Serum ionized calcium concentrations should be monitored, and continuous or intermittent calcium infusion should be performed as necessary.

Citrate regional anticoagulation requires modifications in the hemofiltration solution or dialysate. Citrate is converted to bicarbonate in the liver and metabolic alkalosis is a complication of the therapy. Studies have shown superior safety, efficacy, and costs with citrate compared to unfractionated heparin, although discordant results are found in regard to mortality and kidney outcome. There may be cost-saving implications from citrate regional anticoagulation, with potentially less circuit downtime and fewer circuit changes. Improved biocompatibility with citrate regional anticoagulation may be associated with decreased thrombogenicity and low polymorphonuclear cell degranulation.

The use of intermittent saline solution flushes in the CRRT circuit is an option when no anticoagulation is used in CRRT. Saline solution flushes every 15 to 30 minutes in the arterial tubing of the circuit help wash fibrin strands from the membrane. However, membrane efficacy may be compromised before the system clots and filter half-lives are generally reduced. It is thus essential to measure filter clearances on an ongoing basis through the ratio of solute concentration in effluent (C_{ef}) to C_p. Assessment of C_{ef}:C_p ratio can be done every 12 hours, and a ratio < 0.8 can help predict filter clotting. The volume administered on the flushes must be included to calculate net ultrafiltration.

Other methods for anticoagulation in CRRT include regional heparin/protamine, heparinoids, thrombin antagonists (hirudin and argatroban), and platelet-inhibiting agents (prostacyclin and nafamostat). These have been variably used in CRRT.

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PRESCRIPTION AND DELIVERY

Given the described characteristics of CRRT, indications for the use of a continuous modality are associated to the prolonged time to achieve fluid and metabolic homeostasis and the great chance to adapt the therapy to a patient's need. Fluid overload is a common complication of volume resuscitation strategy used for multiorgan failure, which may compromise the functioning of other organs when kidney capacity to maintain fluid balance is overwhelmed. In these patients, dialytic intervention should be considered as renal support rather than renal replacement, and the inability of achieving adequate fluid balance, even without relevant increases in serum urea nitrogen or serum creatinine levels, may be the sole indication for RRT. In this setting, achieving fluid balance with CRRT facilitates other supportive treatments (eg, antibiotics and nutrition support) to be instituted without fear of increasing fluid overload.

Time to Initiate

Though the optimal timing of dialysis for AKI is not clear, the approach of waiting for AKI complications may delay dialysis therapy initiation. In the absence of an urgent need, clinicians tend to delay RRT initiation. The risk associated with vascular access placement, anticoagulant administration, hypotension, arrhythmia, and risk for RRT dependence are the most common factors responsible for the decision to delay. The concern of performing an unnecessary procedure in patients who may recover kidney function is another major reason to delay. We favor a strategy focusing on RRT as renal support instead of renal replacement, aiming to maintain normal acid-base, electrolyte, and fluid status along with liberal nutritional support. Box 1 shows the factors to consider when deciding about CRRT initiation.

Solute Dose

The ideal CRRT prescription for AKI should incorporate an assessment of the dose delivered.

However, assessing dose in CRRT can be more challenging than it first appears. In patients with AKI, total body volume (V) is higher compared with in patients with end-stage renal disease, often >0.65 L/kg. Thus, we need to account for highly variable body water volumes, urea generation rates, and residual kidney function, as well as for the different clearance methods. The surrogate of solute removal for most studies in CRRT is considered the effluent rate in milligrams per kilogram per hour. However, because filter fouling and clotting can lower the efficacy of solute removal, the true dose delivered may be significantly less than estimated from the effluent volume. Measuring solute removal in the effluent and calculating clearance based on the mass extracted should be the gold-standard method to assess delivered dose (Box 2).

