Renal Replacement Therapy in the ICU

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Objectives: The incidence of acute kidney injury in critically ill patients is increasing steeply. Acute kidney injury in this setting is associated with high morbidity and mortality. There is no doubt that renal replacement therapy for the most severe forms of acute kidney injury can be life saving, but there are a number of uncertainties about the optimal application of renal replacement therapy for patients with acute kidney injury. The objective of this synthetic review is to present current evidence supporting best practices in renal replacement therapy for critically ill patients with acute kidney injury.

Data Sources: We reviewed literature regarding timing of initiation of renal replacement therapy, optimal vascular access for renal replacement therapy in acute kidney injury, modality selection and dose or intensity of renal replacement therapy, and anticoagulation during renal replacement therapy, using the following databases: MEDLINE and PubMed. We also reviewed bibliographic citations of retrieved articles.

Study Selection: We reviewed only English language articles.

Conclusions: Current evidence sheds light on many areas of controversy regarding renal replacement therapy in acute kidney injury, providing a foundation for best practices. Nonetheless, important questions remain to be answered by ongoing and future investigation. (*Crit Care Med* 2019; XX:00–00)

Key Words: acute kidney injury; critical illness; renal replacement therapy

Acute kidney injury (AKI) occurs in about half of critically ill patients (1, 2) and is associated with high morbidity and mortality (1, 3, 4). The incidence of AKI treated with renal replacement therapy (RRT) in this population is increasing steeply over time (5, 6). Paradoxically, contemporary treatments aimed at improving outcomes in critically ill patients—such as low-tidal ventilation for acute respiratory distress syndrome and aggressive volume resuscitation for patients with sepsis—may be hastening the initiation of dialysis in patients with AKI by predisposing patients to acidemia and volume overload (7).

For purposes of this review, we define AKI-RRT as AKI for which RRT is delivered. As we will discuss in more detail later, the evidence regarding the timing of initiation of RRT for AKI is evolving and, thus, the decision when or whether to initiate RRT in a given patient with AKI is somewhat arbitrary and depends heavily on the judgment of the treating clinician, except in certain well-defined circumstances. In that light, we use AKI-RRT as a phenomenological construct that describes the use of RRT in patients with AKI. The conditions that define AKI-RRT vary widely across the evidence we cite in this review.

More than 20% of critically ill patients with AKI will undergo dialysis within the first week of their ICU stay (1). AKI in that setting is associated with a mortality rate around 50% (6) and a six-fold risk of dying in the hospital compared with patients without AKI (1). Clearly, AKI in the ICU is common, and when associated with RRT, is a dreaded event. Although the mortality of patients with AKI-RRT may have decreased somewhat over time (6), that is more likely due to improvements in the general care of critically ill patients (7) than to improvements in dialysis delivery. Nonetheless, wider adoption of evidence-based best practice in RRT for critically ill patients with AKI carries the potential to improve outcomes in a highly vulnerable population.

In this synthetic review, we address the question, "What is the evidence supporting best practice for RRT in critically ill patients with AKI?" To answer that question, we will discuss the evidence in several relevant domains of recent interest: 1) the timing of initiation of RRT in AKI, 2) optimal vascular access for AKI-RRT, 3) RRT modality selection, 4) dose or intensity of RRT, and 5) choice of anticoagulation for RRT. We will focus our discussion on recent evidence.

WHEN SHOULD RRT BE INITIATED FOR AKI IN CRITICALLY ILL PATIENTS?

The optimal timing of initiation of RRT for patients with AKI has been debated for decades. Were RRT risk-free, there would be no debate, but that is not the case. Although RRT in

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its various forms is generally safe, there are recognized associated adverse events, such as hypotension, complications of anticoagulation, allergic reactions to system components, and complications of vascular access (8). There is a strong consensus, however, that the benefits of RRT outweigh the risks when AKI is complicated by refractory hyperkalemia, volume overload, metabolic acidosis, or signs of uremia, such as pericarditis or encephalopathy. Under those circumstances, RRT is considered to be urgent or emergent (9). In addition, RRT is life saving for patients with certain intoxications (10).

Outside these conventional emergent indications, the optimal timing of RRT initiation in AKI is uncertain. The uncertainty is based partly on an understanding of the natural history of AKI, which is characterized by spontaneous recovery of renal function in a substantial proportion of patients. For patients whose AKI may be on the verge of recovery, "early" initiation of RRT might expose them to the risks of RRT without any benefit. On the other hand, delaying treatment could result in increased morbidity owing to the effects of fluid and toxin accumulation (2).

