INTRODUCTION

Despite recent advances in acute kidney injury (AKI) definition, diagnosis, and treatment, many aspects remain subject to controversy. Renal replacement therapies (RRTs) currently remain the most important part of AKI treatment and, although modern technology has made a vast pool of different strategies of extracorporeal renal support easily available, it is still not clear which one is superior to the others in terms of efficacy and outcome. Moreover, evidence-based medicine has not yet defined the best time to prescribe RRT and when and how patients should be weaned from this therapy. This chapter will review most of these aspects, and will provide some theoretical and practical bases for RRT prescription with the goal of helping intensive care unit (ICU) clinicians to understand critical care nephrology.

Acute Kidney Injury and the Critically Ill Patient

A consensus document from the Kidney Disease Improving Global Outcome (KDIGO) Workgroup (1) pointed out all aspects related to AKI definition, diagnosis, and treatment. AKI is now defined and classified according to KDIGO classification: it identifies three different AKI severity levels that should allow the clinicians to uniformly identify and eventually treat this deadly syndrome (Table 133.1). This document also clearly specifies all the supportive measures that can be adopted in case of AKI but also, for the first time, tries to associate AKI staging with a progressively increasing treatment effort: according to these authors, RRT should be at least considered when AKI severity reaches the KDIGO stage II. Before this classification was available, a milestone multinational observational study on about 30,000 critically ill patients that found that, worldwide, AKI incidence is around 6% and that 75% of these underwent a dialytic treatment (2) with an overall mortality of 60.3%. What significantly changed since the publication of that paper is the clinician’s capacity to identify AKI according to the new standard approach that was available in their routine practice all theoretical and technical aspects of RRT prescription, with the goal of helping intensive care unit (ICU) clinicians to understand critical care nephrology.

Indications for Initiation and Cessation

When to Start

Whether and when to start RRT are among the top priorities and most debated issues in the field of severe AKI, and there is no consensus between nephrologists and intensivists. RRT has the following targets when applied in patients with AKI: (1) to optimize fluid balance; (2) to guarantee electrolyte, acid–base, and solute homeostasis; (3) to prevent further injuries to the kidney; (4) to potentially “unload” the injured kidney thus facilitating renal recovery. Current indications for urgent/emergency RRT in clinical practice are well defined: fluid overload, hyperazotemia, hyperkalemia, severe acidosis, and intoxication (Table 133.2) (1). On the other hand, in the absence of these unquestioned indications, there is a global tendency to delay RRT in order to limit potential complications related to the extracorporeal application: biocompatibility, anticoagulation, vascular access, loss of beneficial molecules. Outside the urgent/emergency conditions listed above, a decision for RRT initiation cannot be based solely on azotemia (serum creatinine and/or urea) and a global evaluation including the clinical
context and the trend of laboratory tests, rather than single values, are recommended when deciding whether to start RRT (1). In light of this, the severity of the underlying disease and organ dysfunction—that may affect the recovery of kidney function and tolerance of fluid accumulation—the occurrence of solute burden such as rhabdomyolysis, and the need for nutrition or drug therapies, should be considered. In addition, when medical management—diuretics, bicarbonate, glucose–insulin solutions, beta2-agonists, fluid and nutritional restriction—fails to prevent or treat renal dysfunction, treatment is usually escalated to RRT. Further, there is some interest in the role of biomarkers—neutrophil gelatinase–associated lipocalin, NGAL—as potential predictors of RRT requirement (7).

The timing between initiation of extracorporeal therapy and ICU admission is another issue that should be taken into account for classification purposes of early and late RRTs. Data available from the BEST kidney registry (8) reveal that, when timing was analyzed in relation to ICU admission, “late” RRT was associated with greater crude mortality, covariate-adjusted mortality, RRT requirement, and hospital length of stay (8). Although several studies have suggested a possible positive role of early RRT among AKI patients, contrasting results are available in literature. In 2002, Bouman et al. (9) showed no differences for ICU or hospital mortalities and for renal recovery among patients treated with an early or late RRT. However, if cumulatively considered in systematic review or meta-analysis, by parameters utilized to define the onset, an early initiation of RRT seems to be associated to an improved outcome (10). In a recent meta-analysis, including 15 unique studies published through 2010, comparing early and late initiation of renal support, Karvellas et al. have calculated an odds ratio for 28-day mortality of 0.45 associated with an early RRT (10). Similar results were obtained by Wang and colleagues (11) in a 2012 meta-analysis encompassing data from 2,955 patients; the results of this study have clearly demonstrated that an early initiation of both continuous and intermittent RRT may reduce the mortality of patients with AKI compared with late treatments.

**When to Stop**

Once RRT has been started, timing for stopping is another field of uncertainty as the literature is scarce. Bedside evaluation of weaning RRT implies two fundamental clinical data elements: the state of renal function, and recovery from the morbidity that initially led to RRT. Current guidelines suggest discontinuing RRT when kidney function has recovered and is able to meet patient needs or, globally “is no longer consistent with the goals of care” (1). Many, but not all, patients receiving RRT will recover renal function, so daily evaluation of the appropriateness of treatment is necessary to identify weaning opportunities, including a modality transition—e.g., from continuous to intermittent—or to decide to withdraw treatment for futility (12–13). The assessment of kidney function during RRT is a complex issue and clear recommendations are not available. From a practical clinical point of view, diuresis seems to be the most efficient predictor of RRT weaning success. A large prospective observational study, encompassing 529 patients, showed that urine output was the most significant predictor of successful termination of RRT (14). It is important to underline that, while diuretics increase urine output even in AKI patients, current guidelines suggest “not using diuretics to enhance kidney function recovery, or to reduce the duration or frequency of RRT” (1). In fact, diuretics increase urine output but do not seem to positively influence renal function.

**Unanswered Research Topics**

A number of issues remain unaddressed, warranting future research. The KDIGO guidelines recommend studies to establish reproducible criteria capable of suggesting optimal timing for initiation of RRT in AKI patients (1). Timing—early versus

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### TABLE 133.1 KDIGO Classification of Acute Kidney Injury

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine</th>
<th>Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥0.3 mg/dL (≥26.5 µmol/L) increase or 1.5–1.9× baseline</td>
<td>&lt;0.5 mL/kg/hr for 6–12 h</td>
</tr>
<tr>
<td>2</td>
<td>2.0–2.9× baseline</td>
<td>&lt;0.5 mL/kg/hr for ≥12 h</td>
</tr>
<tr>
<td>3</td>
<td>≥4.0 mg/dL (≥353.6 µmol/L) or ≥3.0× baseline or more or Initiation of RRT or In pediatric patients, decrease in eGFR to &lt;50 mL/min/1.73 m² Anuria for ≥12 h</td>
<td></td>
</tr>
</tbody>
</table>

*Timeframe for serum creatinine increase: either 0.3 mg/dL within 48 hr or 1.5× increase within a wk.

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### TABLE 133.2 Indications for Renal Replacement Therapy

<table>
<thead>
<tr>
<th>General</th>
<th>Renal replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening indications</td>
<td>Nonemergent indications</td>
</tr>
<tr>
<td>Renal support</td>
<td>Specific pediatric indications</td>
</tr>
</tbody>
</table>

**Specific**

- Little or no residual kidney function
- Hyperkalemia/severe acidemia
- Pulmonary edema, uremic complications
- Solute control (hyperkalemia, hypercreatininemia), fluid removal, correction of acid-base abnormalities
- Volume control, nutrition, drug delivery
- Regulation of acid-base and electrolyte status
- Solute modulation, sepsis syndrome
- Inborn error of metabolism

**According to the KDIGO Workgroup, no standard evidence-based criteria for initiating dialysis currently exist in either pediatric or adult patients.**

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late initiation and criteria for weaning—should be correlated with outcome measures, taking into consideration all the variables: dose, modality, materials, and anticoagulation.

**CONTINUOUS, INTERMITTENT, DIFFUSIVE, CONVECTIVE: AN ONGOING MATTER**

**Definitions**

Renal replacement consists of the purification of blood by semi-permeable membranes; a wide range of molecules—from water to urea to low-, middle-, and high–molecular-weight solutes—are transported across such membranes by the mechanism of ultrafiltration (water), convection, and diffusion (solutes) (Fig. 133.1).