The location of substitution solution in the circuit, either pre- or postfilter, also affects the clearance of molecules in CRRT (Box 2). Ultrafiltrate removal through the filter increases solute and protein concentrations in the other side of the filter. This increment in concentration is the result of the ratio of ultrafiltrate over plasma flow rate, known as the filtration fraction (FF). The plasma flow rate (Q_{bw}) is determined by Q_b and patient hematocrit (Hct); $Q_{bw} = Q_b\ (1 - \text{Hct})$. When FF is >20%, filter performance is reduced and filter clotting is more likely to occur. Therefore, in postdilution CVVH, $FF = Q_{ef} / Q_b\ (1 - \text{Hct})$ and primary determinants of solute clearances are ultrafiltration rate (Q_{ef}) and the sieving coefficient of membrane (S). $K = Q_{ef} \times S$, where K is clearance in milliliters per minute. For small molecules, as S approaches 1, clearance equals the ultrafiltration rate in postdilution. Clearance can be increased with higher amounts of substitution fluid and ultrafiltrate generated. However, when increasing ultrafiltration rates, Q_b also should be increased to keep FF < 20%. For this reason, achieving higher doses is difficult in postdilution mode.

Prefilter administration of substitution fluid decreases the solute concentration in the blood entering the filter. Thus, it is useful in preventing clotting of the extracorporeal circuit and to extend filter life. However, clearance in predilution hemofiltration is less than in postdilutional hemofiltration for the same Q_{ef} due to dilution of blood entering the filter; and larger FFs (larger Q_{ef} and substitution fluid rate [Q_s]) are attainable in predilutional hemofiltration. The effect on small-solute clearance (K) for predilutional hemofiltration can be calculated: $Q_{ef} \times (Q_b / [Q_b + Q_s])$.

Standard Kt/V is a method used to compare the efficiency of CRRT with hemodialysis of variable frequency (2-7 sessions per week) and peritoneal dialysis (Table 4). The prescribed dose based on the effluent rate should be incremented by 20% to 25%, anticipating temporary disconnections that decrease treatment time and loss of filter efficacy during the course of CRRT.

The KDIGO guideline recommends delivering an effluent volume of 20 to 25 mL/kg/h for CRRT in AKI (*1A*). Dose should be frequently assessed and prescription should be adjusted accordantly (*1B*). Solute clearances are not the sole measure of dialysis adequacy. Fluid removal and fluid balance are equally, if not more, important parameters to be monitored.

Several studies in CRRT and in IHD have suggested that higher RRT doses are associated with improved outcome. However, 2 large multicenter, randomized controlled trials (ATN [Acute Renal Failure Trial Network] Study and RENAL [Randomized Evaluation of Normal Versus Augmented Level] Replacement Therapy study) do not support the hypothesis that a higher RRT dose will improve outcomes. However, in AKI, a marked discrepancy between prescribed and delivered RRT doses can exist and the importance of

Box 1. Factors to Consider for CRRT Initiation

Severity of illness and trajectory
- AKI severity and trend
- Levels of BUN and serum creatinine
- Electrolytes and acid-base disorders
- Fluid balance and evidence of fluid overload
- Urinary output in context of patient's fluid balance and fluid needs
- Presence of other significant organ dysfunction that will require renal support for optimizing care and promoting recovery

Necessity of the procedure
- Likelihood of recovery of kidney function without CRRT: cause and likelihood of reversibility of AKI, based on trend of kidney function parameters
- Both nature and timing of renal insult
- Underlying disease and comorbid conditions
- Presence of oliguria (consider effect of diuretic)
- Concurrent use of vasopressors and ventilator requirements

Risks associated with the procedure
- Vascular access complications: hemorrhage, thrombosis, bacteremia
- Complications of CRRT
- Intradialytic hypotension
- Hypersensitivity to the extracorporeal circuit
- Clearance of trace elements, and antibiotics
- Prolongation of AKI course

Futility
- Likelihood of patient surviving hospital admission
- Concerns about quality of life

Other considerations
- Family wishes
- Health costs
- Machine and nursing availability

Abbreviations: AKI, acute kidney injury; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy.

