

## Delivery of Renal Replacement Therapy in Acute Kidney Injury: What Are the Key Issues?

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**Background and objectives:** The prescription and delivery of renal replacement therapy for acute kidney injury is subject to a wide variation and is conditioned by a multiplicity of factors. A variety of renal replacement therapy modalities are now available to treat acute kidney injury; however, there are no standards for the dosage, choice of modality, and intensity and duration of these therapies. Although several observational and interventional studies have addressed these topics, there are no consensus recommendations in this field.

**Design, setting, participants, & measurements:** The available literature on this topic and draft consensus recommendations for research studies in this area were developed using a modified Delphi approach and an international multidisciplinary network.

**Results:** The following questions were most important: What is the “dosage” of renal replacement therapy delivered to patients with stage 3 acute kidney injury? What is the optimal “dosage” of renal replacement therapy to maximize patient and renal survival? Is there a minimal “dosage” of renal replacement therapy required in patients with single-organ failure? Does modality of renal replacement therapy selected have an effect on patient and/or renal survival? In cases of continuous renal replacement therapy, does citrate anticoagulation confer a benefit?

**Conclusions:** This report summarizes the available evidence and elaborates on the key questions and the methods that should be used so that the goal of standardizing the care of patients with acute kidney injury and improving outcomes can be achieved.

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Given the wide variation in clinical practice relating to the indications for and timing of renal replacement therapy (RRT), patients who receive RRT are considered to have reached stage 3 acute kidney injury (AKI; or stage F of the RIFLE criteria [risk, injury, failure, loss, ESRD]), irrespective of the stage that they are in at the time of RRT initiation (1,2).

In the early 1980s, the options for RRT were limited to intermittent hemodialysis (IHD) and acute peritoneal dialysis (PD). At that time, IHD was routinely performed thrice weekly, typically using acetate-based dialysate, warmed to body tem-

perature, with low-flux cellulosic membrane dialyzers and dialysis machines that lacked accurate volumetric control. IHD treatments in the intensive care setting were frequently complicated by hypotension, as a result of the amount of ultrafiltration required, often exacerbated by the use of parenteral nutrition. In an attempt to overcome these problems, continuous forms of RRT (CRRT) were developed, based on the original description by Kramer *et al.* (3) of a simple ultrafiltration device. Initially, these devices were spontaneous, using indwelling arterial catheters; however, the clearances derived from such continuous arteriovenous hemofiltration (CAVH) circuits were often insufficient, with additional IHD treatments required (4). For increasing the efficiency, dialysate was added (CAVHD), and then pumped venovenous circuits developed (continuous venovenous hemofiltration [CVVH] and continuous venovenous hemodiafiltration [CVVHDF]), initially by enthusiasts and finally by industry with purpose-designed CRRT

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machines. Before the introduction of specifically designed CRRT machines, the volumes of fluid that could be exchanged safely had been limited by the technology available, but now much higher volume exchanges are feasible. Just as CRRT has moved forward in the past 25 yr, so has IHD, with the introduction of bicarbonate-based dialysates, the understanding of the importance of thermal balance and dialysate sodium concentration to prevent intradialytic hypotension (5), synthetic membrane dialyzers, and IHD machines with biofeedback control. In addition, in the past decade, a midway technique between CRRT and IHD has been pioneered, variously known as "hybrid" therapies, including extended duration dialysis (EDD), sustained low-efficiency dialysis (SLED), and the batch dialysate Genius system (Table 1). Despite the increasing technological sophistication of RRT, key clinical management issues such as the optimal dosing of therapy and whether the selection of treatment modality has an impact on patient and renal survival remain to be determined.

## Materials and Methods

A multidisciplinary stakeholder committee that comprised representation from the 18 leading international professional societies of critical care and nephrology was convened. The committee was designed to include clinicians who are involved in adult medicine and pediatrics, as well as basic scientists and representatives from translational research, policy development, and the National Institutes of Health. Six focus groups were then created to review specifically key topics within the field of AKI.