A number of criteria have been used over the decades to shed light on the issue of "early" versus "late" initiation of RRT. These include a host of biomarkers, used either to define "early" and "late," or to predict which patients with AKI might benefit from RRT. Most recently, investigators have classified "early" and "late" by the time to initiation of RRT relative to the diagnosis of AKI. Both types of studies typically analyze important outcomes such as mortality and duration of RRT.

Several kidney injury biomarkers have been tested for their ability to predict the need for RRT in AKI (11). A recent meta-analysis showed that a number of biomarkers fulfill this criterion, including conventional analytes like serial plasma creatinine and urea concentrations, as well as novel markers such as neutrophil gelatinase-associated lipocalin (NGAL) and interleukin 18 (12). The authors of the meta-analysis advised caution in interpreting the results because the included studies were heterogeneous and most of them did not standardize the criteria for initiating RRT, thus introducing substantial opportunity for confounding by indication (12). NGAL has been extensively studied as a kidney injury marker under a variety of circumstances. NGAL may be problematic in critically ill patients with AKI, however, since it appears to be a marker for systemic inflammation as well as kidney injury, such that the systemic inflammatory signal may swamp the kidney injury signal (11, 12). Indeed, in a small pilot forerunner of the ongoing STandard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial, including many patients with sepsis, baseline whole-blood NGAL concentration was uniformly high and did not discriminate patients who eventually underwent RRT from those who did not (13).

The U.S. Food and Drug Administration recently approved a kidney injury test that reports the product of two urinary biomarkers of cell-cycle arrest: tissue inhibitor of metalloproteinase (TIMP)–2 and insulin growth factor binding protein (IGFBP)–7 (TIMP-2 × IGFBP-7). A recent meta-analysis showed the product of these two biomarkers predicted the need for dialysis with reasonable accuracy, the area under the receiver operating characteristic curve (AUC) being 0.86 (12). Although the investigators urged caution based on small sample size, if future studies support the existing data, this biomarker could help discriminate patients with AKI who are likely to recover kidney function without the need for RRT from those in whom prompt intervention may be beneficial.

The "furosemide stress test" is another promising biomarker (14, 15). In a cohort study of 77 patients with early AKI, Chawla et al (14) administered IV furosemide (1 mg/kg for diuretic-naïve patients or 1.5 mg/kg for diuretic-exposed patients) and measured urinary volume 2 hours after injection. A volume less than 200 mL had 87% sensitivity and 84% specificity of worsening of AKI (14). The test predicted the need for RRT remarkably well (AUC, 0.86 ± 0.08) and outperformed a number of other biomarkers (15). Larger trials are needed to confirm these intriguing results.

Assessing the value of biomarkers as predictors of RRT may be subject to bias insofar as the assay result might influence the decision to start RRT (12). Large trials have mitigated this bias through blinding (16).

A comprehensive meta-analysis of studies that defined "early" and "late," based either on biochemical variables or on timing, found no difference in mortality, or ICU or hospital length of stay between the early and late RRT initiation groups (17). Only seven of the reviewed studies, however, were randomized, prospective trials, and sample size was relatively small. Furthermore, most of the reviewed studies were observational and included only patients who underwent RRT. The meta-analysis, therefore, provides no information about the impact of a "late" strategy in which some patients might recover before requiring RRT.

Recently, the results of three major randomized trials were published (18–20). Although they provide much new information, they do not entirely resolve the question of whether early RRT benefits patients with AKI. In the Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients with Acute Kidney Injury: The ELAIN Randomized Clinical Trial (20), 231 critically ill patients from a single center in Germany were randomized to either early (within 8 hr of diagnosis of Kidney Disease: Improving Global Outcomes [KDIGO] stage 2 AKI) or delayed (within 12 hr of diagnosis of stage 3 AKI or for conventional indications) initiation of continuous RRT (CRRT) (20). On average, patients in the early arm underwent RRT within 6 hours of reaching stage 2 AKI and those in the late arm 25.5 hours. Patients in the early group had a significantly lower 90-day mortality (39.3% vs 54.7%), a higher rate of recovery of renal function by day 90 (53.6% vs 38.7%), as well as a shorter duration of RRT dependence, mechanical ventilation, and hospital length of stay.

