Renal Replacement Therapy in Acute Kidney Injury

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Although the use of renal replacement therapy (RRT) to support critically ill patients with acute kidney injury (AKI) has become routine, many of the fundamental questions regarding optimal management of RRT remain. This review summarizes current evidence regarding the timing of initiation of RRT, the selection of the specific modality of RRT, and prescription of the intensity of therapy. Although absolute indications for initiating RRT—such as hyperkalemia and overt uremic symptoms—are well recognized, the optimal timing of therapy in patients without these indications continues to be a subject of debate. There does not appear to be a difference in either mortality or recovery of kidney function associated with the various modalities of RRT. Finally, providing higher doses of RRT is not associated with improved clinical outcomes.

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Acute kidney injury (AKI) is 1 of the most common serious complications in critically ill patients. Severe AKI occurs in more than 1 of every 20 patients requiring intensive care unit (ICU) care[1] and has been associated with mortality rates ranging from 50% to more than 70%.[1-4] In the absence of any effective pharmacologic therapies for AKI, its management remains supportive, focused on optimizing fluid balance, maintaining nutrition, preventing or treating electrolyte and acid-base disturbances, adjusting the dosing of medications that are excreted by the kidney, and avoiding secondary hemodynamic and nephrotoxic renal injury. Although these conservative therapies provide the initial underpinning of AKI management, renal replacement therapy (RRT) using 1 or more of the multiple modalities of dialysis and hemofiltration is often required. This review summarizes current evidence regarding the timing of the initiation of RRT, the selection of the specific modality of RRT, and the prescription of intensity of therapy.

Timing of the Initiation of Renal Replacement Therapy

The issue of when to initiate RRT in patients with AKI has been debated nearly as long as hemodialysis has been part of the armamentarium of clinical medicine. In 1960, in their seminal article on prophylactic dialysis in acute kidney injury, Paul Teschan and colleagues wrote:

> "While there is increasing recognition of the value of earlier dialysis, the *published* consensus, and the practice in many centers at present, is still to apply dialysis to relatively ill rather than to relatively healthy patients. This is implied by the usually quoted indications for dialysis, namely, definite or progressive clinical uremic illness and/or progressive potassium intoxication, occurring despite careful suppressive therapy."[5]

Emergent initiation of RRT in AKI in response to these standard indications—volume overload unresponsive to diuretic therapy; electrolyte and acid-base disturbances refractory to medical management, particularly severe hyperkalemia and metabolic acidosis; and overt uremic manifestations, such as pericarditis and encephalopathy—can be characterized as "rescue" therapy, in which initiation of treatment forestalls imminent death. More commonly, however, current practice is to initiate RRT pre-emptively, well before the development of these advanced complications, in patients with severe AKI in whom imminent recovery of kidney function is unlikely. The conundrum regarding the optimal timing for initiation of renal support in AKI derives in large part from uncertainty in predicting if and when kidney function will recover. In the absence of robust predictive markers, initiating therapy earlier increases the probability of exposing patients who might uneventfully recover kidney function if managed conservatively to the potential risks of RRT.

This tension between benefits of earlier treatment and risks of unnecessary treatment has been central to the long-standing debate over the timing of therapy. In 1960, Teschan and colleagues opined:

> "We would urge that dialyses applied to patients who might otherwise survive should not under any circumstances be considered to be superfluous. Rather, the judgment of whether to undertake dialysis should also be made in view of the possible risks of *not* employing this procedure. We would question both the wisdom and the safety of subjecting patients to several days of avoidable nausea, vomiting, drowsiness and thirst, which not only implies significant discomfort to the patient but may also impose considerable risk of aspiration, pneumonia and other unexpected 'complications.'"[5]

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One of the primary factors that has changed over the ensuing half-century is our concept of what constitutes "early" as opposed to "late" therapy. At the time that Teschan and colleagues were pioneering the use of prophylactic dialysis, conventional management was to wait until severe uremic symptoms were present.[5,6] In contrast, as the technology for RRT has become safer and treatment has become more routine, practices that in previous decades would have been considered "early" therapy are now considered to represent the "late" initiation of RRT. Despite increased safety, RRT remains associated with numerous risks—including catheter-related complications from insertion and infection; mechanical complications associated with the extracorporeal circuit, including the risk of severe blood loss; electrolyte disturbances and hemodynamic compromise associated with fluid and electrolyte shifts during treatment; and activation of humoral and cellular mediators from exposure to the extracorporeal circuit.[7-9] Exposure of blood to bioincompatible surfaces in the extracorporeal circuit and recurrent episodes of dialysis-associated hypotension have been postulated to delay recovery of kidney function.[7,9–12] In addition, consideration must also be given to the financial implications of the earlier initiation of treatment.