During **diffusion**, movement of solute depends upon their tendency to reach the same concentration on each side of the membrane; the practical result is the passage of solutes from the compartment with the highest concentration to the compartment with the lowest. Other components of the semi-permeable membrane deeply affect diffusion: thickness and surface, temperature, and diffusion coefficient. **Dialysis** is a modality of RRT and is predominantly based on the principle of diffusion: a dialytic solution flows through the filter in a manner counter (countercurrent) to blood flow in order to maintain the highest solute gradient from inlet to outlet port.

During **convection**, the movement of solute across a semi-permeable membrane takes place in conjunction with significant amounts of **ultrafiltration** (water transfer across the membrane). In other words, as the solvent (plasma water) is pushed across the membrane in response to the transmembrane pressure (TMP) by ultrafiltration (UF), solutes are carried with it, as long as the porosity of the membrane allows the molecules to be sieved from blood. The process of UF is governed by the UF rate (Qf), the membrane UF coefficient (Km), and the TMP gradient generated by the pressures on both sides of the membrane (see the legend of Fig. 133.1).

The hydrostatic pressure in the blood compartment is dependent on blood flow (Qb). The greater the Qb, the greater the TMP. In modern RRT machines, UF control throughout the filter is obtained by the use of a pump, which generates suction to the UF side of the membrane. Modern systems are optimally designed in order to maintain a constant Qb; it is worth noting that, when the filter is “fresh,” the initial effect of the UF pump is to retard UF production, generating a positive pressure on the UF side. Thus, TMP is initially dependent only on Qb. As the membrane fibers foul, a negative pressure is necessary to achieve a constant Qb. In this case, a progressive increase of TMP can be observed up to a maximal level in which clotting is likely, membrane rupture may occur and, above all, solute clearance may be significantly compromised. In fact, if it is true that the size of molecules cleared during convection exceeds that during diffusion, because they are physically dragged to the UF side, it is also true that this feature is seriously limited by the protein layer that progressively closes filter pores during convective treatments (15). A peculiar membrane capacity, termed adsorption, has been shown to have a major role in higher–molecular-weight toxins (16); however, membrane adsorptive capacity is generally saturated in the first hours from the beginning of the treatment. This observation notes the scarce impact of the adsorption component on solute clearance and suggests relying only on the effects of mass separation processes such as diffusion and convection (17). As UF proceeds, and plasma water and solutes are filtered from blood, hydrostatic pressure within the filter is lost, and oncotic pressure is gained because blood concentrates and hematocrit increase. The fraction of plasma water that is removed from blood during UF is called filtration fraction; it should be kept in the range of 20% to 25% to prevent excessive hemococoncentration within the filtering membrane and to avoid the critical point where oncotic pressure is equal to TMP and a condition of filtration/pressure equilibrium is reached. Finally, replacing plasma water with a substitute solution completes the **hemofiltration** (HF) process and returns purified blood to the patient. The replacement fluid can be administered after the filter, a process called postdilution HF. Otherwise, the solution can be infused before the filter in order to obtain predilution HF, whereas predilution plus postdilution replacement is obtained on mixed infusion of substitution fluids both before and after filtering the membrane. While postdilution allows a urea clearance equivalent to therapy delivery (i.e., 2,000 mL/hr; see below) predilution, despite a theoretical reduced solute clearances, prolongs the circuit lifespan, and reduces hemo-concentration and protein-caking effects occurring within filter fibers. Conventional HF is performed with a highly permeable, steam-sterilized membrane with a surface area of about 1 m², and with a cutoff point of 30 kd (Fig. 133.2).

**Concept of RRT Dose**

The conventional view of RRT dose is that it is a measure of the quantity of blood purification achieved by means of extracorporeal techniques. As this broad concept is too difficult to measure and quantify, the **operative** view of RRT dose is that it is a measure of the quantity of a representative marker solute that is removed from a patient. This marker solute is considered to

![Figure 133.1](image-url)
be reasonably representative of similar solutes, which require removal for blood purification to be considered adequate. This premise has several major flaws: the marker solute cannot and does not represent all the solutes that accumulate in renal failure; its kinetics and volume of distribution are also different from such solutes; finally, its removal during RRT is not representative of the removal of other solutes. This is true both for end-stage renal failure and acute renal failure. However, a significant body of data in the end-stage renal failure literature (18–23) suggests that, despite all of the above major limitations, a single-solute marker assessment of dialysis dose appears to have a clinically meaningful relationship with patient outcome and, therefore, clinical utility. Nevertheless, the HEMO study, examining the effect of intermittent hemodialysis (IHD) doses, enforced the concept that “less dialysis is worse,” but failed to confirm the intuition that “more dialysis is better” (23). Thus, if this premise seems useful in end-stage renal failure, it is accepted to be potentially useful in AKI for operative purposes. Hence, the amount (measure) of delivered dose of RRT can be described by various terms: efficiency, intensity, frequency, and clinical efficacy; each will be discussed below.

The efficiency of RRT is represented by the concept of clearance (K), i.e., the volume of blood cleared of a given solute over a given time. K does not reflect the overall solute removal rate (mass transfer) but, rather, its value normalized by the serum concentration. Even when K remains stable over time, the removal rate will vary if the blood levels of the reference molecule change. K depends on solute molecular size and transport modality—diffusion or convection—as well as circuit operational characteristics—blood flow rate (Qb), dialysate flow rate (Qd), ultrafiltration rate (Qf), hemodialyzer type, and size. K can normally be used to compare the treatment dose during each dialysis session, but it cannot be employed as an absolute dose measure to compare treatments with different time schedules. For example, K is typically higher in IHD than in continuous renal replacement therapy (CRRT) and sustained low-efficiency daily dialysis (SLEDD). This is not surprising, since K represents only the instantaneous efficiency of the system. However, mass removal may be greater during SLEDD or CRRT. For this reason, the information about the time span during which K is delivered is fundamental to describe the effective dose of dialysis.

The intensity of RRT can be defined by the product “clearance × time” (Kt). Kt is more useful than K in comparing various RRTs. A further step in assessing dose must include frequency of the Kt application over a particular period (e.g., a week). This additional dimension is given by the product of intensity × frequency (Kt × treatment days/week = Kt d/w). Kt d/w is superior to Kt, since it offers information beyond a single treatment—patients with AKI typically require more than one treatment. This concept of Kt d/w offers the possibility to compare disparate treatment schedules—intermittent, alternate-day, daily, continuous. However, it does not take into account the size of the pool of solute that needs to be cleared; this requires the dimension of efficacy.

The efficacy of RRT represents the effective solute removal outcome resulting from the administration of a given treatment to a given patient. It can be described by a fractional clearance of a given solute (K/V), where V is the volume of distribution of the marker molecule in the body, K/V is an established marker of adequacy of dialysis for small solutes correlating with medium-term (several years) survival in chronic hemodialysis patients (23). Urea is typically used as a marker molecule in end-stage kidney disease to guide treatment dose, and a K/VUREA of at least 1.2 is currently recommended. As an example, we can consider the case of a 70-patient who is treated 20 hr/d with a postfilter HF of 2.8 L/hr at a zero balance. The patient’s K/VUREA will be 47 mL/min (2.8 L/hr = 2,800 mL/60 min) because we know that during postfilter HF, ultrafiltered plasmatic water will drain all urea across the membrane, making its clearance identical to UF flow. The treatment time (t) will be 1,200 minutes (60 minutes for 20 hours). The urea volume of distribution will be approximately 42,000 mL (60% of 70 kg, 42 L = 42,000 mL)—that is, roughly equal to total body water. Simplifying our patient’s K/VUREA, we will have 47 × 1,200/42,000 = 1.34.

However, K/VUREA application to patients with AKI has not been rigorously validated. In fact, although the application of K/V to the assessment of dose in AKI is theoretically intriguing, many concerns have been raised because problems intrinsic to AKI can hinder the accuracy and meaning of such dose measurement. These include the lack of a metabolic steady state, uncertainty about the volume of distribution of urea (VUREA), a high-protein catabolic rate, labile fluid volumes, and possible residual renal function, which changes dynamically during the course of treatment. Furthermore, delivery of prescribed dose in AKI can be limited by technical problems such as access recirculation, poor blood flows with temporary venous catheters, membrane clotting, and machine malfunction. Furthermore, clinical issues such as hypotension

![Figure 133.2](image-url)
and vasopressor requirements can be responsible for solute disequilibrium within tissues and organs.

