

Renal Replacement Therapy in Acute Kidney Injury

Paul M. Palevsky

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) care¹ 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

From VA Pittsburgh Healthcare System and University of Pittsburgh School of Medicine, Pittsburgh, PA.

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Address correspondence to Paul M. Palevsky, MD, Room 7E123 (111F-U), VA Pittsburgh Healthcare System, University Drive, Pittsburgh, PA 15240. E-mail: palevsky@pitt.edu

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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.

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 multi-system 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"

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.

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