CLINICAL SUMMARY

- The optimal indications and timing of initiation of renal replacement therapy in critically ill patients with acute kidney injury is not known.
- There is no evidence that any single modality of renal replacement therapy is associated with improved survival or recovery of kidney function, although slower modalities (e.g., CRRT, PIRRT) may be better tolerated in hemodynamically unstable patients and may permit achievement of more negative fluid balance.
- Augmented doses of renal replacement therapy in critically ill patients with acute kidney injury are not associated with improved outcomes.

Although numerous studies over more than a half century have attempted to resolve the issue of optimal timing, the level of evidence guiding current practice remains weak, derived primarily from retrospective and observational cohort studies and small underpowered prospective trials. A series of observational studies published in the 1960s and early 1970s compared outcomes of patients with AKI who were treated in the years immediately before and after adoption of strategies using prophylactic initiation of dialysis.[13-15] In each series, during the earlier periods when dialysis was initiated "late" (blood urea nitrogen [BUN] levels >163-200 mg/dL), mortality rates were higher than subsequently when dialysis was started earlier (BUN levels <93-150 mg/dL).[13-15] Subsequently, 2 small prospective studies compared more intensive strategies of dialysis management, with earlier initiation of therapy, to more "conventional" management.[16,17] In the first study, 18 patients with post-traumatic AKI were assigned to either a more intensive regimen that maintained the predialysis BUN level at <70 mg/dL and the serum creatinine at <5 mg/dL or to a less intensive strategy in which dialysis was not performed until the BUN level approached 150 mg/dL, the serum creatinine level reached 10 mg/dL, or other indications for dialysis were present.[16] Five of 8 patients (64%) assigned to the more intensive regimen survived compared with 2 of 10 patients (20%) assigned to the less intensive strategy ($P = .14$). Major complications, including hemorrhage and sepsis, were also less frequent with earlier and more intensive dialysis. In the subsequent study, 34 patients with severe AKI were randomized in a paired fashion when their serum creatinine reached 8 mg/dL to either an intensive regimen, designed to maintain the predialysis BUN level at <60 mg/dL and the serum creatinine at <5 mg/dL, or to a delayed and less intensive regimen, in which the BUN value was allowed to reach 100 mg/dL and the serum creatinine reached 9 mg/dL.[17] The mean time from onset of AKI to initiation of dialysis was 2 days shorter (5 ± 2 days vs 7 ± 3 days) in the more intensive regimen. Mortality was slightly higher with the earlier and more intensive therapy (58.8% vs 47.1%); however this difference did not reach statistical significance ($P = .73$). On the basis of these data, conventional teaching was that in the absence of specific metabolic indications or symptoms, dialysis should be initiated when the BUN value approached a level of approximately 100 mg/dL but that no benefit was associated with earlier initiation of therapy.

The topic of timing of therapy then remained quiescent until the late 1990s, when Gettings and colleagues published a retrospective analysis of the timing for the initiation of continuous renal replacement therapy (CRRT) in 100 consecutive patients with post-traumatic AKI.[18] They observed that 39.0% of patients who were started on CRRT when their BUN level was <60 mg/dL (mean BUN level, 42.6 ± 12.9 mg/dL) survived compared with 20.3% of patients in whom CRRT was not begun until their BUN level was >60 mg/dL (mean BUN level, 94.5 ± 28.3 mg/dL; $P = .041$). Although this was not a randomized study, demographic factors and severity of illness at admission were comparable in the 2 groups, although rhabdomyolysis was more common in the early-initiation group and multisystem organ failure was seen more often in the late-initiation group.