These aspects are particularly evident during IHD, less so during SLEDD, and even less so during CRRT. This difference is due to the fact that, after some days of CRRT, the patients’ urea levels approach a real steady state. Access recirculation is also an issue of lesser impact during low-efficiency continuous therapies. Finally, because the therapy is applied continuously, the effect of compartmentalization of solutes is minimized and, from a theoretical point of view, single-pool kinetics can be applied (spKt/V) with a reasonable chance of approximating true solute behavior. In a prospective study on continuous therapies, the value of clearance predicted by a simple excel software applying formulas for K calculation showed a significant correlation between estimated K and that obtained from direct blood and dialysate determinations during the first 24 treatment hours, irrespective of the continuous renal replacement modality used (24,25).

The major shortcoming of the traditional solute marker–based approach on dialysis dose lies beyond any methodologic critique of single-solute kinetics-based prescriptions: in patients with AKI, the majority of whom are in intensive care, a restrictive (solute-based only) concept of dialysis dose seems grossly inappropriate. In these patients, the therapeutic needs that can be or need to be affected by the “dose” of RRT are more than the simple control of small solutes as represented by urea. They include control of acid–base, toxicity, potassium, magnesium, calcium, phosphate, intravascular volume, extravascular volume, temperature, and the avoidance of unwanted side effects associated with the delivery of solute control. In the critically ill patient, it is much more important (e.g., in the setting of coagulopathic bleeding after cardiac surgery) for 10 units of fresh frozen plasma, 10 units of cyroprecipitate, and 10 units of platelets to be administered rapidly without inducing fluid overload (because 1 to 1.5 L of ultrafiltrate is removed in 1 hour) than for Kt/V to be of any particular value at all. A dose of RRT is about prophylactic volume control. In a patient with right ventricular failure, AKI, ARDS, who is receiving lung-protective ventilation with permissive hypercapnia and with acidemia, inducing a further life-threatening deterioration in pulmonary vascular resistance, the “dose” component of RRT that matters immediately is acid–base control and normalization of pH 24 hours a day. The Kt/V (or any other solute-centric concept of dose) is essentially a byproduct of such dose delivery. In a young man with trauma, rhabdomyolysis, and a rapidly rising serum potassium already at 7 mMol/L, the beginning dialysis dose is all about controlling hyperkalemia. In a patient with fulminant liver failure, AKI, sepsis, and cerebral edema awaiting urgent liver transplantation, and whose cerebral edema is worsening because of fever, RRT dose is centered on lowering the temperature without any toxicity shifts that might increase intracranial pressure. Finally, in a patient with pulmonary edema after an ischemic ventricular septal defect requiring emergency surgery, along with AKI, ischemic hepatitis, and the need for inotropic and intra-aortic balloon counterpulsation support, RRT dose mostly concerns removing fluid gently and safely so that the extravascular volume falls while the intravascular volume remains optimal. Solute removal is just a byproduct of fluid control. These aspects of dose must explicitly be considered when discussing the dose of RRT in AKI, for it is likely that patients die more often from incorrect “dose” delivery of this type than incorrect dose delivery of the Kt/V type. Although each and every aspect of this broader understanding of dose is difficult to measure, clinically relevant assessment of dose in critically ill patients with AKI should include all dimensions of such a dose, and not one dimension picked because of a similarity with end-stage renal failure. There is no evidence in the acute field that such solute control data are more relevant to clinical outcomes than volume control, acid–base control, or toxicity control.

**RRT Prescription**

**Theoretical Aspects**

Despite all the uncertainty surrounding its meaning and the gross shortcomings related to its accuracy in patients with AKI, the idea that there might be an optimal dose of solute removal continues to have a powerful hold in the literature. This is likely due to evidence from ESRD, where a minimum K/V of 1.2 thrice weekly is indicated as standard (23). However, the benefits of greater K/V accrue over years of therapy. In AKI, any difference in dose would apply for days to weeks. The view that it would still be sufficient to alter clinical outcomes remains somewhat optimistic. Nonetheless, the hypothesis that higher doses of dialysis may be beneficial in critically ill patients with AKI must be considered by analogy and investigated. Several reports exist in the literature dealing with this issue. Furthermore, the concept of predefined dose is a powerful tool to guide clinicians to a correct prescription and to, at least, avoid under treatment.

Brause et al. (26), using continuous venovenous hemofiltration (CVVH), found that higher Kt/V values (0.8 vs. 0.53) correlated with improved uremic control and acid–base balance; no clinically important outcome metric was affected. Investigators from the Cleveland clinic (27) retrospectively evaluated 844 patients with AKI requiring CRRT or IHD over a 7-year period. They found that, when patients were stratified for disease severity, dialysis dose did not affect outcome in patients with very high or very low scores, but did correlate with survival in patients with intermediate degrees of illness. A mean Kt/V greater than 1.0 or TACUREA below 45 mg/dL was associated with increased survival. This study was retrospective with a clear post hoc selection bias. Therefore, the validity of these observations remains highly questionable.

Daily IHD, compared to alternate-day dialysis, also seemed to be associated with improved outcome in a randomized trial (28). Daily hemodialysis resulted in significantly improved survival (72% vs. 54%, p = 0.01), better control of uremia, fewer hypotensive episodes, and more rapid resolution of AKI. However, several limitations limited this study: sicker, hemodynamically unstable patients were excluded, undergoing CRRT instead. Furthermore, according to the mean TACUREA reported, it appears that patients receiving conventional IHD were under-dialyzed. In addition, this was a single-center study with all the inherent limitations in regard to external validity. Finally, the second daily dialysis was associated with significant differences in fluid removal and dialysis-associated hypotension, suggesting that other aspects related to “dose,” beyond solute control—such as inadequate and episodic volume control—may explain the findings. Clearly, further studies need to be undertaken to assess the effect of dose of IHD on outcome.

In a randomized controlled trial of CRRT dose, continuous venovenous postdilution hemofiltration (CVVH) at 35 or 45 mL/kg/hr was associated with improved survival when
compared to 20 mL/kg/hr in 425 critically ill patients with AKI (29). Applying Kt/V dose assessment methodology to CVVH, at a dose of 35 mL/kg/hr in a 70-kg patient treated for 24 hours, a treatment day would be equivalent to a Kt/V of 1.4 daily. Despite the uncertainty regarding the calculation of V urea, CVVH at 35 mL/kg/hr would still provide an effective daily delivery of 1.2, even in the presence of an underestimation of V urea by 20%. Many technical and/or clinical problems—including filter clotting, high filtration fraction in the presence of vascular access dysfunction with fluctuations in blood flow, circuit down-time during surgery or radiological procedures, and filter changes—can make it difficult, in routine practice, to apply such a strict protocol by pure postdilution HF. Equally important is the observation that this study was conducted over 6 years in a single center, uremic control was not reported, the incidence of sepsis was low compared to the typical populations reported to develop AKI in the world, and the final outcome was not the accepted 28- or 90-day mortality typically used in ICU trials. Thus, despite the interesting findings, the external validity of this study remains untested.

Another prospective randomized trial conducted by Bouman et al. (9) assigned patients to three intensity groups: early high-volume HF (72–96 L/24 hr); early low-volume HF (24–36 L/24 hr); and late low-volume HF (24–36 L/24 hr). These investigators found no difference in terms of renal recovery or 28-day mortality. Unfortunately, prescribed doses were not standardized by weight, causing a wide variability in RRT dose ultimately delivered to patients. Furthermore, the number of patients was small, making the study insufficiently powered and, again, the incidence of sepsis was low compared to the typical populations reported to develop AKI in the world.

Notwithstanding the problems we raise with these studies, they must be seen in light of an absolute lack of any previous attempt to adjust AKI treatment dose to specific target levels. The differences between delivered and prescribed dose in patients with AKI undergoing IHD were analyzed by Evanson and coworkers (30). The authors found that a high patient weight, male gender, and low blood flow were limiting factors affecting RRT administration, and that about 70% of dialysate delivered a Kt/V of less than 1.2. A retrospective study by Venkatarman et al. (31) also showed, similarly, that patients receive only 67% of prescribed CRRT therapy. These observations underline that RRT prescriptions for AKI patients in the ICU should be monitored closely if one wishes to ensure adequate delivery of prescribed dose.