An overall research agenda was developed by the committee as an iterative process using a three-step modified Delphi procedure. Briefly, this consisted first of a literature review phase before the meeting, designed to identify key unanswered questions. Then at a 3-d conference, the focus group questions were presented to the entire committee. Feedback was provided, and during the subsequent 2 d, the questions were refined by the focus group using a previously published method (6). The facilitators provided input to improve the quality of each research question using criteria developed by the AGREE collaboration (7). Once the focus group had developed a final set of research questions with input from the entire committee, the third step in the Delphi process was to survey individually each of the members to determine the priority for each research question. This was done in real time at the conference. Prioritization was then accomplished by asking each member to assign a ranking to each of the research questions. Overall,

research priorities generated from nephrologists and intensivists were similar and highly correlated ( $r^2 = 0.5$ ,  $P = 0.0022$ ).

## Results

The work group considered the following questions most important:

1. What is the "dosage" of renal replacement therapy delivered to patients with stage 3 AKI?
2. What is the optimal "dosage" of RRT to maximize patient and renal survival?
3. Is there a minimal "dosage" of RRT required in patients with single-organ failure?
4. Does modality of RRT selected have an effect on patient and/or renal survival?
5. In cases of CRRT, does citrate anticoagulation confer a benefit?

## Discussion

### *Dosage of RRT*

In patients with stage 5 chronic kidney disease (CKD), treated by regular dialysis, the term "dosage" is used to describe urea clearance achieved during RRT. The evidence from CKD suggests that urea *per se* is not a major azotemic toxin and similarly is unlikely to play a major pathogenic role in patients with AKI; however, the measurement of urea is readily available and inexpensive and is used as a surrogate for nitrogen protein turnover. Thus, urea generation rates will differ between patients as a result of patient-specific factors, such as age, gender, and race, and also disease-specific factors, including muscle injury and/or breakdown, sepsis, and liver disease, and is also influenced by medical therapy such as nutritional support.

The dosage of RRT delivered to patients includes not only small solute clearances but also larger "middle" molecules. The amount of these other molecules removed will depend on the modality used, greater for convective than dialysis-based techniques, and "middle" molecule clearance by intermittent therapies is also affected by both frequency and duration of therapy. In addition to solute clearances, the prescription and delivery of renal support to patients with stage 3 AKI includes other key aspects of medical management, including sodium and water balance and correction of acid-base imbalance. There

Table 1. Comparison of various modalities for treating adult patients with stage 3 AKI<sup>a</sup>

Parameter	Modality			
	IHD	Hybrid	CRRT	PD
Blood flow (ml/min)	200 to 300	125 to 200	75 to 200	Nil
Dialysate flow (ml/min)	500 to 900	100 to 200	0 to 40	25 to 33
Filtration flow (ml/min)	0 to 750	0	0 to 50	Nil
Anticoagulation	Usually	Yes	Usually	No
Duration (h)	4 to 6	8 to 16	24	24
Frequency	Daily/alternate-day	Daily	Daily	Daily

<sup>a</sup>Although intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT) can be performed without anticoagulation, most units use anticoagulants. AKI, acute kidney injury.

are fundamental differences in terms of providing RRT in patients with CKD compared with AKI; for example, patients with CKD become sodium loaded between dialysis sessions and treatment has to be designed to remove this additional sodium, whereas in AKI, patients are often initially resuscitated with large volumes of high-sodium fluids but thereafter usually receive low-sodium fluid. Thus, in AKI, sodium balance and flux are often variable and will be affected by RRT delivery and modality.

Traditionally, in studies in patients with AKI, the dosage of treatment has been assessed by urea clearance in dialysis-based modalities and by ultrafiltration volume (a surrogate of urea clearance) in the convective therapies. There is a paucity of data regarding "adequate" treatment dosage of IHD to be delivered in AKI. One retrospective study reported that dialysis dosage did not have any impact on patient survival in patients at the extremes of illness severity (8), whereas for patients with intermediate severity of illness, the delivery of dialysis dosage in excess of the 50th percentile ( $Kt/V$  approximately 1) was associated with lower mortality risk than lower dosages. Because of the lack of prospective studies addressing the minimum dosage of RRT required in AKI, a consensus panel convened by the multinational Acute Dialysis Quality Initiative (ADQI) recommended that patients with AKI receive at least the minimum dosage that is considered appropriate for patients with ESRD (1). Because of the difficulty in assessing the volume of distribution of urea in patients with AKI, several studies have shown that the delivered dosage of IHD can be markedly lower than that prescribed and is not routinely measured in clinical practice (8–11).