In the past decade, there have been multiple additional studies comparing early and late initiation of dialysis.[19-32] The majority have been retrospective cohort studies or prospective observational studies and have used a wide variety of definitions for "early" and "late"

dialysis, with only 2 small randomized controlled trials. In the first of these trials, Bouman and colleagues randomized 106 critically ill patients with AKI to early high-volume continuous venovenous hemodiafiltration (CVVHDF) (n = 35), early low-volume CVVHDF (n = 35), and late low-volume CVVHDF (n = 36).[19] Hemodiafiltration was initiated in the 2 early-therapy groups within 12 hours of meeting study inclusion criteria, whereas it was withheld in the late group until metabolic or clinical criteria were met. There were no significant differences in survival among the 3 groups. Of note, of the 36 patients randomized to late therapy, 6 were never treated with RRT; 4 recovered kidney function and 2 died before meeting the criteria for late initiation of therapy. In the other randomized trial, 36 patients with AKI after coronary artery bypass surgery were randomized when their urine output was ≤30 mL/h and their serum creatinine had increased by ≥0.5 mg/dL per day.[20] In the early group, dialysis was started when the urine output remained <30 mL/h for 3 consecutive hours, whereas in the late group it was not started until the urine output fell to <20 mL/h for at least 2 hours. Only 28 patients (14 in each group) actually received protocol treatment; the remaining 8 patients did not fulfill the criteria for initiation of therapy. Of the patients treated per protocol, 12 patients in the early group (86%) were alive at 2 weeks compared with only 2 patients (14%) in the late group ($P < .01$).

A recent systematic review and meta-analysis of studies comparing early and late initiation of renal support published between 1985 and July 2010 by Karvellas and colleagues included 15 unique studies, including the 2 randomized controlled trials just described[33] (Fig 1). They calculated an odds ratio for 28-day mortality of 0.45 (95% confidence interval [CI], 0.28-0.72) associated with early initiation of renal support but noted that the methodologic quality of the included studies was low. In evaluating both the primary studies and the pooled conclusions of this meta-analysis, it is important to recognize a critical methodologic flaw affecting the majority of studies evaluating the timing of RRT. The vast majority of these studies restricted their analyses to patients who received RRT. However patients who do not receive early RRT can follow several paths: in addition to the late initiation of RRT, patients may die before initiation of dialysis or may survive and recover kidney function without ever requiring renal support. Limiting the comparison to patients treated early or late neglects the large number of patients who meet criteria for early treatment but never undergo dialysis. Thus rather than "early" vs "late," the issue would be more appropriately framed as "early" vs "not early" initiation of therapy.

The issue of the severity of volume overload as an indication for initiation of renal support has garnered considerable attention and deserves special mention. Multiple studies have demonstrated that the severity of volume overload at initiation of RRT is a strong predictor of mortality.[34-37] For example, in a pediatric cohort of patients undergoing CRRT, Sutherland and colleagues observed an increase in mortality from 29.4% in patients whose fluid gain was <10% of premorbid body weight as opposed to 65.6% in patients with ≥20% fluid overload at initiation of therapy.[37] After adjusting for comorbidities, the presence of ≥20% fluid overload was associated with an odds ratio for death of 8.5 (95% CI, 2.8-25.7). Similarly, Bouchard and colleagues observed an adjusted odds ratio for death of 2.1 (95% CI, 1.3-3.4) associated with the presence of >10% fluid overload at initiation of RRT in a cohort of 396 critically ill adult patients.[36] These data need to be interpreted with caution, as association does not imply causality. It is likely that many patients with more severe fluid overload required