Two recent large randomized trials, the Randomised Evaluation of Normal versus Augmented Level of Replacement Therapy (RENAAL) (32) and the Acute Renal Failure Trial Network (ATN) (33) studies, seemed to definitely refute the concept that a “higher” dose is better. These two large multicenter, randomized controlled trials did not show improved outcome with a “more intensive dose” (40 and 35 mL/kg/hr, respectively) compared to a “less intensive dose” (25 and 20 mL/kg/hr, respectively). Based upon these findings, the current KDIGO guidelines recommend delivering an effluent volume of 20 to 25 mL/kg/hr for CRRT in patients with AKI (1). In addition, by comparing two multicenter CRRT databases, Uchino et al. (34) found that patients with AKI treated with low-dose CRRT did not have worse short-term outcome compared to patients treated with what is currently considered the standard (higher) dose. In particular, comparing patients from The Beginning and Ending Supportive Therapy (BEST) study (2) and from The Japanese Society for Physician and Trainees Intensive Care (JSEPTIC) Clinical Trial Group, the authors observed no differences between groups of patient treated with a dose of 14.3 and 20.4 mL/kg/hr (34). Finally, considering that high-dose CRRT could lead to electrolyte disorders, removal of nutrients and drugs (e.g., antibiotics) and high costs (35), but at the same time low dose may expose patients to undertreatment, potentially worsening outcome, seeking the range of adequate treatment dose is a crucial issue. At this time, a delivered dose (without downtime) between 20 and 35 mL/kg/hr may be considered clinically acceptable (36). A CRRT dose prescription below 20 mL/kg/hr and over 35 mL/kg/hr may be definitely identified as the dose-dependent range, where the dialytic intensity is likely to negatively affect outcomes, due to both under- and overdialysis. On the other hand, the prescriptions lying between these two limits can be considered as practice-dependent and variables such as timing, patients characteristics, comorbidities, or concomitant supportive pharmacologic therapies may have a significant role for patients’ outcome and should trigger a careful prescription and a closest monitoring of dose delivery.

**Practical Aspects**

During RRT, clearance depends on circuit blood flow (Qb), hemofiltration (Qf), or dialysis (Qd) flow, solute molecular weights, and hemodialyzer type and size. Qf, as a variable in delivering RRT dose, is mainly dependent on vascular access and the operational characteristics of machines utilized in the clinical setting. Qf is strictly linked to Qb, during convective techniques, by filtration fraction. Filtration fraction does not limit Qf, but when Qf/Qb ratio exceeds 0.3, it can be estimated that dialyzer will not be completely saturated by blood-diffusing solutes. The search for specific toxins to be cleared, furthermore, has not been successful despite years of research, and urea and creatinine are generally used as reference solutes to measure renal replacement clearance for renal failure. While available evidence does not allow the direct correlation of the degree of uremia with outcome in chronic renal disease, in the absence of a specific solute, clearances of urea and creatinine blood levels are used to guide treatment dose. During UF, the driving pressure forces solutes, such as urea and creatinine, against the membrane and into the pores, depending on membrane sieving coefficient (SC) for that molecule. SC expresses a dimensionless value and is estimated by the ratio of the concentration of the solutes in the filtrate divided by that in the plasma water, or blood. An SC of 1.0, as is the case for urea and creatinine, demonstrates complete permeability, and a value of 0 reflects complete impermeability. Molecular size over approximately 12 kDa and filter porosity are the major determinants of SC. The K during convection is measured by the product of Qs and SC. Thus, different from diffusion, there is a linear relationship between K and Qs, the SC being the changing variable for different solutes. During diffusion, the linear relationship is lost when Qs exceeds about one-third of Qf. As a rough estimate, we can consider that during continuous slow-efficiency treatments, RRT dose is a direct expression of Qs/Qf, independent of which solute must be removed from blood. During continuous treatment, it has now been suggested to deliver at least a urea clearance of 2 L/hr, with the clinical evidence that 35 mL/kg/hr may be the best prescription (i.e., about 2.8 L/hr in a 70-kg patient). Other
authors suggest a prescription based on patient requirements, i.e., as a function of the urea generation rate and catabolic state of the single patient. It has been shown, however, that during continuous therapy, a clearance less than 2 L/hr will almost definitely be insufficient in an adult critically ill patient. For more exact estimations, simple computations have been shown to adequately estimate clearance (23,37). Tables 133.3 and 133.4 show a potential flow chart that could be followed each time an RRT prescription is indicated.

### From Continuous to Intermittent: One Treatment Fits All?

Clearance-based dose quantification methods may not be adequate to compare effectiveness. For example, peritoneal dialysis (PD), traditionally providing less urea clearance per week than IHD, has comparable patient outcomes. Furthermore, when EKR (equivalent renal urea clearance corrected for urea volume) is used to compare intermittent and continuous therapies, it does not appear to be equivalent in terms of outcome; typically, PD patients have better comparable outcomes with less EKR, than IHD patients (38). When the critical parameter is metabolic control, an acceptable mean blood urea nitrogen level of 60 mg/dL—easily obtainable in a 100-kg patient with a 2 L/hr CVVH in a computer-based simulation—has been shown to be very difficult to reach, even by intensive IHD regimens (37). In addition to the benefits specifically pertaining to the kinetics of solute removal, increased RRT frequency results in decreased ultrafiltration requirements per treatment. The avoidance of volume swings related to rapid ultrafiltration rates may also represent another dimension of dose where comparability is difficult.

Despite the development of new membranes, sophisticated dialysis machinery, tailored dialysate composition, and continuous dialysis therapies, a relationship between the frequency of RRT (continuous vs. intermittent) delivery has not been fully established. Most recently, the Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock (39) concluded that, based on the present scientific evidence, continuous RRT should be considered equivalent to IHD for the treatment of AKI. However, the use of continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients was suggested (39). In a large comparative trial randomizing 166 critically ill patients with AKI to either CRRT or IHD (40), the authors found that the CRRT population, despite randomization, had significantly greater severity of illness scores. This could, in part, explain why, despite better control of azotemia and a greater likelihood of achieving the desired fluid balance, CRRT had increased mortality. Another more recent smaller trial at the Cleveland Clinic (41) failed to find a difference in outcome between one therapy and another. In recent years, a meta-analysis on this issue has been unable to solve the debate of continuous versus intermittent treatment. A meta-analysis of

### Table 133.3 Algorithm for RRT Prescription

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>Operational Variables</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid balance</td>
<td>Net ultrafiltration</td>
<td>Continuous management of negative balance (100-300 ml/hr) is preferred in hemodynamically unstable patients. Complete monitoring (CVC, SG, arterial line, ECG, pulse oximeter) is recommended.</td>
</tr>
<tr>
<td>Adequacy and dose</td>
<td>Clearance/modality</td>
<td>2000-3000 ml/hr K (or 35 ml/kg/hr) for CRRT. Consider first CVVHD; if IHD is selected, a daily every 4-hr prescription is recommended. Prescribe a Kt/V &gt; 1.2.</td>
</tr>
<tr>
<td>Acid-base</td>
<td>Solution buffer</td>
<td>Consider bicarbonate buffered solutions to be preferable to lactate buffered solutions in case of lactic acidosis and/or hepatic failure.</td>
</tr>
<tr>
<td>Electrolyte</td>
<td>Dialysate/replacement</td>
<td>Electrolyte solutions without K + are preferred for patients with AZI. Manage accurately Mg, PO4.</td>
</tr>
<tr>
<td>Timing</td>
<td>Schedule</td>
<td>Early and intense RRT is suggested.</td>
</tr>
<tr>
<td>Protocol</td>
<td>Staff/machine</td>
<td>Well-trained staff should routinely utilize RRT monitors according to predefined institutional protocols.</td>
</tr>
</tbody>
</table>

CVC, central venous catheter; SG, Swan-Ganz catheter; ECG, electrocardiogram; CRRt, continuous renal replacement therapy; CVVHD, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis.