The Artificial Kidney Initiation in Kidney Injury (AKIKI) trial was larger, performed in 31 centers in France. In that trial, 620 critically ill patients were randomized to either early RRT (within 6 hr of diagnosis of KDIGO 3 AKI) or delayed (for conventional indications) (19). In either group, patients could receive either CRRT or intermittent hemodialysis (IHD) or transition from one modality to the other. There was no difference in survival

or dialysis-free survival between the groups. Furthermore, there were more catheter-related bloodstream infections in the early-strategy group (10% vs 5%; $p = 0.03$) (19). Finally, it is important to note that almost half the patients randomized to the delayed treatment arm did not ultimately receive RRT.

In the 29-center Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis (IDEAL-ICU) trial (18), 488 patients with early septic shock and AKI were randomized to either early or delayed RRT (mixed modalities), based on the time after meeting the "failure" criterion of the Risk, Injury, Failure, Loss and End-stage renal failure (21) scale: within 12 hour in the early arm and within 48 hours in the delayed arm. Patients in the delayed arm were eligible to receive RRT before 48 hours if they met conventional criteria for urgent RRT or to receive no RRT if they recovered renal function spontaneously. The trial was stopped early for futility. There was no difference between groups in the primary outcome of 90-day mortality. Twenty-nine percent of patients assigned to the delayed arm recovered renal function before requiring RRT.

Beyond the number of sites for patient recruitment, there were some important differences among AKIKI, ELAIN, and IDEAL-ICU that could explain the discrepancy in outcomes. First, the triggers chosen for early or delayed RRT were different among the trials; the delayed treatment criterion in ELAIN was similar to the early-treatment criterion in both AKIKI and IDEAL-ICU. Second, RRT modality was almost exclusively CRRT in the ELAIN trial, whereas AKIKI and IDEAL-ICU allowed a mix of modalities. All the trials were powered to detect large differences in outcomes between groups (18% for AKIKI and IDEAL-ICU and 15% for ELAIN) (18–20). This calls into question the power of the studies to detect the reported differences. The interested reader is referred to more detailed critiques of ELAIN and AKIKI (22, 23).

Pending the results of that trial, expanding on the available data may help to inform our practice. Several recent observational studies have shown that contemporary RRT is commonly initiated before the development of classical or conventional indications, most often for oliguria or anuria (24–26). Whether these practice patterns have had any impact (positive or negative) on mortality is unclear, although it is tempting to speculate that any improvement over time in outcome in patients with AKI-RRT (6) may be attributable to earlier RRT intervention. Those who support such a view point to the results of a post hoc analysis of the AKIKI trial, examining mortality by timing of RRT regardless of group assignment. The investigators found that patients who did not undergo RRT had the lowest mortality rate (37%). Those who had RRT early had a mortality rate of 49% and those whose RRT was delayed, 62% (19). A similar analysis of the IDEAL-ICU trial data (18) shows the following mortality by treatment: no dialysis, 26%; early RRT, 56%; delayed RRT without urgent indications, 55%; and delayed RRT with urgent indications, 68%. Thus, although a substantial proportion of patients assigned to the delayed treatment arm never required RRT and had the lowest mortality rate, those who had delayed RRT for urgent or conventional indications had the highest mortality rate.

Taken together, the findings of the trials to date appear to favor a delayed RRT strategy for patients with AKI, tempered by a willingness to respond to the characteristics of each individual patient so as to avoid urgent or emergent indications for RRT. Such an approach will require close attention to the trajectory of each patient's manifestation of AKI. In that light, patients with refractory oliguria are likely to benefit from early initiation of RRT. A larger, pragmatic trial is underway (STARRT-AKI, NCT02568722) and is likely to shed additional light on the critical question of timing of initiation of RRT in critically ill patients (13).

One situation that might precipitate prompt initiation of RRT is extreme fluid overload, short of the other urgent or emergent conventional indication for RRT. Fluid overload is associated with increased mortality in critically ill patients, especially those with kidney failure (27, 28). It is unclear whether fluid overload is a marker of severity of illness or a causal agent. Regardless, there is clear evidence that massive fluid accumulation is associated with increased time on the ventilator and increased ICU length of stay (29, 30). Unfortunately, there is no evidence from interventional trials to guide fluid removal strategies in hemodynamically stable patients, let alone in patients who are dependent on vasopressor medications (31). In the absence of such evidence, fluid management should be individualized to each patient. For hemodynamically stable patients with fluid overload, a trial of diuretic drugs before initiating RRT usually is safe and prudent (31). Response to loop diuretics in such circumstances has been associated with improved survival (32).

WHAT IS THE OPTIMAL VASCULAR ACCESS FOR RRT IN AKI?