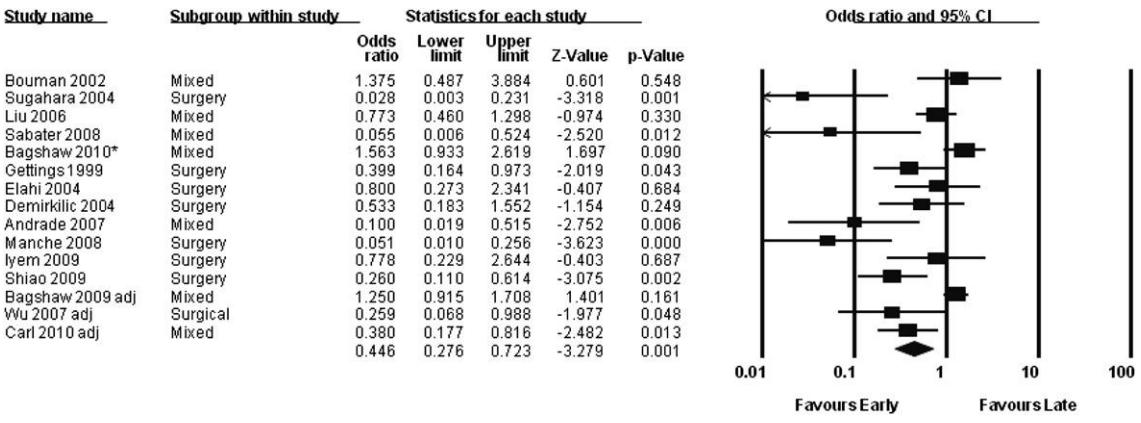

Figure 1. Forrest plot of pooled odds ratios for mortality of studies comparing early to late initiation of renal replacement therapy published between 1985 and July 2010. Using a random effects model, the calculated pooled odds ratio is 0.45 (95% confidence interval [CI], 0.28-0.72). Reprinted with permission from Karvellas CJ, Farhat MR, Sajjad I, et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. Crit Care 2011;15:R72.

more aggressive volume resuscitation, potentially suggesting a greater severity of their underlying critical illness. Although these analyses adjusted for severity of illness, residual confounding is a concern. Although these data provide a strong caution regarding overly aggressive volume administration, the hypothesis that earlier initiation of renal support to prevent or reverse volume overload still needs to be tested in prospective clinical trials.

Modality of Renal Replacement Therapy

Over the past 3 decades, the use of various forms of continuous and prolonged intermittent RRT (PIRRT) in the management of critically ill patients with AKI has increased dramatically. These modalities are characterized by a "go slow" approach, prolonging the daily duration of therapy while reducing the rate of solute clearance and net ultrafiltration, based on the rationale that slower, gentler treatment will be better tolerated in hemodynamically compromised patients. Whether this approach is associated with better clinical outcomes, including improved survival and recovery of kidney function, remains a subject of debate.

Comparing outcomes between modalities is complicated. Patients treated with continuous or extended-duration therapy are more likely to have greater severity of illness and be hemodynamically unstable. Comparing outcomes between CRRT or PIRRT and conventional intermittent hemodialysis (IHD) in observational cohorts is therefore subject to selection bias. Not unexpectedly, observational studies have generally found higher unadjusted mortality when comparing CRRT to conventional IHD.[38-44] Although statistical compensation for the inherent differences in patient characteristics can be provided by adjusting for differences in demographics, chronic comorbidities, and severity of illness using multivariate and propensity score–adjusted analyses, such analyses have yielded varying conclusions ranging from improved survival[42] to no difference in outcome[39] to increased mortality[44] associated with CRRT.

Several randomized controlled trials comparing intermittent to continuous RRT have been performed,[45-50] although many of these trials have been hampered by issues of patient selection and protocol adherence, excluding patients or having them cross between treatment arms because of hemodynamic instability. The largest of these trials, the Hemodiafe study, enrolled 360 patients across 21 ICUs in France.[49] Patients were well matched with regard to severity of illness, with more than 85% of patients requiring vasopressor support and more than 95% being ventilator dependent. Only 6 of the 184 patients (3%) randomized to intermittent therapy needed to cross over to continuous therapy, although 31 of the 175 patients (18%) randomized to CRRT crossed over; 14 (8%) per protocol to allow transfer out of the ICU and 17 (10%) predominantly because of bleeding complications associated with anticoagulation or difficulty maintaining circuit patency. No difference in survival at 2, 60, or 90 days (60-day survival, 31.5% with IHD vs 32.6% with CRRT; $P = .98$) or recovery of kidney function was observed between groups. It should be noted, however, that the median