### Table 133.4 Schematic Example of a Possible Prescription for a Continuous Treatment in a 70-kg Patient

<table>
<thead>
<tr>
<th>Estimated Urea Clearance (KCALC)</th>
<th>Notes</th>
<th>Value of Q to Obtain 35 ml/kg/hr</th>
<th>Value of Q to Obtain a K/V of 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVVH postdilution</td>
<td>K&lt;sub&gt;KALC&lt;/sub&gt; = Q&lt;sub&gt;do&lt;/sub&gt;</td>
<td>Always keep filtration fraction &lt;20% (Q&lt;sub&gt;f&lt;/sub&gt; must be $5\times Q_{do}$)</td>
<td>Q&lt;sub&gt;do&lt;/sub&gt;: 41 ml/min or 2,450 ml/hr</td>
</tr>
<tr>
<td>CVVH predilution</td>
<td>K&lt;sub&gt;KALC&lt;/sub&gt; = Q&lt;sub&gt;do&lt;/sub&gt; / (1 + (Q&lt;sub&gt;rep&lt;/sub&gt; / Q&lt;sub&gt;do&lt;/sub&gt;))</td>
<td>Filtration fraction computation changes (keep &lt;20%)</td>
<td>For a Q&lt;sub&gt;do&lt;/sub&gt; of 200 ml/min: Q&lt;sub&gt;rep&lt;/sub&gt;: 53 ml/min or 3,200 ml/hr</td>
</tr>
<tr>
<td>i. CVVHD</td>
<td>K&lt;sub&gt;KALC&lt;/sub&gt; = Q&lt;sub&gt;do&lt;/sub&gt;</td>
<td>Keep Q&lt;sub&gt;f&lt;/sub&gt; = 3× Q&lt;sub&gt;do&lt;/sub&gt;</td>
<td>Q&lt;sub&gt;rep&lt;/sub&gt;: 41 ml/min or 2,450 ml/hr</td>
</tr>
<tr>
<td>ii. CVVHDF postdilution (50% convective and diffusive K)</td>
<td>K&lt;sub&gt;KALC&lt;/sub&gt; = Q&lt;sub&gt;do&lt;/sub&gt; + Q&lt;sub&gt;rep&lt;/sub&gt;</td>
<td>Consider both notes of CVVH and CVVHD</td>
<td>Q&lt;sub&gt;rep&lt;/sub&gt;: 20 ml/min or 1,750 ml/hr</td>
</tr>
</tbody>
</table>

Q<sub>b</sub>, blood flow rate; Grep, replacement solution flow rate; Q<sub>uf</sub>, ultrafiltration flow rate (Q<sub>uf</sub> = Q<sub>do</sub> + Q<sub>rep</sub>); Q<sub>net</sub>, net fluid loss; Q<sub>do</sub>, dialysate solution flow rate.

b) V<sub>1440</sub>: 42 L during an ideal session of 24 hr (1,440 min). Net ultrafiltration (patient fluid loss) is considered zero in K<sub>KALC</sub> for simplicity.

- Urea volume of distribution, V (L); patient’s body weight (kg) × 0.6.
- Estimated fractional clearance (K<sub>V</sub> / K<sub>V</sub> ideal) × (min/h)/ V (mL).
- 35 ml/kg/hr roughly corresponds to a K<sub>V</sub> of 1.4 K<sub>V</sub> ideal of 1 approximately corresponds to 25 ml/kg/hr.
- Filtration fraction calculation (postdilution): Q<sub>uf</sub>/Q<sub>do</sub> × 100; filtration fraction calculation (predilution): Q<sub>uf</sub>/Q<sub>do</sub> + Q<sub>rep</sub> × 100.
13 studies conducted by Kellum and coauthors, concluded that, after the stratification of 1,400 patients according to disease severity, when similar patients were compared, CRRT was associated with a significant decrease in the risk of death (42). However, when the same data were analyzed the same year by another group (43), no difference in outcome could be detected. Thus, it remains uncertain whether the choice of RRT modality (intermittent or continuous) actually matters to patient outcome. A recent randomized controlled trial comparing IHD and continuous venovenous hemodiafiltration (CVVHDF) concluded that, provided strict guidelines to improve tolerance and metabolic control are used, almost all patients who have AKI as part of their multiorgan dysfunction syndrome can be treated with IHD (44).

Given the lack of clear outcome data, the community of critical care nephrologists might then consider compromise solutions. One such solution could be represented by hybrid techniques such as SLEDD. Hybrid techniques have been given a variety of names such as slow, low-efficiency extended daily dialysis (SLEDD), prolonged intermittent daily RRT (PIDIRRT), extended daily dialysis (EDD), or simply extended dialysis (45–48), depending on variations in schedule and type of solute removal (convective or diffusive). Theoretically speaking, the purpose of such therapy would be the optimization of the advantages offered by either CRRT or IHD, including efficient solute removal with minimum solute disequilibrium, reduced ultrafiltration rate with hemodynamic stability, optimized delivery to prescribed ratio, low anticoagulant need, diminished cost of therapy delivery, efficiency of resource use, and improved patient mobility. Initial case series have shown the feasibility and high clearances potentially associated with such approaches. A single, short-term, single-center trial comparing hybrid therapies to CRRT has shown satisfying results in terms of dose delivery and hemodynamic stability. New technology which can be used in the ICU by nurses to deliver SLEDD with convective components offers further options from a therapeutic, logistic, and cost-effectiveness point of view.

One last aspect may be relevant: if short-term hard outcomes are not impacted by RRT modality, it may not be the case for long-term ones. In fact, IHD has been suspected to cause long-term chronic kidney disease in AKI patients. Two recent studies (49,50)—a meta-analysis and a retrospective analysis—noted that, compared with CRRT, IHD prescription for AKI treatment is significantly and strongly associated with a lower possibility of recovery of renal function. If these data are further confirmed, IHD should be abandoned for the treatment of AKI.

**TECHNICAL NOTES**

RRT Modalities: Description and Nomenclature

Apart from what evidence-based medicine dictates, continuous therapies are utilized in 80% of ICUs worldwide, while IHD (17%) and PD (3%) have less common utilization (2). In the 1980s, a passionate debate between simple CAVH and complex early CVVH lasted for the decade, stimulating the industries to produce increasingly effective equipment and monitoring systems. Accurate ultrafiltration control is now obtained by integrated roller volumetric pumps—for blood, replacement fluid, dialysate, and effluent—and scales. These monitors display pressure measurements of all crucial segments of the circuit: catheter inlet and outlet, filter inlet and outlet, UF, and dialysate ports. This information, integrated with adequate alarm systems, has allowed the ICU staff to increase filter efficiency and lengthen circuit patency, with the ability to detect potential sources of clotting, thereby improving patient safety. Complete monitoring of fluid balance is also provided by continuous recording of the history of the last 24 hours of treatment. When an alarm occurs, a “smart” message on the screen suggests the most appropriate intervention required. A complete range of ICU RRT therapeutic modalities includes IHD, slow continuous ultrafiltration (SCUF), CVVH, continuous venovenous hemodialysis (CVVHD), CVVHDF, and therapeutic plasma exchange (TPE) described in more detail in Table 133.5 and Figure 133.3.

**FIGURE 133.3** Schematic representation of most common continuous RRT set-ups. Block triangle represents blood flow direction; gray triangle indicates dialysate/replacement solutions flows. V-V: venovenous; Uf: ultrafiltration; Quf: replacement solution prefilter; Qpre: replacement solution post-filter; Do: dialysate out; Di: dialysate in; Qd: blood flow; Quf: ultrafiltration flow; Qr: replacement solution flow; QDi: dialysate solution flow.
Continuous venovenous hemodialysis (CVVHD)  Technique where blood is driven through a highly permeable dialyzer via an extracorporeal circuit in venovenous mode and a counter current flow of dialysate is delivered on the dialysate compartment. The ultrafiltrate produced during membrane transit is replaced in part or completely to achieve blood purification and volume control. If replacement fluid is delivered after the filter, the technique is defined postdilution hemofiltration. If it is delivered before the filter, the technique is defined predilution hemofiltration. The replacement fluid can also be delivered both pre and post filter. Clearance for all solutes is convective and equals UF rate. $Q_b$, 100–250 ml/min; $Q_u$, 15–60 ml/min.

Continuous venovenous hemofiltration (CVVHf)  Technique where blood is driven through a highly permeable filter via an extracorporeal circuit in venovenous mode. The ultrafiltrate produced during membrane transit is in excess of the patient’s desired weight loss. UF is used only for fluid control in overloaded patients (i.e., congestive heart failure resistant to diuretic therapy). $Q_b$, 100–250 ml/min; $Q_u$, 5–15 ml/min (Fig. 133.2).

Continuous venovenous hemodiafiltration (CVVHDF)  Technique where blood is driven through a highly permeable dialyzer via an extracorporeal circuit in venovenous mode and a counter current flow of dialysate is delivered on the dialysate compartment. The ultrafiltrate produced during membrane transit is in excess of the patient’s desired weight loss. A replacement solution is needed to maintain fluid balance. Solute clearance is both convective and diffusive. $Q_b$, 100–250 ml/min; $Q_u$, 15–60 ml/min; $Q_d$, 15–60 ml/min (Fig. 133.2).