Box 2. Methods to Assess Dose in CRRT

Dialysate Side

CVVH

Prescribed dose = $Q_s + Q_{net}$

Delivered dose = $Q_{ef} = (Q_s + Q_{net}) \times (FUN/BUN)$

CVVHD

Prescribed dose = $Q_d + Q_{net}$

Delivered dose = $Q_{ef} = (Q_d + Q_{net}) \times (FUN/BUN)$

CVVHDF

Prescribed dose = $Q_s + Q_d + Q_{net}$

Delivered dose = $Q_{ef} = (Q_s + Q_d + Q_{net}) \times (FUN/BUN)$

Correcting for predilution effect

Delivered dose = $Q_{net} \times \{[Q_{bw} / (Q_{bw} + Q_s)] + Q_d \times [Q_{bw} / (Q_{bw} + Q_s)]\} \times S$

Dialysis clearance

K_d (mL/min) = [EUN (mg/mL)$\times Q_{ef}$] / prefilter BUN (mg/mL)

Blood Side

Urea clearance

$K_B = Q_b \times (BUN_i\ [mg/dL] - BUN_f\ [mg/dL]) / BUN_i\ [mg/dL]$

Normalized clearances

CVVH, CVVHD, and CVVHDF postfilter dilution

StdKt/V= $Q_{ef} \times [10.080/(W \times 0.55)] \times S$

CVVH and CVVHDF prefilter dilution

StdKt/V= $Q_{ef} \times [Q_{bw} / (Q_{bw} + Q_s)] \times [10.080 / (W \times 0.55)] \times S$

Equivalent renal urea clearance

EKR = $G - \{[(V_t \times BUN_t) - (V_0 \times BUN_0)] / T\} / TAC_{BUN}$

where TAC_{BUN} = [(preBUN + postBUN) × t] + [(postBUN + postBUN) × 60] + {(pre2BUN × θ) / [2 × (t+60+θ)]}

Abbreviations and definitions: BUN, blood urea nitrogen concentration; BUN_f, outflow BUN concentration; BUN_i, inflow BUN concentration; preBUN, pre-treatment BUN; postBUN, post-treatment BUN; pre2BUN, pre-treatment BUN of the next treatment; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; EUN, amount of urea nitrogen removed (mL/min); FUN, effluent fluid urea nitrogen; G, net urea generation rate (in mg/min); Q_{bw}, plasma flow rate, calculated as $Q_b \times (1 -$ hematocrit), eg, when hematocrit is 0.3 and Q_b is 100 mL/min, the Q_{bw} = 70 mL/min; Q_d, dialysate flow rate; Q_{ef}, effluent flow rate (mL/min); Q_{net}, net ultrafiltration rate; Q_s, substitution fluid rate; Q_{uf}, ultrafiltration rate; S, sieving coefficient; StdKt/V, standard Kt/V; TAC_{BUN}, time-averaged BUN concentration (mg/mL); UF, ultrafiltration; V, urea volume of distribution; subscripts 0 and t refer to values at time 0 and t, T is the duration between 0 and t; W, body weight.

dose cannot be underestimated. We believe that the relationship between RRT dose and survival is affected by the overall severity of disease. In severely ill patients, for whom a higher metabolic and fluid removal demand is imposed, adequate doses will affect patient outcome and possibly recovery of kidney function. However, in patients at the extremes of illness severity, too low or too high, CRRT dose will not affect overall survival. High doses may not be beneficial, and can be potentially harmful, as they will increase the clearance of essential elements and antibiotics. Thus, monitoring of dose is fundamental in critically ill patients.

Fluid Balance

Besides small-solute clearance, other aspects of adequacy should be considered (volume control, acid-base, nutritional status, etc) in order to find an ideal dose of dialysis during AKI. Fluid removal is an important and often the major goal of renal replacement for AKI. Fluid overload has been implicated as an independent factor associated with nonrecovery of kidney function and mortality in children and adults with AKI. Although the interpretation of studies assessing the relationship between fluid overload and mortality is difficult because sicker patients may receive more fluids and more severe AKI is often oliguric, several studies have implicated fluid overload as more than a marker of severity and as a cause of increased mortality. In this context, CRRT should be considered for patients not achieving adequate fluid balance in IHD techniques (Box 2). As discussed, CRRT should be used to achieve fluid balance by adjusting the operational parameters within each modality.

Drug Dosing

Removal of drugs by CRRT in critically ill patients is complex, involving factors affecting the patient, drug characteristics, and CRRT procedure. In critically ill patients with AKI, pharmacokinetic parameters are variable and less predictable than in non-AKI and non–critically ill patients. Volume of distribution, drug metabolism, and drug elimination are frequently affected by volume overload, decreased protein binding, and organ blood flow distribution, among others.