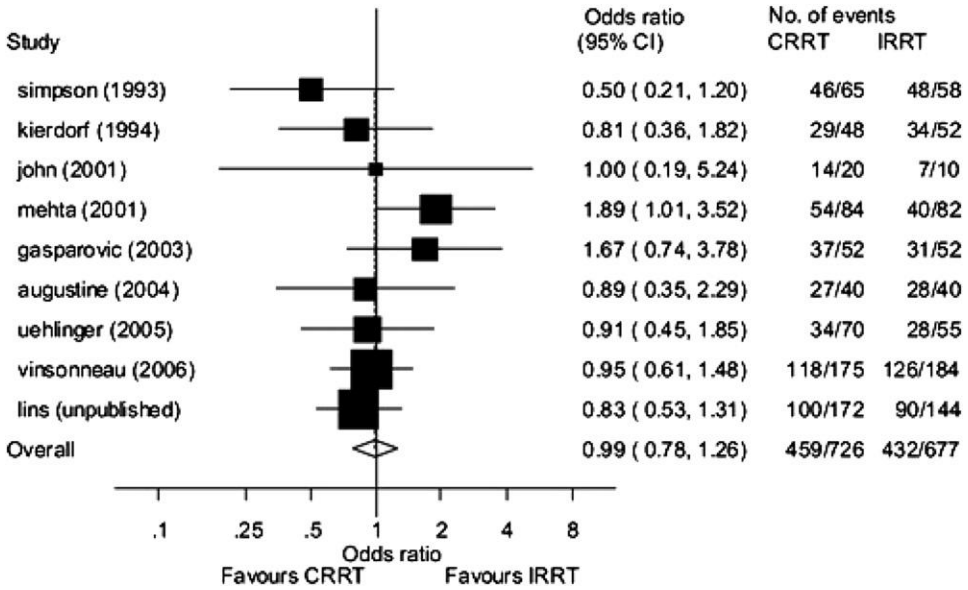

Figure 2. Forrest plot of pooled odds ratios for mortality from 9 randomized trials comparing intermittent renal replacement therapy (IRRT) to continuous renal replacement therapy (CRRT). Using a random effects model, the calculated pooled odds ratio is 0.99 (95% confidence interval [CI], 0.78-1.26). Reprinted with permission from Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. Crit Care Med 2008;36:610-617.

treatment duration for each IHD session was 5.2 hours, significantly longer than is typical in clinical practice.

Three systematic reviews and meta-analyses of modality for renal support in AKI have been published in the past 5years, all of which found no differences in mortality or recovery of kidney function across modalities[51-53] (Fig 2). Analyses have suggested, however, that the cost of CRRT is higher than that of intermittent therapy[52] and that continuous therapy is more effective at attaining negative fluid balance.[36]

Based on these data, the recent Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury recommended that continuous and intermittent modalities of RRT be used as complementary therapies, with the suggestion that CRRT be used preferentially for hemodynamically unstable patients.[54] In patients with acute brain injury or increased intracranial pressure resulting from intracranial hemorrhage, fulminant liver failure, or other causes, IHD has been associated with greater decreases in cerebral perfusion than has CRRT.[55-59]

Only limited comparisons between PIRRT and either intermittent or continuous therapy are available. These comparisons have demonstrated similar hemodynamic stability and metabolic control[60-62] and comparable clinical outcomes[63] with prolonged IHD compared with CRRT. Peritoneal dialysis (PD) has long been used as a dialytic therapy in AKI; however only few studies have directly compared PD to other modalities of renal support. Although Phu and colleagues found substantially higher mortality associated with PD compared with continuous venovenous hemofiltration (CVVH) (47% vs 15%; $P = .005$) in a 70-patient single-center study, the interpretation of this study must be tempered by issues related to PD technique (use of rigid catheters, locally prepared acetate-buffered dialysate, manual exchanges, and an open drainage system)[64]. In addition, it is possible that the low-dose anticoagulation used during CVVH had an independent beneficial effect in the large proportion of patients (69%) with falciparum malaria–associated AKI.[65] In contrast, Gabriel and colleagues have demonstrated biochemical and patient outcomes with high-volume PD comparable to those seen with IHD.[66-68]

A final issue related to modality of therapy is the relative benefits of convective (hemofiltration) vs diffusive (hemodialysis) therapies. Convective therapies are generally thought to provide better clearance of solutes with molecular weights >1000 Da.[69,70] It has therefore been suggested that convective therapies might provide an added benefit in patients with sepsis-associated AKI through enhanced removal of proinflammatory mediators.[71] However the cytokine clearances attainable with even high-volume CVVH are trivial in comparison to endogenous production, and cytokine removal by hemofiltration is nonselective and results in removal of both proinflammatory and anti-inflammatory mediators.[72] In addition, the effects of convective solute flux as the result of internal filtration/backfiltration and protein concentration polarization along the membrane surface when high-flux membranes are used may minimize the differences in solute clearance between convective and diffusive therapies [73]. More importantly, no clinical trials have demonstrated better outcomes with hemofiltration compared with hemodialysis.

Intensity of Renal Support in Acute Kidney Injury

Just as it has been hypothesized that prevention of severe metabolic derangements by earlier initiation of RRT in AKI might be beneficial, prevention or correction of severe metabolic derangements by providing more intensive RRT has also been proposed. Most studies evaluating the effect of more intensive RRT have quantified the dose of therapy in terms of the clearance of low-molecular-weight solutes, such as urea. It should be recognized, however, that modeling intensity of RRT based solely on urea clearance provides an incomplete assessment of the adequacy of therapy, ignoring the clearance of higher-molecular-weight solutes and, even more importantly, the management of extracellular volume.

