Indications and timing of renal replacement therapy in acute kidney injury

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The optimal timing for initiation of renal replacement therapy in patients with acute kidney injury remains uncertain. Conventionally accepted indications include volume overload, hyperkalemia, metabolic acidosis, overt uremia, and even progressive azotemia in the absence of specific symptoms; however, precise definitions for these indications are lacking. Data from recent observational trials have suggested that early initiation of renal replacement therapy may be associated with decreased mortality; however, the results of these studies are inconclusive. Existing data on timing of initiation of renal replacement therapy in acute kidney injury that guide current clinical practice are summarized and issues that need to be addressed in future clinical trials are discussed. (Crit Care Med 2008; 36[Suppl.]:S224–S228)

KEY WORDS: renal replacement therapy; acute kidney injury; volume overload; hyperkalemia; metabolic acidosis

Conventional indications for initiating renal replacement therapy (RRT) in acute kidney injury (AKI) include volume overload, hyperkalemia, metabolic acidosis, and overt uremic manifestation such as encephalopathy and pericarditis (Table 1). Acute dialysis also is indicated when AKI occurs in the setting of acute intoxication with a dialyzable drug or toxin. While these indications are well accepted, they also are subject to interpretation. How severe a degree of volume overload, hyperkalemia, or metabolic acidosis? What, if any, medical therapies should be tried before initiating RRT? If diuretic therapy is initiated, what dose constitutes diuretic resistance? In many patients, RRT is initiated in the absence of specific indications in response to persistent oliguria unresponsive to volume administration or progressive azotemia without uremic manifestations. Observation practice patterns within and across institutions suggest that there is no uniform standard of care and that wide variations in clinical practice prevail (1).

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In the past, the paradigm for management of severe AKI was that patients died *with*, but did not die *of*, their renal failure, so long as acute uremic complications were prevented. The corollary of this view was that management of RRT merely needed to assure that patients did not succumb to hyperkalemia, metabolic acidosis, or volume overload; and that overt uremic complications, such as pericarditis and encephalopathy, were prevented. During the past decade, this paradigm has been challenged by data demonstrating that AKI is an independent risk factor for mortality (2–6). An implication of these data is that the specific management of RRT may impact the outcomes of AKI and that optimization of renal support may reduce its high mortality (7–9). Although multiple recent clinical trials have prospectively evaluated the impact of dose (10–13) and modality (14–17) of RRT, the literature on timing of initiation of RRT in AKI is far less robust. In the remainder of this review, we will summarize the current data on timing of initiation of RRT in AKI that guide current clinical practices (Table 2) and discuss issues that need to be addressed in future clinical trials.

1950S to 1970S: Retrospective Case Series and Observational Studies

The concept of prophylactic hemodialysis in AKI was introduced by Dr. Teschan and colleagues (18, 19) almost 50 yrs ago, within the first decade after the introduction of hemodialysis into routine clinical practice for the management of severe acute renal failure. In their landmark report, Dr. Teschan and colleagues described their experience using "prophylactic" hemodialysis in 15 patients with oliguric acute renal failure treated at the Renal Center of the U.S. Army Surgical Research Unit (18). Hemodialysis was initiated before the blood nonprotein nitrogen reached 200 mg/dL and obvious uremic symptoms appeared. Although no control group was included in this report, the authors stated that the results contrasted dramatically with their own past experience in patients in whom dialysis was not initiated until "conventional" indications were present, with a mortality rate of only 33% and with patients experiencing a "stable, convalescent clinical course . . . free from uremic symptoms or chemical imbalances . . ." (18).

Subsequently, multiple retrospective case series and observational studies in the 1960s and early 1970s compared "early" initiation of hemodialysis (as defined by blood urea nitrogen [BUN] concentrations ranging from <93 mg/dL to levels of approximately 150 mg/dL) to "late" initiation of therapy (as defined by BUN levels of 163 mg/dL to >200 mg/dL) (20–22). All of these studies (Table 2) demonstrated improved survival with earlier initiation of hemodialysis.