The elimination by CRRT imposes more complexity because several therapy-related factors affect drug clearance: dialyzer type, CRRT mode, and prescription flow rates. As a result, the frequent variation on CRRT use makes generalized dosing recommendations impractical; however, some general rules apply. The larger the volume of distribution of lipid-soluble drugs, reduce the amount removed during CRRT. Drugs with limited protein binding are removed by CRRT more efficiently. Convective therapies, CVVH and CVVHDF, are expected to have higher removal of solutes with large molecular weights. The proportion of drug removal by CRRT is associated with filter pore size and is represented by the sieving coefficient of the drug. The sieving coefficient of a drug is highest during the first hours of filter use and progressively declines as protein builds up a layer on the membrane and decreases the number of unclotted fibers. Prefilter substitution fluid dilutes the blood reaching the

Table 4. Proposed Parameters for Delivered Dose Assessment

Parameter	Measurement	Tools
Solute		
Very small waste products	K^+, Na^+, HPO_4^-	Blood levels of K^+; phosphate clearance; pH, bicarbonate, AG, SID, SIG, Δgap
Small waste products	Urea	Clearance (mL/min); EKR (mL/min); StdKt/V
Middle-sized molecules	Serum β_2-microglobulin	β_2-microglobulin clearance
Fluid	Weight; input-outputs; BIA; BNP	Weight changes; fluid accumulation; fluid overload; BIVA; BNP profile

Abbreviations: AG, anion gap; BIA, bioelectrical impedance analysis; BIVA, bioelectrical impedance vector analysis; BNP, brain natriuretic peptide; EKR, equivalent renal urea clearance; SID, strong ion difference; SIG, strong ion gap; StdKt/V, standard Kt/V.

hemodialyzer and reduces drug clearance. Increased Q_b or Q_d can increase drug clearance. Drug adsorption to the filter is an additional issue, especially with polyacrylonitrile filters, with the extent of adsorption being difficult to quantify. For drugs expected to be significantly removed by CRRT, extra doses are required to prevent underdosing, and when available, therapeutic drug monitoring should be used to guide drug dosing in CRRT.

In septic patients, we need to consider that the altered volume of distribution increases drug half-life and affects the protein-binding capacity of many antimicrobials. The variability in body size and fluid composition often determines delayed achievement of antibiotic pharmacodynamic targets and results in potentially subtherapeutic antibiotic concentrations at the infection site. Considering the challenges of predicting drug elimination by CRRT, the benefits of cautious antibiotic dosing to avoid antibiotic toxicity should be individually evaluated against the benefits of adequate antibiotic concentrations in these patients.

Nutritional Support

CRRT techniques allow for an unrestricted volume of nutritional support. However, it may also determine losses of nutrients that are water soluble and have low molecular weight. The estimated loss of amino acid in patients on CRRT is 10 to 20 g/d, depending on ultrafiltration volume. Water-soluble vitamins, micronutrients, and trace elements are also lost during CRRT and should be replaced during prolonged therapy. The KDIGO guideline recommends up to 1.7 g/kg/d of protein in patients receiving CRRT (*2D*). Carbohydrates should be given at 5 to 7 g/kg/d, and lipids, at 1.2 to 1.5 g/kg/d.

CRRT offers an opportunity to measure catabolic rates when steady state is achieved because effluent solute nitrogen concentrations represent urea nitrogen generation and the associated protein breakdown as urea nitrogen is 16% of protein content. In patients with AKI receiving CRRT, normalized protein catabolic rate is known to be 1.4 to 1.8 g/kg/d.

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CRRT APPLICATIONS

CRRT in Sepsis and Multisystem Organ Failure

Patients with multiple organ dysfunction syndrome frequently develop AKI and are more likely to receive CRRT when renal support is indicated. In these patients, in addition to providing more time to achieve fluid balance and metabolic homeostasis, CRRT has been used with the concept of modulator of the immune response. The effects of CRRT on modulating levels of inflammatory mediators have been studied for 2 decades. Different techniques have been developed; high-volume hemofiltration (HVHF), high-adsorption hemofiltration, high-cutoff membranes, and hybrid systems such as coupled plasma filtration absorbance. Experimental and small clinical studies of humans have suggested that HVHF might improve hemodynamic profile and mortality, but larger trials did not confirm this effect. In the IVOIRE (High Volume Hemofiltration for Sepsis with AKI) trial, HVHF at 70 mL/kg/h showed no benefit on mortality, early improvements in hemodynamic profile, or organ function as compared to contemporary standard-volume hemofiltration at 35 mL/kg/h. In a recent