Once the decision is made to initiate hemodialysis in patients with AKI, a dialysis catheter needs to be placed. Tunneled, cuffed catheters are rarely used for initial vascular access in patients with AKI, partly because the average duration of dialysis dependence for patients with AKI is less than 2 weeks (33, 34). (Patients with AKI who are likely to require dialysis for longer than 2 wk, based on their course to date, should have a tunneled, cuffed catheter placed to reduce the risk of bloodstream infection.) In general, femoral or internal jugular (IJ) insertion sites appear to carry equivalent risk of bloodstream infections and catheter dysfunction (35, 36), although patients' body habitus may influence the rate of catheter-related infections by site of catheter insertion. A large study in which patients were randomly assigned to catheter insertion in the IJ or femoral site showed that patients with high body mass index (BMI > 28.4) had a higher rate of catheter bacterial colonization upon removal from the femoral versus the IJ site. Conversely, those with low BMI (< 24.2) had a higher rate of catheter bacterial colonization when the IJ site was used. There was no difference in the rate of catheter-related bloodstream infection in that study (37). These observations suggest that the femoral vein should be the dialysis catheter insertion site of last resort in overweight or obese patients.

A left IJ catheter, because of its more tortuous route into the superior vena cava than that of a right IJ catheter, may have a

higher incidence of catheter malfunction and subsequent central venous stenosis (38); thus, the right IJ insertion site is preferred. The subclavian insertion site should be avoided in any patient likely to develop end-stage kidney disease because it is most strongly associated with the development of central vein stenosis (9), which can result in intractable venous hypertension in the ipsilateral upper extremity after placement of an arteriovenous access for hemodialysis. Catheter length is critical for proper function. In one single-center study, IJ catheters whose length allowed placement of the tip in the right atrium (rather than the superior vena cava) were more likely to provide uninterrupted dialysis treatments with better measures of adequacy, without an increase in atrial arrhythmias (39). To achieve proper catheter tip placement in that study, a 20 cm catheter was used in the right IJ insertion site and a 24 cm catheter in the left (39). No patients with right atrial tip placement suffered atrial perforation in that study, in which soft silicone catheters were used exclusively. Perforation of great vessels, including the right atrium, occurs in only about 0.25% of catheter placements, and almost always appears to be attributable to operator error during catheter insertion rather than to the location of the catheter tip (40). Furthermore, most perforations were reported in the 1970s and 1980s, when more rigid catheters were used (40). To minimize the risk of perforation, proper insertion technique is essential, and soft silicone catheters should be used. If the clinician chooses the femoral site, a catheter at least 24 cm long should be inserted in order to place the tip in the inferior vena cava and thus minimize the risk of recirculation of blood in the dialysis circuit, leading to inadequate dialysis (41).

WHAT IS THE OPTIMAL RRT MODALITY FOR PATIENTS WITH AKI?

CRRT have intuitive appeal over IHD in critically ill patients with AKI. There are several complications of IHD that can, at least theoretically, be obviated by CRRT. The most problematic of these is intradialytic hypotension, which results from fluid removal on dialysis at a rate that exceeds vascular refilling from the intracellular and interstitial compartments. Intradialytic hypotension is a common complication in critically ill patients who often have the vexing combination of fluid overload and hemodynamic instability. Other potential problems with IHD include rapid shifts in electrolyte concentration and pH. Thus, CRRT seems like an ideal modality for dialysis of critically ill patients, as it would be predicted to cause—by virtue of its slow, continuous nature—less hypotension and less radical electrolyte and pH perturbation than IHD.

Indeed, several early observational trials suggested that CRRT conferred a survival advantage compared with IHD (42, 43). Well conducted, prospective trials, however, did not confirm these initial impressions. For example, the Hemodiafe study, conducted in 21 centers in France, showed no difference in the survival of critically ill patients randomized to CRRT or IHD (44). One meta-analysis of nine relatively small and heterogeneous trials found no difference in survival between patients assigned to CRRT or IHD and no difference in rate of renal recovery (45). A comprehensive systematic review of 30 randomized clinical trials and eight cohort studies likewise found no difference in survival or renal recovery in patients assigned to CRRT versus IHD (46). Finally, a recent meta-analysis that included studies of CRRT, IHD and an intermediate modality, sustained low-efficiency dialysis, found no survival advantage of one modality over another (47).