1970S to 1980S: Small Prospective Clinical Trials

The first prospective evaluation of "prophylactic" dialysis in acute renal fail-

ure was reported by Dr. Conger in 1975 (23). In this study, conducted on the U.S. Naval Hospital Ship USS *Sanctuary* between April and October 1970, 18 patients with post-traumatic AKI were assigned alternately to an intensive hemodialysis regimen that maintained predialysis BUN <70 mg/dL and serum creatinine <5 mg/dL, or to a nonintensive regimen in which dialysis was not carried out until BUN and serum creatinine approached 150 mg/dL and 10 mg/dL, respectively, or clinical indications for therapy (e.g., hyperkalemia, volume overload, or uremic encephalopathy) supervened. Survival was 64% (five of eight patients) in the intensive treatment group as compared with 20% (two of ten patients) with the nonintensive dialysis strategy ($p = .14$). In addition, major complications, including hemorrhage and Gram-negative sepsis, were less frequent in the intensive hemodialysis arm.

Table 1. Conventional indications for renal replacement therapy in acute kidney injury

Intravascular volume overload unresponsive to diuretic therapy
Hyperkalemia refractory to medical management
Metabolic acidosis refractory to medical management
Concomitant intoxication with dialyzable drug or toxin
Overt uremic symptoms
Encephalopathy
Pericarditis
Uremic bleeding diathesis
Progressive azotemia in the absence of specific symptoms

Approximately a decade later, Dr. Conger and associates (24) re-examined the intensity of hemodialysis in 34 patients treated at the University of Colorado Health Sciences Center Hospitals. Pairs of patients were assigned randomly when serum creatinine reached 8 mg/dL to either an intensive regimen, designed to maintain the predialysis BUN <60 mg/dL and serum creatinine <5 mg/dL or to a less intensive regimen in which BUN and serum creatinine were permitted to reach 100 mg/dL and 9 mg/dL, respectively. While the treatment strategies in this study were not designed to strictly evaluate timing of imitation of therapy, the average time from onset of AKI to initiation of dialysis was 5 ± 2 days in the intensive therapy arm as compared with 7 ± 3 days in the nonintensive regimen. Mortality was higher in the more intensively dialyzed group; however, given the small sample size, this difference was not statistically significant ($p = .73$).

On the basis of these data, the conventional teaching became that in the absence of specific symptoms, hemodialysis should be initiated when BUN reaches a level of approximately 100 mg/dL, but that no additional benefit was associated with earlier initiation or more intensive therapy. It should be recognized, however, that the studies on which this argument is based had inadequate statistical power to draw definitive conclusions.

The Past Decade

No additional studies examining the timing of initiation of hemodialysis or other modalities of renal replacement therapy were published until the end of the 1990s. During the past decade, however, multiple studies have re-examined this issue, focusing almost exclusively on the timing of initiation of continuous renal replacement therapy (CRRT). In 1999, Dr. Gettings and colleagues (25) published a retrospective analysis of the timing of initiation of CRRT on outcomes in 100 consecutive patients with post-traumatic AKI. Patients were classified as early or late initiation of therapy based on

Table 2. Summary of studies evaluating the timing of initiation of renal replacement therapy (RRT)

Study	Yr	Mode of RRT	Study Design	No.	Criteria for Initiation of RRT		Survival (%)	
					Early	Late	Early	Late
Parsons et al (20)	1961	IHD	Retrospective	33	BUN 120–150 mg/dL	BUN >200 mg/dL	75	12
Fischer et al (21)	1966	IHD	Retrospective	162	BUN ~150 mg/dL	BUN >200 mg/dL	43	26
Kleinknecht et al (22)	1972	IHD	Retrospective	500	BUN <93 mg/dL	BUN >163 mg/dL	73	58
Conger (23)	1975	IHD	RCT	18	BUN <70 mg/dL or S_{Cr} <5 mg/dL	BUN ~150 mg/dL, S_{Cr} ~10 mg/dL, or clinical indications	64	20
Gillum et al (24)	1986	IHD	RCT	34	S_{Cr} 8 mg/dL Treatment goal: BUN <60 mg/dL, S_{Cr} <5 mg/dL	BUN ~100 mg/dL or S_{Cr} ~9 mg/dL	41	53
Gettings et al (25)	1999	CRRT	Retrospective	100	BUN <60 mg/dL	BUN >60 mg/dL	39	20
Bouman et al (12)	2002	CRRT	RCT	106	<12 hrs after meeting AKI definition	BUN >112 mg/dL, S_K >6.5 mmol/L, or pulmonary edema	LV: 69 HV: 74	LV: 75
Demirkiliç et al (26)	2004	CRRT	Retrospective	61	UOP <100 mL/8 hr	S_{Cr} >5.0 mg/dL or S_K >5.5 mmol/L	77	45
Elahi et al (27)	2004	CRRT	Retrospective	64	UOP <100 mL/8 hr	BUN ≥4 mg/dL, S_{Cr} >2.8 mg/dL, or S_K >6 mmol/L	78	57
Piccinni et al (28)	2006	CRRT	Retrospective	80	<12 hrs after ICU admission	"Conventional" indications	55	28
Liu et al (29)	2006	IHD & CRRT	Observational	243	BUN ≤76 mg/dL	BUN >76 mg/dL	65	59