systematic review and meta-analysis, there was no difference in 28-day mortality or kidney function recovery, lengths of ICU and hospital stays, vasopressor dose decreases, and adverse events using HVHF for septic AKI. Pilot trials in septic patients using high-permeability hemofilters with increased pore size, which aids the filtration of inflammatory mediators, have demonstrated positive immunomodulation, altering neutrophil phagocytosis and mononuclear cell function ex vivo. More studies are needed to confirm these effects.

CRRT in Heart Failure

Although diuretics are the mainstay of therapy for acute decompensated heart failure (ADHF), improved understandings of the pathophysiology of decreased kidney function in the context of ADHF and the limitations of conventional therapy have led clinicians to use different forms of extracorporeal therapy. Intermittent isolated ultrafiltration, SCUF, and CVVH have been used as extracorporeal therapy to treat ADHF. In isolated ultrafiltration and SCUF, the extracorporeal blood circuit is adapted for isotonic fluid removal by a pressure gradient. In CVVH, the substitution fluid allows for correction of metabolic acidosis and electrolyte disturbances. In addition, recent evidence suggests that myocardial depressant factors such as IL-8 and anti–monocyte chemoattractant protein 1, which is effectively removed by hemofiltration, may have adverse effects on cardiac function. Four randomized trials (Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized With Acute Decompensated Congestive Heart Failure [UNLOAD], Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure [RAPID-CHF], Cardiorenal Rescue Study in Acute Decompensated Heart Failure [CARESS-HF], and Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure [AVOID-UF]) compared ultrafiltration with diuretic therapy in patients with ADHF. The RAPID-CHF trial showed that early use of ultrafiltration in patients with congestive heart failure resulted in significant weight loss and fluid removal and was well tolerated. In the UNLOAD study, safety and efficacy of SCUF as an alternative therapy was confirmed: ultrafiltration led to greater weight and fluid loss than intravenous diuretics and reduced the overall use of heart failure resources at 90 days. The CARRESS-HF trial compared ultrafiltration to stepped pharmacologic therapy (bolus, high doses of continuous infusion loop diuretics, addition of thiazide diuretic, and intravenous inotrope and/or vasodilator). In the study, weight loss was the same in the 2 groups; however, ultrafiltration therapy was associated with a higher rate of adverse events and higher increments in serum creatinine levels. The most recent AVOID-HF trial showed a trend toward a longer time to a new event of heart failure decompensation, with significantly fewer patients being rehospitalized for heart failure or cardiovascular causes at 30 days in the ultrafiltration group. The results suggest no negative impact on kidney function with excess fluid removed with adjustable ultrafiltration. A number of questions and concerns are still unresolved, including the need for anticoagulation, complications related to extracorporeal circuit, and the effect of ultrafiltration on kidney function and long-term outcomes. Given the high cost, complexity of ultrafiltration, and available evidence from these randomized controlled trials, ultrafiltration cannot be adopted as a first-line therapy for AHDF.

CRRT in Acute Brain Injury

In patients with acute brain injury, AKI is a frequent complication, occurring in 8% to 23% of patients and recognized as an independent predictor of poor outcome. In patients with acute brain injury, RRT presents a major problem because conventional IHD may exacerbate the reduction in cerebral perfusion and increase cerebral edema. Rapid urea removal from the plasma and water shift to the intracellular compartment can worsen brain edema. The phenomenon is known as dialysis disequilibrium syndrome. Mechanisms associated with this syndrome have been linked to the identification of different urea transporters in the brain of rats with chronic uremia. Reduced intensity of dialysis leads to slower urea removal and increases the time for osmotic gradient adjustment in the brain.