Only one study has evaluated the effect of daily and alternate-day IHD on the outcome among patients with AKI (9). This reported both lower mortality (28 versus 46%;  $P = 0.01$ ) and shorter duration of AKI ( $9 \pm 2$  versus  $16 \pm 6$  d;  $P = 0.001$ ) in the daily IHD group, although the dosage of dialysis delivered to the alternate-day group was exceptionally low (mean delivered  $Kt/V$   $0.94 \pm 0.11$ ). This probably accounted for the markedly increased time-averaged urea concentration and the high incidence of complications including gastrointestinal bleeding, mental status alterations, and infections reported in this group; however, one important finding was the reduction in the number of intradialytic hypotensive episodes in the daily IHD group as a result of the lower ultrafiltration rates required compared with the alternate-day treatment group.

Several studies have looked at dosage in CRRT. In one of the largest studies, Ronco *et al.* (12) randomly assigned 425 patients to one of three CVVH dosages, defined by achieved daily ultrafiltration rates of 20, 35, and 45 ml/kg per h. Mortality was markedly lower in the intermediate- and high-dosage arms (43 and 42%, respectively) compared with the low-dosage arm (59%;  $P < 0.001$ ). This reported survival benefit of higher dosage therapy was not substantiated in a later but smaller study (13); however, a more recent study reported a significant increase in 90-d patient survival from 34 to 59% by addition of a dialysis dosage of  $18 \pm 5$  ml/kg per h to CVVH with an ultrafiltration rate of  $25 \pm 5$  ml/kg per h (14). Although definite conclusions on the optimal dosage of CRRT cannot be drawn,

the available data suggest that CVVH should be dosed  $>20$  to 25 ml/kg per h to either provide an ultrafiltration rate of at least 35 ml/kg per h or be supplemented with additional dialysis. Two large, multicenter, randomized, prospective trials that are under way in the United States and Australia and New Zealand are designed to define further the optimal dosing strategy of RRT in AKI.

Older studies that used PD in critically ill patients reported markedly reduced urea and creatinine clearances in patients who had multiple organ failure and were on vasopressors, compared with IHD and CRRT (15), probably related to changes in mesenteric blood flow. More recently, CRRT was reported to be superior to PD in treating patients with malaria-induced AKI (16), and this may have been due to the dosage of PD delivered, because the rate of creatinine clearance and correction of acidosis were much inferior during PD therapy; however, PD has been shown to be a clinically effective therapy in treating AKI, particularly in children after cardiac surgery. Very few studies have monitored the dosage of PD delivered to patients in AKI; one such study reported a weekly  $Kt/V$  urea in excess of 2.1, with a median creatinine clearance of 74.3 L/wk per  $1.73 \text{ m}^2$  in children after cardiac surgery (17). Just as no studies have examined the optimum dosage of PD required for patients with single-organ and/or multiple-organ failure, there is a similar paucity of data on the recently introduced hybrid treatments (*e.g.*, Genius, EDD, SLED). Preliminary studies suggest that EDD systems have comparable small solute clearances to conventional CRRT but are less effective in terms of middle molecule clearances (18).

#### Modality of RRT

Although it is widely perceived that CRRT is superior to IHD in hemodynamically unstable, critically ill adult patients, prospective, randomized clinical trials have failed to confirm this supposition. In many of the earlier trials, there was a bias for the more critically ill patients to receive CRRT rather than IHD. For example, Swarz *et al.* (19) retrospectively compared patients who were treated with CVVH or IHD and reported a two-fold greater mortality in patients who were treated with CVVH; however, after adjustment for severity of illness, there was no difference. Similarly, in another prospective study, mortality was 79% in patients who were treated with CRRT compared with 59% in the IHD-treated group, but after adjustment for comorbidities, the modality of RRT was no longer a risk factor for outcome (20).