Since the available evidence shows no clear superiority of one modality of RRT over another, the choice may best be based on resource availability, local expertise, and the immediate needs of the patient. Most clinicians favor, and guidelines support (9), the use of CRRT for patients in shock or with hemodynamic instability, but even hemodynamically unstable patients may benefit from IHD for emergency treatment of extreme hyperkalemia or intoxications (48). In order to minimize hemodynamic perturbation in critically ill patients on IHD, the prescription may need to be modified. Exacerbation of hemodynamic instability may be mitigated by extending treatment time (an average of 5.2 hr per session in the Hemodiafe trial [44]), for example, raising the bath sodium concentration to 145–150 mmol/L and reducing the bath temperature to 35°C.

Many patients transition from one modality to another during the course of their AKI, usually from CRRT to IHD as their hemodynamic instability resolves. Increasingly, hybrid modalities that provide RRT for 6–18 hours per day, collectively referred to as prolonged intermittent RRT (PIRRT), are used either as an initial modality or as a transition between CRRT and IHD (49). PIRRT has the advantage over CRRT of intermittently freeing the patient from the extracorporeal circuit, for procedures, imaging studies, or physical therapy, for example. PIRRT, by its intermittent nature, poses a particular challenge in the dosing of medications removed during the treatment, especially antibiotics (50, 51). There are no convincing data that demonstrate a difference in important clinical outcomes with PIRRT, compared with other RRT modalities (49).

RRT comprises two processes across a semipermeable filter membrane: convection, the movement of bulk fluid and its dissolved solutes driven by a pressure gradient; diffusion, the movement of low molecular weight solutes driven by their concentration gradient. In the context of RRT, first process is called hemofiltration and the second hemodialysis. When both processes are combined, it is known as "hemodiafiltration." Extraction of medium-sized and large molecules from the blood is greater with convective rather than diffusive methods. Several studies have examined effects of convective modalities on cytokines in patients with sepsis and AKI (52–55). One of those studies showed enhanced reduction in plasma tumor necrosis factor-alpha concentration with a convective modality compared with a diffusive modality (53). Convective modalities such as continuous venovenous hemofiltration (CVVH), therefore, have been speculated to be advantageous. A meta-analysis of pooled data from randomized trials of hemodialysis versus hemofiltration, however, found no difference in patient survival or duration of RRT dependence (56). Similarly, a randomized multicenter trial of CVVH versus continuous venovenous hemodialysis in 78 critically ill patients with AKI

showed no improvement in severity of illness at 1 week or in 60-day mortality (57). Thus, current evidence does not provide a reason to choose a convective modality over a diffusive modality in the treatment of patients with AKI.

CRRT is strongly recommended over IHD for the management of AKI in patients with acute brain injury, in whom acute perturbations in plasma solute concentration may exacerbate intracranial hypertension which, in combination with systemic hypotension, may lead to critical cerebral hypoperfusion (58). In patients with acute liver failure and hyperammonemia, an observational cohort study suggests CRRT may improve survival compared with IHD (59), although no prospective trial has yet confirmed those preliminary observations.

WHAT IS THE OPTIMAL AMOUNT (DOSE) OF RRT THAT SHOULD BE DELIVERED?

The amount (dose) of RRT is a continuous variable and is measured either by urea kinetics in IHD or by total effluent volume in CRRT. Because kidney failure is thought to exert its deleterious effects at least partly through "uremic toxin" accumulation, one might reasonably expect that removing more toxins would lead to better outcomes. In other words, the higher the dose of RRT, the better. On the other hand, there may be risks to high-dose RRT—for example, removal of antibiotics or other critical medications, removal of amino acids, depletion of essential minerals—that outweigh its potential benefits. It is not surprising; therefore, that the ideal dose of RRT delivered to critically ill patients with AKI has been controversial.

The results of several relatively small trials provided no clear guidance on the issue of dose of RRT, with some supporting the concept that "more is better," (60, 61) and others showing no improvement in survival or recovery of renal function with higher doses of RRT (62, 63). Two large, well-conducted trials provide a more definite answer to the question of dose. In one trial, Palevsky et al (34) randomized 1,124 patients to low-intensity RRT (effluent rate 20 mL/kg/hr for CRRT or thrice weekly IHD treatments) or high-intensity RRT (effluent rate 35 mL/kg/hr for CRRT or six treatments weekly for IHD). (Fewer than 3% of the treatments used PIRRT.) Patients were permitted to move between treatment modalities during the trial, as their hemodynamic status changed. The study found no significant differences in mortality or renal recovery rate between low-intensity and high-intensity groups (34). The other trial, using CRRT exclusively, randomized 1,508 patients to either 25 mL/kg/hr or 40 mL/kg/hr and also found no significant differences in mortality or rate of renal recovery (33).