The dose of IHD is dependent on both the intensity of therapy delivered with each individual treatment, usually quantified in terms of the urea reduction ratio or the fractional clearance of urea (Kt/V_{urea}), and the frequency with which the treatments are provided. No prospective studies have evaluated the effect of dose per treatment on outcomes; the single prospective study of intensity of conventional IHD assessed the effect of increasing the frequency of treatment from every other day to daily while maintaining a constant dose per treatment[74] (Table 1). Although this study reported a marked improvement in mortality with daily hemodialysis sessions (46% with alternate-day therapy vs 28% with daily dialysis; $P = .01$), the delivered Kt/V_{urea} was substantially lower in both treatment arms (0.94 ± 0.11 in the alternate-day group and 0.92 ± 0.16 in the daily dialysis group) than the target of 1.2 per treatment, potentially accounting for high rates of altered mental status, gastrointestinal bleeding, and sepsis in the alternate-day arm. Thus rather than demonstrating a benefit to augmenting an adequate dose of therapy, this study demonstrated that a dose of therapy that is inadequate when delivered every other day becomes sufficient when delivered on a daily schedule.[75] In contradistinction, the Hanover Dialysis Outcome Study, which compared standard (daily) to intensified (more frequent) PIRRT found no differences in survival at either day 14 or day 28.[76]

During continuous therapy, there is equilibration of low-molecular-weight solutes between the blood and dialysate and/or ultrafiltrate,[77] although the degree of equilibration may be reduced by administration of replacement fluids before filtering or by fouling of the membrane

Table 1. Studies of Intensity of Renal Replacement Therapy in Acute Kidney Injury

Study	N	Dose of RRT		Mortality		p Value
		Less-Intensive Arm	More-Intensive Arm	Less-Intensive Arm	More-Intensive Arm	
Conventional Intermittent Hemodialysis						
Schiffl et al[74]	160	Every other day Delivered Kt/V 0.94 ± 0.11	Daily Delivered Kt/V 0.92 ± 0.16	46%*	28%*	.001
Prolonged Intermittent Hemodialysis						
Faulhaber-Walter et al[76]	156	Daily Target BUN: 56-70 mg/dL	1-2× per day Target BUN <42 mg/dL	44.4%†	38.7%†	.47
Continuous Renal Replacement Therapy						
Ronco et al[79]	425	CVVH: 20 ml/kg/h	CVVH: 35 ml/kg/h CVVH: 45 ml/kg/h	59%*	57%* (35 ml/kg/h) 58%* (45 ml/kg/h)	<.001
Bouman et al[19]	106	CVVH: 24-36 L/d	CVVH: 72-96 L/d	25.7%†	28.2%†	.80
Saudan et al[80]	206	CVVH Q_{UF}: 25 ± 5 ml/kg/h	CVVHDF Q_{UF}: 24 ± 6 ml/kg/h Q_D: 18 ± 5 ml/kg/h	39%†	59%†	.03
Tolwani et al[81]	200	CVVHDF: 20 ml/kg/h	CVVHDF: 35 ml/kg/h	56%‡	49%‡	.23
Bellomo et al[82]	1508	CVVHDF: 25 ml/kg/h	CVVHDF: 40 ml/kg/h	44.7%¶	44.7%¶	.99
Combined Modalities						
Palevsky et al[8]	1124	IHD: 3× per wk Delivered Kt/V 1.32 ± 0.37 PIRRT: 3× per wk CVVHDF: 20 ml/kg/h	IHD: 6× per wk Delivered Kt/V 1.31 ± 0.33 PIRRT: 6× per wk CVVHDF: 35 ml/kg/h	51.5%§	53.6%§	0.47

Abbreviations: CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis; PIRRT, prolonged intermittent renal replacement therapy; Q_D, dialysate flow rate; Q_{UF}, ultrafiltration rate; RRT, renal replacement therapy.
*Mortality 15 days after discontinuation of study therapy.
†Twenty-eight–day mortality.
‡Thirty-day mortality.
§Sixty-day mortality.
¶Ninety-day mortality.