IHD, intermittent hemodialysis; CRRT, continuous renal replacement therapy; RCT, randomized controlled trial; BUN, blood urea nitrogen; S_{Cr}, serum creatinine; AKI, acute kidney injury; UOP, urine output; ICU, intensive care unit; S_K, serum potassium; LV, low-volume hemofiltration; HV, high-volume hemofiltration.

BUN at initiation of therapy, using a value of 60 mg/dL to separate the two groups. In the early group, CRRT was initiated on hospital day 10 ± 15, with a mean BUN of 43 ± 13 mg/dL, as compared with initiation of therapy after 19 ± 27 days with a mean BUN of 94 ± 28 mg/dL in the late group. Survival was 39% in the early initiation group, as compared with 20% in the late group ($p = .041$). Although baseline demographic characteristics and severity of illness scores of patients in the two groups were comparable, a greater percentage of patients in the late cohort had multisystem organ failure or sepsis. In addition, the rationale for earlier as opposed to later initiation of therapy in individual patients was not provided. Although the timing of therapy may merely have reflected random variation in physician behavior, it is more likely that individual patient characteristics contributed to nonrandom decisions regarding the timing of therapy. For example, 56% of patients in the early initiation arm were oliguric on the first day of CRRT, as compared with only 39% in the late initiation group. Thus, the observed differences in outcome may well have been confounded by unreported differences underlying the decision for early as opposed to late initiation of therapy.

Similar results have been reported in two retrospective analyses of timing of CRRT in patients following cardiac surgery (26, 27). Dr. Demirkiliç and colleagues (26) reported on a series of 61 patients treated at a single center in Turkey between March 1992 and September 2001 who required postoperative continuous venovenous hemodiafiltration (CVVHDF) after undergoing cardiac surgery. In the 27 patients treated before June 1996, CVVHDF was not initiated until the serum creatinine level exceeded 5 mg/dL or the serum potassium level exceeded 5.5 molEq/L despite medical therapy, independent of urine output (group 1), while in the remaining 34 patients, treated after June 1996, CVVHDF was initiated as soon as the urine volume was <100 mL for 8 hrs, despite administration of furosemide (group 2). Treatment was initiated 2.6 ± 1.7 days after surgery in group 1 as compared with 0.9 ± 0.3 days after surgery in group 2. Early initiation was associated with lower intensive care (17.6% vs. 48.1%; $p < .05$) and hospital mortality (23.5% vs. 55.5%; $p < .05$) and decreased duration of both mechanical ventilation and intensive care length of stay. Similarly, Dr. Elahi and colleagues (27) identified 64 consecutive patients who underwent cardiac surgery between January 2002 and January 2003 in a single center in the United Kingdom and who received postoperative CVVHDF. In 28 patients, the CVVHDF was not initiated until BUN was ≥84 mg/dL, the creatinine was ≥2.8 mg/dL, or the serum potassium was >6 molEq/L despite medical therapy, regardless of urine output (group 1), while in the remaining 36 patients CVVHDF was initiated when the urine volume was <100 mL for 8 hrs despite furosemide infusion (group 2). As in the prior study, the reported demographic and baseline clinical characteristics of the two groups were similar. The interval between surgery and initiation of renal support was 2.6 ± 2.2 days in group 1 as compared with 0.8 ± 0.2 days in group 2. Hospital mortality was 43% in group 1 and 22% in group 2 ($p < .05$).