Two meta-analyses, using aggregate data from the two large trials and others, concluded that there was no difference between high-dose and standard-dose RRT with respect to either survival or rate of renal recovery (64, 65). A recent meta-analysis, combining individual patient data from seven trials (n = 3,682), drew the same conclusion regarding patient survival (66). Thus, there appears to be no benefit to high-dose RRT.

Lest one conclude that at least high-dose RRT seems not to be inferior to standard-dose, there are several observations to consider. Patients randomized to high-dose RRT had significantly lower rate of renal functional recovery (66) and significantly higher rates of hypophosphatemia (34, 64). The latter complication may perhaps impair tissue oxygen delivery (67). Furthermore, there is reason to believe that patients who receive high-dose CRRT often may receive inadequate antibiotic treatment due to a higher drug removal rate (68). These risks of high-dose RRT serve to emphasize that the available literature indicates the dose of RRT above which there is no benefit with respect to important clinical outcomes (a ceiling), but it has yet to define the "optimal" dose, which may be below the "standard" dose used in trials to date. Indeed, it may be misleading to think of a single optimal dose of dialysis. Rather, it may be more sensible to dose RRT dynamically over the patient's course, termed "precision CRRT" in a recent consensus statement (69). Such an approach would be directed toward defined goals for control of specific solutes, pH or volume status, with the dose of RRT adjusted continuously to achieve and maintain such goals (69).

WHAT TYPE OF ANTICOAGULATION SHOULD BE USED?

Exposure of blood to the extracorporeal circuit during RRT promotes clotting. Blood clotting in the extracorporeal circuit results in treatment interruption and limits the effectiveness of the treatment. Methods to prevent coagulation, therefore, often have been incorporated into RRT prescriptions. Systemic anticoagulation for RRT carries the risk of bleeding, however, which must be balanced with the need to provide adequate RRT. A variety of strategies have been developed to mitigate the risk of bleeding.

For IHD, most treatments can be performed without any anticoagulant (34), because of the short duration and high blood flow rate. In patients at high risk of bleeding, even CRRT can be successfully performed without any anticoagulant and without sacrificing filter longevity or performance (70). A vascular access that delivers consistently high blood flow rate is key to preventing clotting in the extracorporeal circuit. Hemofiltration and hemodiafiltration (convective modalities) are associated with a higher risk of filter clotting than hemodialysis, because of higher hemoconcentration in the filter (71).

When anticoagulation is required for RRT, it may be either systemic or regional, that is, of the RRT filter only. Systemic anticoagulation usually is done by infusing unfractionated heparin. Most regional anticoagulation for CRRT is accomplished by infusing a trisodium citrate solution into the bloodline immediately before the filter, thereby chelating calcium. The dialysis fluid or replacement fluid must be calcium-free in this methodology. The regional citrate anticoagulation (RCA) is reversed by infusing a calcium solution into the circuit immediately before the blood returns to the patient. Systemic heparin and RCA are equally effective at preventing clotting, but RCA seems to be associated with fewer bleeding complications (72). The citrate infusion rate must respond to momentary changes in the blood flow rate through the circuit, and calcium infusion rate must then be precisely adjusted in order

to prevent hypo- or hypercalcemia. Citrate is metabolized to bicarbonate principally by the liver, so patients with intact liver function must be monitored for the development of metabolic alkalosis. Patients with impaired liver function or shock will accumulate citrate, generating a high anion gap metabolic acidosis and systemic calcium chelation, which may require an increase in the calcium infusion rate (73). Because of the complexity inherent in RCA, current guidelines recommend its use in CRRT only for patients without shock or liver failure and only by centers with an established RCA protocol (9).

CONCLUSIONS

AKI in critically ill patients is increasing in prevalence and is associated with high morbidity and mortality. There is no doubt that RRT in this setting can be life-saving. RRT has become much more sophisticated over the past decades, with more available modalities, each with its merits in particular situations. Evidence offers us guidance about best practices for vascular access in patients requiring RRT. We now have clear guidance about the optimal ceiling dose of RRT, and a consensus is emerging about the need to individualize and continuously adjust the patient's dose according to the immediate and evolving goals of treatment. The advantages and disadvantages of different strategies for anticoagulation during RRT are clearly delineated. We remain unsure, however, about the timing of initiation of RRT, apart from that driven by traditional emergent indications. Ongoing trials will shed light on this critical issue.

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