The goal in patients with acute brain injury and increased intracranial pressure (ICP) is to maintain cerebral perfusion pressure (CPP) > 60 mm Hg. Thus, MAP has to be maintained in order to preserve CPP (CPP = MAP − ICP). In IHD, intradialytic hypotension can cause a decrease in MAP and CPP and increase ICP by compensatory cerebral vasodilation. This may result in infarction or secondary injury. In these patients, IHD should be avoided because it is associated with a more significant increase in ICP compared to CRRT. Using computed tomography to measure brain density, brain water content has been shown to be increased after IHD, whereas no changes were observed after CRRT. In addition, CRRT can also be used to maintain hypernatremia and thereby reduce brain swelling. This can be adjusted as described next. The KDIGO AKI guideline, in recommendation 5.6.3, suggests "CRRT, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (*2B*)"

Correction of Severe Electrolyte Abnormalities

Patients with AKI who have severe electrolyte abnormalities often need RRT. IHD is the usual treatment of choice, but certain abnormalities are best corrected slowly to prevent neurologic sequelae.

Hyponatremia and Hypernatremia

Hypo- and hypernatremia can be managed with CRRT by adjusting the composition of the substitution fluids and dialysate. A key advantage with CRRT is that plasma sodium concentration can be manipulated to safely achieve and maintain any specific range of sodium levels. A fundamental principle is that the correction of sodium should not be >8 mEq/L in 24 hours (Box 3).

Hypokalemia and Hyperkalemia

If a hyperkalemic patient cannot tolerate IHD or the hyperkalemia is not life-threatening, CRRT is an option. Increasing the volume of substitution or dialysate solution (to increase effluent volume and hence clearance) and using solution with zero or low (2 mEq/L) potassium concentration can rapidly decrease serum potassium levels. In order to prevent hypokalemia during CRRT, substitution fluid and/or dialysate should contain 3 to 4 mEq/L of potassium. Correction of hypokalemia can be performed with potassium infusion. Serum potassium levels should be monitored every 2 to 4 hours, especially if zero potassium solutions are used, and should continue after CRRT is discontinued.

Removal of Poisons and Myoglobin

Continuous hemofiltration can be used to enhance elimination of toxins that have a large volume of distribution, tight tissue binding, or slow intercompartmental transfer. However, highly protein-bound drugs are not removed effectively with the technique. Although molecules as large as 20,000 to 40,000 Da can be cleared through CRRT membranes, in contrast to IHD or hemoperfusion, the CRRT clearance rate is lower, which often causes IHD to be the treatment of choice.

Lithium is a mood stabilizer with low molecular weight (<7 Da) that is not protein bound and has a volume of distribution of 0.6 to 0.9 L/kg. The preferred method of treatment is IHD because clearance can reach 170 mL/min. Although CRRT clearance is much slower (48-62 mL/min with CVVHDF), lithium equilibrates slowly between the extracellular and intracellular fluids and a rebound increase in serum lithium levels often occurs after cessation of IHD. In cases of severe intoxication, the use of CRRT can minimize rebound and be useful in hemodynamically unstable patients who cannot tolerate hemodialysis.

Using CRRT with super-high-flux dialyzers may be effective for myoglobin removal and could be an intervention to prevent rhabdomyolysis-induced AKI. However, there is insufficient evidence to define whether CRRT offers benefit over conventional therapy for patients with rhabdomyolysis or for prevention of rhabdomyolysis-induced AKI.

Box 3. Adjustment of Rate Substitution Fluid for Correction of Hyponatremia and Hypernatremia

Hyponatremia

In an example discussed by Dangoisse et al, an approach for correcting serum [Na^+] involves adding SW to 5-L bags of preprepared substitution/dialysis fluid with [Na^+] of 140 mEq/L. For example, in a patient with a serum [Na^+] of 110 mEq/L, decrease [Na^+] by adding 1,000 mL of SW to the substitution fluid to reach an [Na^+] of 117 mEq/L. When the patient's serum [Na^+] has equilibrated to 117 mEq/L, [Na^+] in the substitution fluid can be adjusted to 122 mEq/L.