Dr. Piccinni and colleagues (28) have described the use of "early isovolemic hemofiltration" in oliguric patients with sepsis. In their report, they compare outcomes in 40 patients with sepsis and oliguria in whom high volume (45 mL/kg/hr) hemofiltration with no net fluid removal was initiated within 12 hrs of intensive care admission as compared with 40 historical controls, in whom renal replacement therapy was initiated for conventional indications. In the patients treated with isovolemic hemofiltration, 28-day survival was 55% as compared with 27.5% in the historical control cohort. Although the authors describe early isovolemic hemofiltration in terms of early initiation of therapy, comparison of the interval between onset of renal dysfunction and initiation of therapy is not provided and biochemical indexes of renal function at initiation of renal support are similar, with a trend toward higher BUN and serum creatinine in the early isovolemic hemofiltration cohort (110 ± 38 mg/dL vs. 120 ± 30 mg/dL and 1.7 ± 2 vs. 1.8 ± 2, respectively), suggesting that the actual timing of treatment was not significantly different between groups.

Dr. Liu and colleagues (29) analyzed data on the timing of initiation of renal replacement therapy (both intermittent and CRRT) from the Program to Improve Care in Acute Renal Disease, a multicenter observational study of AKI. They stratified the 243 patients in the database who received RRT into early and late initiation groups based on the median BUN (76 mg/dL) at initiation of therapy. Although patients in the late (BUN, >76 mg/dL) group had a reduced burden of organ failure, the survival rates at 14 days and 28 days in this group (75% and 59%, respectively) were slightly lower than in the early (BUN, ≤76 mg/dL) group (8% and 65%, respectively). After adjustment for age and clinical factors and stratification by site and initial modality of RRT in a multivariate analysis, the relative risk of death associated with dialysis initiation with more severe azotemia (using the early initiation group as the comparator) was 1.85 (95% confidence interval, 1.16–2.96). Using a propensity analysis to adjust for factors predicting initiation of therapy at a higher as compared with a lower BUN, they also found an increased relative risk for death in the high BUN group (2.07; 95% confidence interval, 1.30–3.29).

There are several important limitations that must be considered in analyzing the results of these retrospective studies. First, the use of BUN as a surrogate measure for duration of AKI is problematic. Urea generation is not constant, with wide variation in generation rates from patient to patient and even within an individual patient as the degree of catabolic stress waxes and wanes. Similarly, the volume of distribution of urea in critically ill patients is highly variable and inconstant. Thus, the rate of increase in BUN will vary across patients, and may not even be constant in an individual patient over time. Second is the issue of bias by indication. Renal support was initiated for oliguria in the early groups and for azotemia or hyperkalemia in the late groups in both of the postcardiac surgery studies (26, 27). Although the reasons for early and late initiation of treatment in the studies by Dr. Gettings and colleagues (25) and Dr. Liu and colleagues (29) were not specified, it is likely earlier initiation was prompted by volume overload and electrolyte disturbances, whereas late initiation of therapy was more likely to be prompted by progressive azotemia. Whether there is a relationship between indication for therapy and outcome is not known. Most importantly, the design of all four of these studies limited analysis to patients who received renal replacement therapy, ignoring the subset of patients with AKI who recover or die without RRT.

Only one recent study has attempted to address the timing of CRRT prospectively (12). Dr. Bouman and colleagues randomized 106 critically ill patients

with AKI at two centers to three groups: early high-volume CVVHDF (n = 35), early low-volume CVVHDF (n = 35), and late low-volume CVVHDF (n = 36). Treatment was initiated in the two early groups within 12 hrs of meeting study inclusion criteria (the presence of oliguria for >6 hrs despite hemodynamic optimization or a measured creatinine clearance of <20 mL/min on a 3-hr timed urine collection), while in the late group renal support was not initiated until BUN was >112 mg/dL, potassium was >6.5 mEq/L, or pulmonary edema was present. No significant differences in survival were observed among the three groups. Of note, however, the overall 28-day mortality for subjects in this study was only 27%, substantially lower than mortality rates reported in most other studies of critically ill patients with AKI, suggesting a lower disease burden in this cohort. In addition, as a result of the small sample size, the statistical power of the study was low.