Hybrid techniques  Slow low efficiency daily dialysis (SLEDD), prolonged daily intermittent RRT (PDIRR), extended daily dialysis (EDD), extended daily dialysis with filtration (EDDF), extended HD.

Hemoperfusion (HP)  Blood is circulated on a bed of coated charcoal powder to remove solutes by adsorption. The technique is specifically indicated in cases of poisoning or intoxication with agents that can be effectively removed by charcoal. Polymixin hemoperfusion has been attempted for endotoxin removal in gram-negative septic AKI patients (44). This treatment may cause platelet and protein depletion.

Plasmapheresis (PP)  A treatment that uses specific plasma filters. Molecular weight cutoff of the membrane is much higher than that of hemofilters (100,000–1,000,000 kDa): plasma as a whole is filtered and blood is reconstituted by the infusion of plasma products such as frozen plasma or albumin. This technique is performed to remove proteins or protein bound solutes.

High-flux dialysis (HFD)  A treatment that uses highly permeable membranes in conjunction with an UF control system. Because of the characteristics of the membrane, UF occurs in the proximal part of the filter, that is counterbalanced by a positive pressure applied to the dialysate compartment: this causes in the distal part of the filter a phenomenon called back filtration, that consist in convective passage of the dialysate into the blood. Diffusion and convection are combined, but thanks to the use of a pyrogen-free dialysate replacement solution, UF is avoided.

Plasma Therapy  The term “plasma therapy” actually encompasses two therapies: plasma adsorption and plasma exchange. In plasma adsorption, plasma separated from blood cells flows along one or more columns that contain different adsorbents, after which the processed plasma is reinfused back to the patient. Plasma exchange is a single-step process in which blood is separated into plasma and cells and the cells are returned back to the patient while the plasma is replaced with either donor plasma or albumin. With respect to sepsis, it has been argued that plasma therapy is likely to be effective in patients with sepsis-associated thrombotic microangiopathy (48).

### TABLE 133.5 Extracorporeal Blood Purification Techniques

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent hemodialysis (IHD)</td>
<td>A prevalently diffusive treatment in which blood and dialysate are circulated in counter current mode and, generally, a low permeability, cellulose-based membrane is employed. Dialysate must be pyrogen free but not necessarily sterile, since dialysate–blood contact does not occur. The UF rate is equal to the scheduled weight loss. This treatment can be typically performed 4 hr thrice weekly or daily. $Q_b$, 150–300 ml/min; $Q_u$, 300–500 ml/min.</td>
</tr>
<tr>
<td>Peritoneal dialysis (PD)</td>
<td>A predominantly diffusive treatment where blood, circulating along the capillaries of the peritoneal membrane, is exposed to dialysate. Access is obtained by the insertion of a peritoneal catheter, which allows the abdominal instillation of dialysate. Solute and water movement is achieved by the means of variable concentration and toxicity gradients generated by the dialysate. This treatment can be performed continuously or intermittently.</td>
</tr>
<tr>
<td>Slow continuous ultrafiltration (SCUF)</td>
<td>Technique where blood is driven through a highly permeable filter via an extracorporeal circuit in venovenous mode. The ultrafiltrate produced during membrane transit is not replaced and it corresponds to weight loss. It is used only for fluid control in overloaded patients (i.e., congestive heart failure resistant to diuretic therapy). $Q_b$, 100–250 ml/min; $Q_u$, 5–15 ml/min (Fig. 133.2).</td>
</tr>
<tr>
<td>Continuous venovenous hemofiltration (CVVH)</td>
<td>Technique where blood is driven through a highly permeable filter via an extracorporeal circuit in venovenous mode. The ultrafiltrate produced during membrane transit is replaced in part or completely to achieve blood purification and volume control. If replacement fluid is delivered after the filter, the technique is defined postdilution hemofiltration. The replacement fluid can also be delivered both pre and post filter. Clearance for all solutes is convective and equals UF rate. $Q_b$, 100–250 ml/min; $Q_u$, 15–60 ml/min.</td>
</tr>
<tr>
<td>Continuous venovenous hemodialysis (CVVHd)</td>
<td>Technique where blood is driven through a low permeability dialyzer via an extracorporeal circuit in venovenous mode and a counter current flow of dialysate is delivered on the dialysate compartment. The ultrafiltrate produced during membrane transit corresponds to patient’s weight loss. Solute clearance is mainly diffusive and efficiency is limited to small solutes only. $Q_b$, 100–250 ml/min; $Q_u$, 15–60 ml/min (Fig. 133.2).</td>
</tr>
<tr>
<td>Continuous venovenous hemodiafiltration (CVVHDF)</td>
<td>Technique where blood is driven through a highly permeable dialyzer via an extracorporeal circuit in venovenous mode and a counter current flow of dialysate is delivered on the dialysate compartment. The ultrafiltrate produced during membrane transit is in excess of the patient’s desired weight loss. A replacement solution is needed to maintain fluid balance. Solute clearance is both convective and diffusive. $Q_b$, 100–250 ml/min; $Q_u$, 15–60 ml/min; $Q_d$, 15–60 ml/min (Fig. 133.2).</td>
</tr>
<tr>
<td>Hybrid techniques</td>
<td>Slow low efficiency daily dialysis (SLEDD), prolonged daily intermittent RRT (PDIRR), extended daily dialysis (EDD), extended daily dialysis with filtration (EDDF), extended HD.</td>
</tr>
<tr>
<td>Hemoperfusion (HP)</td>
<td>Blood is circulated on a bed of coated charcoal powder to remove solutes by adsorption. The technique is specifically indicated in cases of poisoning or intoxication with agents that can be effectively removed by charcoal. Polymixin hemoperfusion has been attempted for endotoxin removal in gram-negative septic AKI patients (44). This treatment may cause platelet and protein depletion.</td>
</tr>
<tr>
<td>Plasmapheresis (PP)</td>
<td>A treatment that uses specific plasma filters. Molecular weight cutoff of the membrane is much higher than that of hemofilters (100,000–1,000,000 kDa): plasma as a whole is filtered and blood is reconstituted by the infusion of plasma products such as frozen plasma or albumin. This technique is performed to remove proteins or protein bound solutes.</td>
</tr>
<tr>
<td>High-flux dialysis (HFD)</td>
<td>A treatment that uses highly permeable membranes in conjunction with an UF control system. Because of the characteristics of the membrane, UF occurs in the proximal part of the filter, that is counterbalanced by a positive pressure applied to the dialysate compartment: this causes in the distal part of the filter a phenomenon called back filtration, that consist in convective passage of the dialysate into the blood. Diffusion and convection are combined, but thanks to the use of a pyrogen-free dialysate replacement solution, UF is avoided.</td>
</tr>
<tr>
<td>High-volume hemofiltration (HVHF)</td>
<td>A treatment that utilizes highly permeable membranes and hemofiltration with a high volume setting. $Q_b$, &gt;200 ml/min; $Q_u$, &gt;35 ml/kg/hr.</td>
</tr>
<tr>
<td>High-cutoff hemofiltration or hemodialysis</td>
<td>A technique aimed at removing inflammatory mediators (e.g., cytokines) in septic patients. HCO membranes are porous enough to achieve the removal of larger molecules (approximately 15–60 kD) by diffusion. Its ability to remove cytokines in ex vivo and in vivo studies has now been shown to be greater than that of any other technology so far (45) and has increased survival in experimental models of sepsis (46). HCO therapy seems to have beneficial effects on immune cell function and preliminary human studies using intermittent hemodiafiltration with HCO membranes have confirmed its ability to remove marker cytokines IL-6 and IL-1 receptor antagonist, with a decreased dosage of norepinephrine in patients with sepsis (47). Predictably, albumin losses are significant, but may be attenuated by using HCO membranes in a diffusive rather than convective manner while still preserving the effect on cytokine clearance.</td>
</tr>
<tr>
<td>Plasma Therapy</td>
<td>The term “plasma therapy” actually encompasses two therapies: plasma adsorption and plasma exchange. In plasma adsorption, plasma separated from blood cells flows along one or more columns that contain different adsorbents, after which the processed plasma is reinfused back to the patient. Plasma exchange is a single-step process in which blood is separated into plasma and cells and the cells are returned back to the patient while the plasma is replaced with either donor plasma or albumin. With respect to sepsis, it has been argued that plasma therapy is likely to be effective in patients with sepsis-associated thrombotic microangiopathy (48).</td>
</tr>
</tbody>
</table>