Six randomized, prospective, controlled trials that compared CRRT and IHD from Europe and the United States have been published in the past 5 yr. The smallest of these trials was designed to compare the effects of CVVH and IHD on systemic hemodynamics and splanchnic perfusion in patients with septic shock, with an overall mortality of 70% in both the CVVH and IHD groups (21). In a multicenter US trial of 166 patients with AKI, Mehta *et al.* (22) reported intensive care unit (ICU) and hospital mortality rates of 59.5 and 65.5%, respectively, in patients who were randomly assigned to CRRT as compared with 41.5 and 47.6%, respectively, in patients who were randomly assigned to IHD ( $P < 0.02$ ). Again, after covariate adjustment,

there was no difference in mortality attributable to modality of RRT. In addition, in this study, there was a high rate of crossover between the treatment modalities. In a single US center trial, 80 patients were studied, and although greater hemodynamic stability and fluid removal were reported during CVVHD compared with IHD, there was no difference in survival (23). Similarly, a Swiss study that randomly assigned 125 patients to either CVVHD or IHD reported an ICU mortality of 34 and 38%, respectively, for the two modes of RRT and no difference in final hospital mortality (24). Another trial, from Zagreb, of 104 patients again failed to show any superiority of CRRT over IHD (25). In addition, the largest of the recent studies, the Hemodiafe study, a multicenter, randomized, controlled trial of 359 patients, reported no difference in mortality according to mode of RRT used (IHD *versus* CVVHD) (26). This study is noteworthy because IHD was successfully delivered to patients despite marked hemodynamic instability with very little crossover between treatment groups. The authors deliberately chose cooled dialysate in combination with a very high dialysate sodium concentration to minimize cardiovascular instability during IHD and compared with other studies delivered the highest Kt/V dosage in the IHD group.

Meta-analyses comparing outcomes among the various modalities of RRT have been published, suggesting no difference in patient outcome or a possible advantage of CRRT in the critically ill patient (27,28). These analyses did not include the more recent Swiss and French studies and were compounded by the various modalities used in the CRRT groups, varying from CAVH, to CVVH, to CVVHD (29).

Many ICU patients have hemodynamic instability; coupled with the frequency of intradialytic hypotension during IHD, this has led to the suggestion that CRRT may be associated with an increased likelihood for recovery of renal function (21,30,31). This improvement in renal recovery in survivors has been supported by two recent reports of clinical practice, although in both studies, only a minority of patients received IHD (32,33). Although this benefit has been reported in surviving patients, this potential advantage may be reduced by mortality (31).

Studies comparing other forms of RRT have been limited. No studies have directly compared hybrid treatments with either IHD or CRRT, although hybrid therapies have been shown to provide similar hemodynamic stability and solute control when compared with CRRT (18). Although PD is widely used in pediatric practice, more and more units are using various forms of CRRT and hybrid technologies, but as of yet, there are no comparative data.

In summary, analysis of the currently published studies do not allow evidence-based guidelines for the selection of RRT modality for the treatment of AKI. The modality chosen should therefore be guided by the individual patient's clinical status, medical and nursing expertise, and the availability of equipment; however both the frequency and the duration of IHD and/or filtration treatments should be adjusted to minimize episodes of intradialytic hypotension by avoiding high ultrafiltration rates.

### *Choice of Hemodialyzer/Hemofilter Composition*

Until recently, there was a marked cost difference between unmodified cellulosic (cuprophane), modified cellulosic, and synthetic membranes. Laboratory experiments showed that synthetic membranes tended to cause less activation of complement and mononuclear cells, and studies were set up to evaluate whether membrane choice affected outcomes in AKI.

Because of the differences reported in original studies, several meta-analyses have been conducted (33–35). These showed that although there was a possible patient survival and renal recovery advantage when synthetic membranes were compared with cuprophane membranes, there was no difference between synthetic and altered cellulosic membranes. As cuprophane membranes have been phased out over time and the price differential between synthetic and modified cellulosic membranes have narrowed, the impact of membrane choice on patient outcome has become somewhat *passé*.