caused by clotting and by protein concentration polarization.[78] The dose of CRRT has therefore been quantified based on effluent flow rates (the sum of the ultrafiltrate and dialysate) normalized to body weight. In a seminal study of 425 critically ill patients randomized to effluent flow rates of 20, 35, or 45 mL/kg per hour, Ronco and colleagues observed an increase in survival 15 days after discontinuation of CRRT from 41% in the lowest-dose group to 57% and 58%, respectively, in the 2 higher-dose groups ($P < .001$).[79] However subsequent small studies yielded conflicting results,[19,80,81] and a definitive multicenter randomized controlled trial found no benefit to higher doses of CVVHDF.[82] In this study, the Randomized Evaluation of Normal Versus Augmented Level (RENAL) Replacement Therapy study, 1508 patients in 35 ICUs in Australia and New Zealand were randomly assigned to 2 doses (25 or 40 mL/kg per hour) of CVVHDF during ICU care. The mean duration of study therapy and overall duration of RRT were 6.3 ± 8.7 days and 13.0 ± 20.8 days, respectively, in the higher-intensity arm and 5.9 ± 7.7 days and 11.5 ± 18.0 days, respectively, in the less-intensive arm, reflecting the use of nonprotocol hemodialysis after ICU discharge. Survival to 90 days was 55.3% in both treatment arms ($P = .99$).

In contrast to the studies that compared lower and higher doses of individual modalities of RRT, the Veterans Administration/National Institutes of health Acute Renal Failure Trial Network study randomized 1124 critically ill patients to lower- or higher-intensity RRT using a strategy that allowed patients to shift between modalities as hemodynamic status changed over time.[8] In the intensive arm, CVVHDF was provided with a total effluent flow of 35 mL/kg per hour, and conventional and prolonged IHD were provided 6 times per week (daily, except Sunday) with a target Kt/V_{urea} of 1.2 to 1.4 per treatment; in the less-intensive arm, the dose of CVVHDF was 20 mL/kg per hour, and conventional and prolonged IHD was provided 3 times per week (every other day, except Sunday), with the same target Kt/V_{urea}. Sixty-day all-cause mortality was 53.6% in the more-intensive arm compared with 51.5% in the less-intensive arm ($P = .47$).

Two systematic reviews reported meta-analyses of the pooled results from these trials.[83,84] Both found no significant benefit associated with more intensive RRT, although both observed significant statistical heterogeneity across the studies associated, in 1 analysis,[83] with year of publication and study quality as assessed by Jadad score.

Although the published literature does not support the concept that more RRT is better, the data also suggest that there must be some floor below which mortality will increase, the precise level of which is not known. Based on these data, the KDIGO AKI guidelines recommend delivering an effluent volume of 20 to 25 mL/kg per hour for CRRT and a Kt/V_{urea} of 3.9 per week (the equivalent of 1.2-1.4 3 times per week) when using conventional or

prolonged IHD.[54] Given the well-known discrepancies between prescribed and delivered doses of RRT in the acute setting, prescribing a modestly higher dose of therapy may be necessary to actually deliver the desired target doses. In addition, the delivered dose of therapy should be closely monitored to ensure that the targeted dose is actually achieved. Finally, it is important to recognize that the delivery of treatment must be individualized and that higher doses of therapy may be required for extremely hypercatabolic patients or for control of severe hyperkalemia. However when higher doses of therapy are used, careful attention must be given to the effects on drug clearance and the potential need for enhanced monitoring of drug levels and modification of drug dosing. In addition, in patients receiving intermittent therapy, increased treatment frequency may be required to optimize volume management, even if additional solute clearance is not required.

Summary

Although the use of RRT to support critically ill patients with AKI has become routine, many of the fundamental questions regarding optimal management of RRT remain. Although absolute indications for initiating RRT, such as hyperkalemia and overt uremic symptoms, are well recognized, the optimal timing of therapy in patients without these indications continues to be a subject of debate. The selection of modality does not appear to have a major impact on mortality or recovery of kidney function. Selection of modality for renal support should therefore be based on local expertise and logistic factors, with the emphasis on ensuring that the treatment provided is the safest and most cost-efficient for the particular health setting. Finally, reasonable minimal standards for the delivered dose of therapy appear to have been identified; a process for local quality assurance and performance improvement should be implemented to ensure that these are achieved. The mortality associated with severe AKI remains unacceptably high; however there is little evidence to suggest that this mortality will be substantially altered by improvements in the delivery of renal support. Rather, we must be realistic in our expectations of what dialysis and hemofiltration can accomplish and vigorously pursue other strategies to improve the care of these patients.

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