$Q_b$, blood flow; $Q_u$, dialysis flow; $Q_d$, ultrafiltration rate; UF, ultrafiltration; HCO, high cutoff; IL, interleukin; AKI, acute kidney injury; ICU, intensive care unit.
Anticoagulation

The need for anticoagulation of the CRRT circuit arises from the fact that the contact between blood and the tubing of the circuit and the membrane of the filter induces activation of the coagulation cascade and platelets activation; this extracorporeal activation inevitably results in filter or circuit clotting. It is evident that the anticoagulation strategy will change depending on the prescribed RRT schedule, being a priority feature of continuous treatments where blood–artificial surface interaction is maximized. The aims of anticoagulation are maintenance of extracorporeal circuit and dialyzer patency; reduction of off-treatment time (down time) that could have a clinical impact in the overall RRT clearance; reduction of treatment cost by, as possible, the utilization of less material; and achievement of the above aims with minimal risk for the patient. In fact, continuous anticoagulation may represent an important drawback of RRT in some categories of patients. This last concept should perhaps be the first rule of anticoagulation management: under no circumstances should the patient be put at risk of bleeding in order to prolong circuit life. The general principle from KDIGO guidelines suggest that anticoagulation for RRT be weighted on assessment of the potential risks and benefits to the patient (1).

Circuit Setup Optimization and No Anticoagulation

Several technical features of RRT circuit are likely to affect the success of any anticoagulant approach. Vascular access has to be of adequate size; tubing kinking should be avoided; blood flow rate should exceed 100 mL/min; pump flow fluctuations must be prevented (in modern machines this event is mainly due to circuit increased resistances rather than flow rate inaccuracies); and a venous bubble trap—where air/blood contact occurs—must be accurately monitored. In this light, another component of circuit setup has to be addressed: plasma filtration fraction should be kept has far as possible below 20% and, when possible or considered correct, predilutional HF should be selected. There is evidence that, when the setup is perfectly optimized, anticoagulants are only a relatively minor component of circuit patency; in fact, whenever the patient’s clinical has risk factors for bleeding—prolonged clotting times, thrombocytopenia—RRT can be safely performed without the utilization of any anticoagulant (51). In these cases, special attention is required to prolong filter survival: optimal vascular access (i.e., high blood flow), reduction of blood viscosity by saline boluses, predilution, and diffusive treatment. Alarm setting is clearly important to identify circuit problems, especially in these cases. Although potentially avoidable, the general indication is for the use of anticoagulation for patients without an increased bleeding risk and not already receiving systemic anticoagulation for his/her disease. In case of intermittent RRT, either low–molecular-weight heparin (LMWH) or unfractionated heparin (UFH) are recommended. LMWH, in patients with chronic IHD, is recommended in order to reduce the risk of heparin-induced thrombocytopenia (HIT), and of long-term side effects (abnormal serum lipids, osteoporosis, hypoadosteronism) (1). For continuous treatments, regional citrate anticoagulation (in the absence of contraindications) is suggested; when citrate is contraindicated (see below), either UFH or LMWH should be administered (1).

Unfractioned Heparin

This agent is the most widely used anticoagulant during continuous RRT, although guidelines suggest citrate anticoagulation as a general rule. UFH is mostly administered as a prefiltro infusion or as systemic infusion in specific cases. It is easy to use as there is a large experience in most centers, is not expensive, quick monitoring—APTT or activated clotting time (ACT)—is readily available, has a short half-life, and an antagonist—protamine—exists. Heparin doses might range from 5 to 10 IU/kg/hr. In patients with very limited circuit duration, it can also be used in combination with protamine (regional heparinization), with a 1:1 ratio (150 IU of UFH per mg of protamine) and strict aPTT monitoring. The problem with UFH is its relative unpredictable bioavailability (monitoring required), the narrow therapeutic index (risk of bleeding), the necessity for antithrombin (AT) level optimization, heparin resistance, and the occurrence of HIT. The balance between heparin dose, aPTT/ACT, filter survival, and potential/actual complications have to be considered during RRT.

Low–Molecular-Weight Heparins

Some centers have gained experience with LMWHs. These have some advantages—predictable kinetics, no monitoring required, reduced risk of HIT—that make this drug particularly efficient for intermittent RRT; a single predialysis dose may be sufficient. The main disadvantages are risk of accumulation in case of kidney failure, requiring dose adaptation or administration interruption; incomplete reversal by protamine; monitoring requires a laboratory test (anti-factor Xa) that might not be easily available, and the drug is certainly more expensive than UFH.

Prostacyclin

This agent is a potentially useful drug for RRT anticoagulation, being the most potent inhibitor of platelet aggregation with the shortest half-life. PGI2 is infused at a dose of 4 to 8 ng/kg/hr, with or without the adjunct of low dose of UFH. PGI2 appears to have a limited efficacy when used alone and hypotension may occur. Because of these drawbacks as well as its high cost, PGI2 use during CRRT is not recommended (52).

Citrate

This form of regional anticoagulation depends on the ability of citrate to chelate calcium, thus stopping the coagulation cascade. Briefly, a calcium-free sodium citrate–containing replacement solution and/or dialysate solution is prepared and administered at the appropriate rate to achieve the desired aPTT (60 to 90 seconds). Citrate is rapidly metabolized in the liver, muscle, and kidney, liberating the calcium and producing bicarbonate (1 to 3 moles ratio). Calcium chloride is administered to replace chelated/dialyzed calcium and maintain normocalcemia. Regional citrate anticoagulation requires a strict protocol, adapted to the treatment modality. This approach is effective in maintaining excellent filter patency and compares favorably with heparin. It also avoids the risk for HIT and does not lead to systemic anticoagulation. The relative drawbacks of this anticoagulation management include the risk for hypocalcemia, hyperkalemia, hypernatremia, metabolic alkalosis—or metabolic acidosis for impaired capacity to metabolize citrate in shock states or liver failure, considered contraindications for citrate anticoagulation—and the cumbersome
TABLE 133.6 Anticoagulation Strategies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>No anticoagulation</td>
<td>Use in patients at high risk of bleeding</td>
<td>Relative shorter circuit lifespan</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>Routine</td>
<td>HIT</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>Routine (alternative to UFH)</td>
<td>HIT</td>
</tr>
<tr>
<td>Prostacycline</td>
<td>Improves circuit lifespan</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Citrate</td>
<td>Routine/improves circuit lifespan</td>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>Daneparnoid</td>
<td>HIT</td>
<td>Insufficient data available</td>
</tr>
<tr>
<td>Argatroban</td>
<td>HIT</td>
<td>Insufficient data available</td>
</tr>
<tr>
<td>Iramidine</td>
<td>HIT</td>
<td>Insufficient data available</td>
</tr>
<tr>
<td>Nafamostatmesilate</td>
<td>HIT</td>
<td>Insufficient data available</td>
</tr>
<tr>
<td>Heparin-coated circuits</td>
<td>Routine</td>
<td>Insufficient data available</td>
</tr>
</tbody>
</table>

HIT, heparin-induced thrombocytopenia.

replacement/dialysate fluid preparation (53). Guidelines suggest using regional citrate anticoagulation for patients with an increased bleeding risk, who are not receiving anticoagulation, and are without contraindications to the agent (1).

Other Strategies

Alternatives to the techniques presented above are here listed in Table 133.6 for completeness.

Unanswered Research Topics

Outcome variables including bleeding, renal recovery, mortality, incidence of HIT, circuit survival, efficiency of treatment, and metabolic complications, should be tested with RCTs designed to compare UFH to LMWH during IHD and CRRT. In addition, citrate should be compared with UFH and LMWH during CRRT. Finally, trials comparing strategies without anticoagulation versus different modalities of anticoagulation are lacking and should be considered in the future.