### *Choice of Anticoagulation during IHD/Hybrid Therapies and CRRT*

Although anticoagulation may not be required for all patients with AKI, anticoagulation is often required, particularly for hybrid therapies and CRRT to prevent clotting in the extracorporeal circuit. The most widely used anticoagulant for RRT in patients with AKI is unfractionated heparin (UFH) (36). Although an effective anticoagulant for IHD in patients with CKD, UFH may be less effective in AKI, because many critically ill patients have reduced levels of antithrombin, especially during CRRT. In addition, heparin is associated with a risk for bleeding and with the development of heparin-induced thrombocytopenia (HIT). Regional heparinization protocols, with reversal of heparin by infusion of protamine into the return line, have been developed to prevent systemic anticoagulation and minimize bleeding risk. Unfortunately, these protocols are cumbersome, may be associated with paradoxical increased risk for bleeding if excess protamine is infused, and do not alter the risk for HIT. If patients with HIT develop thrombosis or other major complications, then systemic anticoagulation with either the heparinoids danaparoid and Fondaparinux or the direct thrombin inhibitors hirudin and Argatroban is required (37) (Table 2). If, however, patients have HIT antibodies but no symptoms or signs of thrombosis, then other anticoagulants, including prostacyclin (prostaglandin I<sub>2</sub>), nafamostat, and citrate, are safe for patients with a history of HIT, provided that all exposure to heparin has ceased and systemic anticoagulation is not required. In the laboratory, there may be cross-reaction between the heparinoids and HIT antibodies, although only occasionally has this led to clinical cross-reactivity. The heparinoids require anti-factor Xa monitoring. Hirudin irreversibly binds to thrombin, and although some hirudin is removed during convective techniques, particularly with polysulphone membranes, the half-life can be markedly extended by the development of anti-hirudin antibodies. The relationship between plasma hirudin concentration and activated partial thromboplastin time is not linear, and the ecarin clotting time is more accurate. Argatroban requires a continuous infusion and requires dosage adjustment in liver disease. Although available

Table 2. Comparison of anticoagulants<sup>a</sup>

Anticoagulant	Half-Life (h)	Monitoring	Regional <sup>b</sup>	LD <sup>c</sup>	MD (h) <sup>c</sup>	Reversal	Clinical Use
UFH	0.6 to 2.0	ACT increased 40% aPTTr 1.5 to 2.0	No	500 IU	0 to 500 IU	Protamine	Standard Cheap
LMWH	5 to 27	antiXa 0.2 to 0.4 IU/ml	No	Tinzaparin 1500 IU, enoxaparin 0.5 mg/kg	0	Protamine VIIa	Predictable
Danaparoid <sup>d</sup>	30	antiXa 0.2 to 0.4 IU/ml	No	2500 IU	0	VIIa	HIT
Hirudin	>35	aPTTr <2.0 ECT	No	0.1 mg/kg	0	HDF VIIa	HIT
Argatroban	0.6 to 1.0	aPTTr <2.0	No	250 µg/kg	1 µg/kg per min	VIIa	HIT
Nafamostat	0.1	aPTTr <2.0	Yes	20 to 40 mg	20 mg/h	Stop infusion	Risk for bleeding
Prostacyclin	0.1	No standard test	Yes	0	2.5 to 5.0 ng/kg per min	Stop infusion	Risk for bleeding
Citrate	0.1	ACT 200 to 250 s Ca <sup>i/tot</sup>	yes	0	3 mmol/L Qb	Stop infusion	Risk for bleeding

<sup>a</sup>ACT, bedside activated clotting test; aPTTr, laboratory activated partial thromboplastin ratio; Ca<sup>tot</sup>, total calcium; Ca<sup>i</sup>, ionized calcium; ECT, ecarin clotting time; HDF, hemodiafiltration; HIT, heparin-induced thrombocytopenia; Qb, blood flow; LMWH, low molecular weight heparin; LD, loading dose; MD, maintenance dose; UFH, unfractionated heparin; VIIa, activated factor VII.

<sup>b</sup>Regional anticoagulant rather than a systemic anticoagulant.

<sup>c</sup>LD and MD based for 4-h IHD in a 70-kg patient with AKI but normal baseline clotting studies. In cases of bleeding, antidote reversal is given.

<sup>d</sup>Danaparoid is not licensed in the United States but is available in other countries.

in North America, it has only recently been introduced in Europe (38).