Alternatively, consider a parallel infusion of D_5W, as discussed by Claure and Bouchard. If the goal [Na^+] is 121 mEq/L, the [Na^+] of the replacement fluid is 140 mEq/L, the [Na^+] of the D_5W (peripheral) is 0 mEq/L, and the desired clearance is 2.5 L/h, then:

$$D_5W \text{ infusion rate} = (\text{goal } [Na^+] / 140) \times \text{desired clearance} = [(140 - 121) / 140] \times 2.5 \text{ L/h} = 340 \text{ mL/h}$$

Hypernatremia

Consider adding 30% NaCl to 5-L bags of preprepared dialysis/substitution fluid containing [Na^+] of 140 mmol/L to correct serum [Na^+] in a patient with hypernatremia. A worked-out example is provided by Dangoisse et al: in a patient with a serum [Na^+] of 163 mEq/L, add 15 mL of 30% NaCl to the substitution fluid to reach an [Na^+] of 155 mEq/L. When the patient's serum [Na^+] has equilibrated to 155 mEq/L, the [Na^+] of the substitution fluid can be adjusted to 150 mmol/L.

Alternatively, consider a parallel infusion of 3% NaCl, as discussed by Claure and Bouchard. If the goal [Na^+] is 160 mEq/L, the [Na^+] of the replacement fluid is 140 mEq/L, the [Na^+] of the 3% NaCl (peripheral) is 513 mEq/L, and the desired clearance is 2.5 L/h, then:

$$3\% \text{ NaCl infusion rate} = [(\text{goal } [Na^+] - 140) / 513] \times \text{desired clearance} = [(160 - 140) / 513] \times 2.5 \text{ L/h} = 0.10 \text{ L/h}$$

$$\text{Replacement fluid rate} = \text{desired clearance} - 3\% \text{ NaCl rate} = 2.5 \text{ L/h} - 0.10 \text{ L/h} = 2.4 \text{ L/h}$$

Note: Based on information in Dangoisse et al (*Nephron Clin Pract.* 2014;128:394-398) and Claure and Bouchard (*Blood Purif.* 2012;34:186-193).

Abbreviations: D_5W: 5% dextrose in water; [Na^+], sodium ion concentration; NaCl, sodium chloride; SW, sterile water.

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COMPLICATIONS AND OUTCOMES FROM CRRT

The most common complications of CRRT are electrolyte imbalances, hypotension, infection, bleeding, and hypothermia. Despite the lower Q_{net} ultrafiltration rate in CRRT, hemodynamically unstable patients may not tolerate the rate of fluid removal necessary to achieve a desired fluid balance.

Hypotension occurs when the hourly Q_{net} exceeds the intradialytic refilling capacity for the patient situation. In patients with compromised refilling capacity, as in diabetic neuropathy, low cardiac ejection fraction, diastolic dysfunction, and sepsis, increased fluid removal is the major risk factor for hypotension. Episodes of hypotension may contribute to delayed kidney recovery. In the presence of ischemia, the vasculature of normal kidneys responds with vasodilation as part of the autoregulatory response to maintain renal blood flow and glomerular filtration rate. In acute tubular necrosis, autoregulation is impaired; as a result, recurrent ischemic tubular injury is more likely to occur, thereby delaying the restoration of function.

Patients receiving CRRT present an increased risk for hypothermia as blood circulates in the extracorporeal circulation for a prolonged time. CRRT-induced hypothermia may mask the presence of fever, and body temperature is thus an unreliable marker of inflammation and infection. Blood warmers should be used in the circuit. However, it is not clear whether induced hypothermia is harmful or beneficial (eg, reduced oxygen consumption, hemodynamic stability, and cerebral protection).

Electrolytes and Acid-Base Disturbances

The frequency of electrolyte imbalance, hypocalcemia, hypophosphatemia, and hypokalemia can be high and increases with higher dose of therapy. In the RENAL trial, hypophosphatemia was the most common electrolyte imbalance, occurring in 65% of patients in the high-intensity CRRT group. Phosphate clearance is significantly high due to larger filter pore size and ongoing intercompartmental mass transfer. Hypophosphatemia can lead to decreases in cardiac output and blood pressure, rhabdomyolysis, respiratory muscle weakness, and granulocyte dysfunction with greater infection rates. Several methods are used to manage hypophosphatemia, including enteral feed with high phosphorus concentrations and intravenous supplementation with sodium phosphate. Phoxillum Renal Replacement Solutions (BK4/2.5 and B22K4/0; Baxter) are substitution solutions for CRRT that include phosphate in a 5-L bag and have just been introduced in the United States.