VASCULAR ACCESS

The fundamental role played by vascular access must be emphasized. In fact, circuit failure is more often due to vascular access inadequacy than insufficient anticoagulation; the optimal dialysis catheter can save the patient from inappropriate increases of the anticoagulation dose. Venovenous RRT relies on the use of a temporary double-lumen catheter. Such catheters are inserted in a central vein and available in different brands, shapes, and sizes. The site of insertion of double-lumen catheters implies a number of considerations (clinician expertise, body habitus of the patient, the presence of other intravenous catheters). The femoral vein is generally the first choice of vascular access; internal jugular or subclavian accesses are often associated with inadequate performance, and the inguinal puncture is safer and easier to perform in coagulopathic critically ill patients. A valid alternative may be achieved by cannulation of the right jugular internal vein with the tip of the catheter reaching the right atrium; circuit blood flow rates with this approach can reach 300 mL/min. Catheter size for adult patients range from 12 to 14 French and length from 16 to 25 cm; the larger and shorter the catheter, the higher the performance. Nonetheless, when the femoral vein is selected, a 20-cm-long catheter with its tip positioned close to the inferior vena cava allows optimal circuit flows. When inadequate blood flow or a catheter malfunction is suspected, venous and arterial lumens should be flushed with saline, with the goal of testing resistance to injection and aspiration. Clotting of a limb of the line versus kinking due to patient’s position must be distinguished. In the first case, a heparin or urokinase lock can be tried for few hours; in the second case, switching of arterial and venous limbs can be attempted. This maneuver increases circuit recirculation, but clinical consequences are negligible. Another approach is a catheter exchange over a guide wire; this is generally not recommended unless vascular access is extremely difficult, as the risk of line infection is significant.

RRT FOR CHILDREN

There are some important differences in the RRT indications, methods, and prescription between children and adult patients; nevertheless, the technique is essentially the same. A priority indication includes the correction of water overload. Different from the adult setting, where solute control may play an key role, it has been shown that restoring an adequate water content in small children is the main independent variable for outcome prediction (54–55). This concept is much more important in critically ill, smaller children, where a relatively larger amount of fluid must be administered in order to deliver an adequate amount of drug infusion, parenteral/enteral nutrition, blood derivatives, and so forth. Corrections of acid–base imbalances and electrolyte disorders is also a strong indication for RRT prescription in children.

Catheter size ranges from 6.5 French (10 cm long) for less than 10-kg patients to 8 French (15 cm long) for 11- to 15-kg patients. Blood priming may be indicated if more than 8 mL/kg of patient’s blood is necessary to fill an RRT circuit. Full anticoagulation must be always maintained in order to avoid excessive blood loss in case of circuit clotting. Predilution HF is generally the preferred modality and is delivered in a continuous fashion. Fluid balance requires strict monitoring and highest accuracy due to the risk of excessive patient dehydration. Prescription of RRT clearance should be titrated on the patient body surface area, an approach that will usually lead to relatively higher doses for small children with respect to adult patients when considered per kilogram (56). Critically ill children below 10 kg body weight and neonates with AKI are often treated with PD; discussion of this topic goes beyond the scope of this chapter. An important exception to this general approach is the case of children with AKI during an extracorporeal membrane oxygenation treatment (ECMO). In this case, the RRT circuit is placed in parallel to the ECMO circuit,
and it is possible to let a significant blood flow run into the filter even in the smallest patients.

Recently, two dialysis monitors specifically dedicated to neonates and infants have been developed and clinically applied: the CARPEDIEM (CArdio Renal PEdiatric Emergency Machine) and the Nidus (Newcastle infant dialysis and ultrafiltration system). The first of these (57–59) is a miniaturized (13 kg) device featuring four mini-roller pumps, as well as all the other technical requirements of a third-generation machine. The monitor is equipped with three circuits with different priming volumes—27.2, 33.5, and 41.5 mL—and filter sizes—0.075, 0.147, and 0.245 m²—to allow optimal adaptability for patients weighting less than 3 kg, from 3 to 6 kg, and from 6 to 10 kg, respectively. One of the most interesting aspects of CARPEDIEM monitor is its accurate management of fluid balance. The machine is equipped with a gravimetric control with a scale sensitivity of 1 g for both infusion and effluent bags. An automatic feedback system adjusts pump speed according to the prescribed and actual delivery of fluid, and the difference between prescribed and achieved fluid balance is always kept at less than 20 g/24 hr. The treatment is terminated if a fluid balance error of 50 g is reached within a single session. The NIDUS (59) is an original machine driven by syringes instead of roller pumps, providing single-needle vascular access. The circuit volume is only 13 mL, and its designers claim that there is no need for circuit blood-priming. Recently, Coulthard and co-workers successfully treated 10 babies weighing between 1.8 and 5.9 kg, with satisfactory results in terms of adequacy of clearance and machine accuracy (59). Further studies into these two interesting devices are anticipated, and there promises to be a significant outcome improvement for neonates with severe AKI requiring RRT.

**PERSPECTIVE FOR THE FUTURE**

The ideal RRT machine for the future should self-set the right RRT technique, modality, and prescription after the clinician has provided all the information for the specific patient. Monitors and material of the future will further increase ease of use, safety measures, and the accuracy of each component of the integrated system, reducing the labor involved. Unfortunately, there is no solution to the ill-conceived use of a perfect system. Furthermore, in the light of progressively increasing severity of critical illness, a monitor able to provide supportive treatment beyond the classic renal indications is currently awaited. In the near future, technical developments in extracorporeal devices will lead to the creation of MOSTs, so that comprehensive replacement or at least support can be provided to multiple organs simultaneously. New machines already include multiple platforms in which different circuits and filters can be used in combination to support renal, heart, liver and lung function. Such machines will ideally be able to automatically detect both “traditional” (urea) and “inflammatory” (cytokines) solutes in critically ill patients’ plasma in order to automatically (or semiautomatically) tailor the therapy towards the “perfect blood purification” system (53).

**CONCLUSIONS**

The mechanisms involved in RRT are founded upon the principle of water and solute transport according to two fundamental mechanisms: diffusion and convection. These mechanisms can be applied into clinical practice as different techniques (intermittent, extended, or continuous RRT) and modalities (HF, hemodialysis, hemodiafiltration, plasmapheresis, hemoperfusion, coupled plasmapheresis, and adsorption). A precise understanding of technical and clinical implications of such therapies seems important to create a correct RRT prescription since, so far, no consensus exists about which modality should be administered to critically ill patients with AKI. Different RRT prescriptions, modalities, and schedules can be administered to critically ill patients with AKI. Clinical effects on critically ill patients depend on the selected RRT strategy and on the severity and complexity of the patient’s clinical picture. Modern versatile machines and flexible operative prescriptions allow the operators to range from highly intermittent high-efficiency therapies to slow continuous HF, depending on the patient’s hemodynamic stability, fluid balance needs, acid-base, and electrolyte derangements. A specific dose of RRT has not been adopted in clinical practice; a standard dose prescription and a strict control of delivered dose should be monitored if one wishes to ensure the adequate delivery of a prescribed dose. The best evidence to date supports an RRT dose in the range of 25 to 35 mL/kg/hr.

**Key Points**

- RRTs currently remain the most important part of AKI treatment. AKI is defined and classified according to KDIGO classification.
- Current indications for urgent/emergent RRT in clinical practice are well defined: fluid overload, hyperkalemia, severe acidosis, and intoxication; each of these parameters can be present at different levels of severity and can be differently evaluated by different clinicians at different centers. Outside these conditions (e.g., in case of sepsis), timing for the start of RRT is currently being debated.
- Once RRT has started, timing for cessation is another field of uncertainty as the literature is scarce.
- During diffusion, movement of solute depends upon their tendency to reach the same concentration on each side of the membrane; dialysis is a modality of RRT and is predominantly based on the principle of diffusion. During convection, the movement of solute across a semipermeable membrane takes place in conjunction with significant amounts of ultrafiltration (water transfer across the membrane).
- The current KDIGO guidelines recommend delivering an effluent volume of 20 to 25 mL/kg/hr for continuous RRT (CRRT) in patients with AKI (without downtime).
- The Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock suggest that CRRT should be considered equivalent to IHD for the treatment of AKI. However, the use of continuous therapies facilitates the management of fluid balance in hemodynamically unstable septic patients.
- The general principle from the KDIGO guidelines suggest that anticoagulation for RRT be weighted on assessment of the potential risks and benefits to the patient but, for continuous treatments, regional
citrate anticoagulation (in the absence of contraindica-
tions) is suggested; when citrate is contraindicated, either unfractioned heparin or LMWH should be
administered.

- Different from the adult setting, where solute control
may play a key role, it has been shown that restoring
an adequate water content in small children is the main
independent variable for outcome prediction.

- In the near future, technical developments in extracor-
pooreal devices will lead to the creation of MOSTs, so
that comprehensive replacement or at least support can
be provided to multiple organs simultaneously.

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