In the past decade, citrate has emerged as a very effective regional anticoagulant for CRRT. Citrate is infused into the prefilter line and works by chelating calcium. Calcium is then re-infused separately or into the return line to maintain a normal systemic ionized calcium. Citrate comes as a sodium salt, and each molecule is indirectly converted to three bicarbonates, so there can potentially be changes in sodium balance and acid-base status depending on the citrate load and the ability of the patient to metabolize citrate adequately. Thus, most centers that used citrate developed their own in-house dialysates and re-infusion fluids. It is only recently that pharmaceutical and dialysis companies have marketed specialized dialysates and re-infusion fluids designed for citrate systems. The advent of these commercially available fluids for citrate-based anticoagulation has increased the use in both adult and particularly pediatric practice, where circuit clotting has been a greater clinical problem. There have been few prospective comparative studies of UFH and citrate anticoagulation; in two such CRRT studies, the median circuit survival time was significantly prolonged with citrate (70 *versus* 40 h and 124 *versus* 38 h) (39,40), with reduced blood transfusion requirement and/or hemorrhage in the citrate groups. In Japan, nafamostat maleate is used as a regional anticoagulant and seems to have a similar efficacy and safety profile to citrate. Although UFH remains the most commonly used extracorporeal anticoagulant for RRT in patients with AKI, there is emerging data to support the safety and potential superiority of regional citrate anticoagulation for CRRT.

#### Choice of Dialysate Buffer for CRRT

Lactate and acetate have been used as the primary buffers for both replacement fluids and dialysates for CRRT, as a result of ease of sterility and prolonged storage life. Lactate and acetate are indirectly metabolized, in the liver and skeletal muscle, through to bicarbonate. The blood lactate level can increase

during lactate-based CRRT if the rate of administration exceeds the rate of metabolism, particularly in patients with preexisting lactic acidosis and/or impaired hepatic function, potentially contributing to increased protein catabolism and impaired myocardial contractility. Relatively recently, commercially available bicarbonate-buffered fluids have been introduced for CRRT, and although no study has shown a significant improvement in patient survival, two studies (41,42) both showed improved cardiovascular stability with bicarbonate-based fluids compared with lactate, with additionally better control of metabolic acidosis.

## Conclusions

While data on the optimal dosage of RRT for patients who have AKI and receive IHD, hybrid techniques, and/or PD are limited, an ultrafiltrate flow rate of 35 ml/kg per h in patients who are treated with CVVH or an additional dialysate clearance of  $18 \pm 5$  ml/kg per h seems to be associated with superior outcomes compared with rates of 20 to 25 ml/kg per h. Two prospective large clinical trials, designed to study the effect of small solute clearance on patient outcomes, are under way and will hopefully guide the design of future trials to address the dosage required to treat optimally patients with single-organ compared with multiple-organ failure and the importance of duration and frequency of treatment with the intermittent modes.

Current data do not suggest that any specific modality of RRT in patients with AKI is superior, although in critically ill patients, PD may be inferior. Until it can be established as to whether an optimal dosage of RRT is required in AKI, it is difficult to compare modalities that differ in the clearance of solutes and sodium flux. Similarly, because no treatment modality has been shown to be superior, the choice of modality should be made on the clinical condition of patients, medical and nursing expertise, and locally available facilities.

The benefit associated with less bioincompatible dialysis

membranes in AKI is uncertain, although, with time and the reduction in the cost of membranes, this has become *passé*.

Heparin remains the most common anticoagulant used in RRT for AKI, yet citrate may potentially offer certain advantages during CRRT. The advent of commercially available dialysates/replacement solutions designed for citrate anticoagulation will allow the effect of different anticoagulants to be investigated further with larger multicenter trials.

Bicarbonate-buffered fluids for CRRT are now commercially available. Although bicarbonate-based fluids are not associated with a survival advantage over standard lactate-based fluids, cardiovascular stability and control of acidosis are significantly improved with bicarbonate. Further trials are required to determine whether variable-dosage bicarbonate fluids are advantageous over fixed-dosage bicarbonate fluids.

## Disclosures

None.

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