Hypomagnesemia is another common complication of prolonged CRRT use. Most commercially available solutions have magnesium, but do not contain phosphate. Additional magnesium may need to be added to the dialysate or substitution fluid to maintain balance.

In addition, sodium and acid-base disturbances can occur during CRRT and should be monitored every 6 to 8 hours. Correction of hyperkalemia, hyponatremia, and hypernatremia are commonly required.

The use of 4% trisodium citrate for circuit anticoagulation can lead to excessive sodium load and hypernatremia. As citrate is metabolized to bicarbonate, there may be metabolic alkalosis during or after prolonged treatment. In contrast, metabolic acidosis can develop in patients not able to metabolize the citrate received during therapy; for example, patients with liver failure or poor peripheral perfusion. In septic patients with high lactate levels, citrate tolerability increases as perfusion improves. Citrate accumulation can be identified early by the pattern of arterial blood gases and ionized and total calcium levels at 6-hour intervals.

Patient Outcomes

Despite the discussed advantages of CRRT, several randomized controlled trials failed to show better patient outcomes with CRRT as compared to IHD. The wide variability and standards for CRRT use and the exclusion of more severely ill patients may have influenced the results of these trials. However, long-term effects of RRT modality on the odds of kidney recovery are another important

issue. The RENAL and ATN randomized controlled trials, which were designed to evaluate the effect of dose on outcomes, provided insights into the impact of RRT on kidney recovery. However, differences between these 2 trials provide data to argue that there may be an effect of RRT modality on kidney recovery. In the RENAL Study, all 1,508 patients meeting the inclusion criteria received CVVHDF. In the ATN Study, of 1,124 patients, those with cardiovascular stability were allocated to receive IHD, and those with cardiovascular instability, CVVHDF. The RRT dependence rate at day 28 among survivors in RENAL was 13.3%, as compared to 45.2% in the ATN Study. At day 60, there were 24.6% of survivors still RRT dependent in the ATN Study, as compared to 5.6% being RRT dependent at day 90 in RENAL. The higher rate of hypotension (37% of IHD sessions) in the ATN Study could explain the association of delayed kidney recovery with IHD.

A systematic review and meta-analysis on dialysis dependence among critically ill survivors of an episode of AKI that required acute RRT identified 7 randomized controlled trials and 16 observational studies. Compared to CRRT, intermittent RRT was associated with 1.7 times increased risk for dialysis dependence. This increased risk was present even when subgroups were analyzed (randomized controlled trials and observational studies pooled separately); however, the increased risk was not statistically significant among randomized controlled trials. In a retrospective cohort study with 1:1 matching of CRRT and intermittent RRT patients with AKI in the ICU, Wald et al followed up those who survived past 90 days after RRT initiation for a median duration of 3 years. Long-term dialysis risk was lower in patients who were given CRRT versus intermittent RRT (hazard ratio, 0.75; 95% confidence interval, 0.65-0.87). Other recent studies from observational cohorts have shown contradictory results and no difference in kidney recovery among patients who underwent IHD as compared to CRRT.

We believe that CRRT and intermittent RRT should be viewed as complementary therapies in patients with AKI. Because transitions between therapies reflect patient progression in the disease course, all the therapies should be considered as part of the nephrologists' armamentarium and used to support patients through their course. One key element in the choice of renal substitution is the tailoring of therapy to the patient. Constant assessment of the patient's metabolic and hemodynamic status and adjustment of the therapy based on clinical criteria are essential for providing the best management of AKI. Issues to consider are as follows: familiarity and comfort of personnel with the technique (ie, centers without practice in continuous techniques may have a higher incidence of iatrogenic complications), complexity of the patient and dose of vasoactive drugs, ultrafiltration necessary to achieve fluid balance, location in the hospital, and need for mobilization and physiotherapy.

Resource Utilization and Costs

Costs for CRRT are usually higher than for intermittent RRT, even when intermittent RRT is used more intensively (such as daily IHD). However, cost analysis for AKI should consider in-hospital ICU costs and costs related to nonrecovery and long-term dialysis dependence. In a study performed to evaluate the cost-effectiveness of intermittent RRT and CRRT in ICU patients with AKI, CRRT had higher direct costs, but the total cost over 5 years (including long-term dialysis dependence costs) was lower with CRRT.

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