Future Directions

From the above discussion, it should be readily apparent that current data remain inadequate to answer the question of appropriate indications and timing of initiation of renal support in AKI. Whether earlier initiation of RRT or provision of therapy in patients currently managed conservatively improves survival remains an open question. Although observational data suggests improved outcomes with early initiation of therapy, this may merely reflect inclusion of patients with a lesser degree of organ injury, whose outcomes would be better regardless of treatment strategy. All of the observational studies have been based on identification of patients with AKI who ultimately were treated with RRT. However, the vast majority of patients with AKI are never treated with RRT (30). Thus, the paradigm for answering the question of timing of initiation of RRT needs to change (Fig. 1). To be able to answer the question, a study must include all patients for whom early initiation of RRT is a consideration. While observational data that include patients who never receive RRT may help inform the question, observational data cannot provide a definitive answer because of the issue of bias by indication.

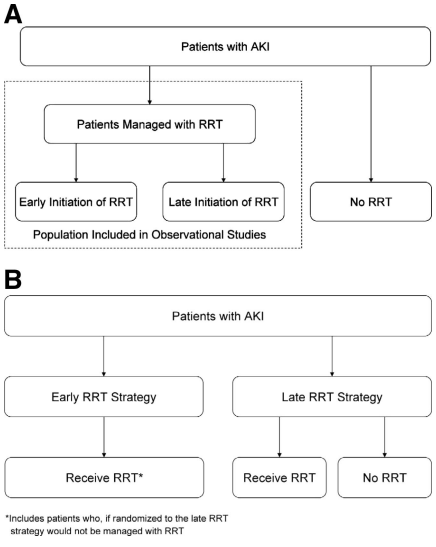

Figure 1. Design of clinical trials of timing of initiation of renal replacement therapy (*RRT*) in acute kidney injury (*AKI*). *A*, design of published observational studies. Study cohorts have consisted of patients treated with RRT and have not included patients with AKI who never receive RRT. *B*, required study design to adequately answer clinical question of timing of RRT in AKI. Not all patients included in the late initiation strategy actually will receive RRT; conversely, some patients included in the early initiation strategy would not be managed with RRT if included in the late initiation strategy.

Ultimately, a definitive answer will require prospective randomized trials. However, the design of such trials poses significant challenges, most critically the need for early identification of patients with persistent and severe renal injury. Unfortunately, current clinical and biochemical parameters are inadequate to prospectively identify the appropriate study cohort. In the study by Dr. Bouman and colleagues (12), six of the 36 patients (16.7%) in the late therapy group never received RRT, two patients because they died before meeting criteria for RRT and four patients because they recovered renal function. Although the RIFLE criteria (a mnemonic for the progression of an acronym for staging of AKI as *r*isk of renal dysfunction, *i*njury to the kidney, *f*ailure of kidney function, *l*oss of kidney function, and *e*nd-stage kidney disease) have been proposed to help stratify severity of renal injury (31), they are inadequate for identification of the necessary study cohort. In a retrospective analysis of >5000 critically ill patients at a single institution, Dr. Hoste and colleagues (30) observed that only 14.2% of patients meeting the RIFLE-Loss criteria (corresponding to the Acute Kidney Injury Network criteria for stage 3 AKI) received RRT. Without reliable markers to identify this population, a substantial number of patients who would not otherwise receive RRT will need to be randomized into an early therapy arm and subjected to the risks of RRT, risks that include morbidity and mortality associated with vascular catheters and the possibility that exposure to hemodialysis may in and of itself delay recovery of renal function and adversely impact patient survival (32). Thus, robust biomarkers and/or clinical predictors of the course of AKI are needed before such a study can be ethically undertaken.

CONCLUSIONS

The optimal timing for initiation of RRT in patients with AKI remains uncertain. Conventionally accepted indications include volume overload, hyperkalemia, metabolic acidosis, overt uremia, and even progressive azotemia in the absence of specific symptoms; however, precise definitions for these indications are lacking. In addition, a number of observational and retrospective analyses have suggested improved survival with earlier initiation of renal support; however, the absence of inclusion of patients with AKI who meet criteria for early initiation of RRT but who never receive therapy limits the validity of these analyses. A definitive answer to this important clinical issue ultimately will require data from prospective randomized controlled trials; however, the conduct of such trials requires more robust biomarkers and/or clinical predictors of the course of AKI than are currently available.

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