The Timing of Renal Replacement Therapy Initiation in Acute Kidney Injury

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Summary: The optimal time to start renal replacement therapy (RRT) in the setting of acute kidney injury (AKI) is one of the most controversial questions in the field of critical care nephrology. An earlier or pre-emptive approach, whereby RRT is initiated in the absence of a life-threatening complication of AKI, may have a variety of plausible benefits. On the other hand, the widespread adoption of such an approach would consume more resources and would have to be justified by evidence of superior patient outcomes. It is possible that a more conservative strategy that reserves the initiation of RRT until an urgent indication is present might confer acceptable patient outcomes without exposing patients who are destined to recover from AKI spontaneously to the risks of unnecessary RRT. Ongoing randomized controlled trials should help bring clarity to this important area of clinical uncertainty.

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The appropriate circumstance for the initiation of renal replacement therapy (RRT) in acute kidney injury (AKI) is a prominent topic of controversy in the field of critical care nephrology. Although the terms *early* and *late* have been used to dichotomize two broad approaches to RRT initiation, there is little consensus about how to define these time intervals. A more practical approach to framing this question could be based on whether one should commence RRT pre-emptively in all patients with severe AKI, as opposed to a strategy of reserving RRT for situations in which RRT is required to correct a life-threatening complication of AKI. In this review, we present the potential advantages and shortcomings of both of these approaches. Furthermore, we discuss recently published work in this area and review the design of ongoing clinical trials that promise to shed light on this question.

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RRT TIMING IN AKI: A PROBLEM WITH DEFINITIONS

Although this clinical dilemma has classically been labeled as a controversy surrounding the *timing* of RRT initiation, this terminology may be inaccurate. For example, late RRT initiation implies that RRT is being delayed with respect to a fixed point in time. This reference time point, which presumably reflects the onset of AKI, frequently is elusive except in cases of AKI in which the kidney insult is readily anticipated (ie, cardiopulmonary bypass, radiocontrast administration) or when AKI is acquired under close medical surveillance and frequent blood tests are being performed (eg, during a prolonged hospitalization). Moreover, even if the precise time of AKI onset is clear, there is no consensus around what would constitute early versus late RRT initiation.

Given the inherent challenges in defining the time since AKI onset, observational studies have used a variety of surrogate markers for the timing of RRT initiation.[1,2] These have included serum urea and creatinine concentrations (with the implication that higher urea or creatinine concentrations represent an AKI episode that has been present for longer),[3,4] AKI stage,[5] and time since intensive care unit (ICU) admission.[6] The assumption that these parameters are reliable surrogates for AKI duration is highly problematic. For example, although a high serum urea concentration may reflect a more protracted course of AKI, urea concentration may be affected by factors that are unrelated to kidney function such as gastrointestinal bleeding, tissue catabolism, or nutritional status. In addition, the time to RRT from ICU admission may be closely affected by variability in ICU admission policies across hospitals.

More recently, the timing of RRT initiation has been studied with respect to the absence or presence of

classic indications at RRT initiation.[7–10] This approach also has been limited by controversy about what should constitute an appropriate trigger for RRT initiation.[11] Life-threatening scenarios such as severe hyperkalemia, profound metabolic acidosis, and severe fluid overload resulting in respiratory failure are complications of AKI that can be corrected with RRT. In such situations, the need to initiate RRT is unequivocal. However, contemporary studies would suggest that RRT frequently is initiated in the absence of a life-threatening indication.[12,13] For example, in the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy trial, which compared two different RRT intensities and remains the largest trial to study an RRT-related intervention in AKI, oliguria was cited as the leading reason to initiate RRT among trial participants.[13] Although oliguria is widely accepted as a marker of severe AKI, it is unclear whether a low or absent urine output, in the absence of another compelling AKI complication, represents a threat to life that justifies the initiation of an invasive intervention such as RRT.

WHAT DO CLINICAL PRACTICE GUIDELINES AND EXPERT PANELS SAY ABOUT THE OPTIMAL TIME TO COMMENCE RRT?

The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury have made two principal statements regarding the timing of RRT initiation in AKI, neither of which was graded.[14] First, there is a straightforward recommendation to initiate RRT "emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist."[14] The second recommendation acknowledged the potential role for RRT even when a classic life-threatening indication was not present and suggested consideration of the "broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single BUN [blood urea nitrogen] and creatinine thresholds alone—when making the decision to start RRT."[14] The latter guideline implicitly calls for clinician judgment and the use of subjective criteria when deciding to start RRT. This is likely a fair reflection of actual clinical practice whereby the clinician's perception of the patient's global condition, as opposed to a single biochemical marker, guides the initiation of RRT. However, it is the inherently subjective nature of the process that has contributed to so much variability in the practice of RRT initiation in AKI.

Acknowledging the uncertainty in this area, the KDIGO Clinical Practice Guideline for AKI recommended the pursuit of research to "Determine [if] early vs late start of RRT….results in improved outcomes (eg, mortality, evolution to chronic kidney disease stage 5) in AKI patients."[14] The Acute Kidney Injury Network, an international working group comprising experts from both nephrology and critical care, identified the question, "When should RRT be initiated, and does timing affect outcome?" as the highest-ranked priority research topic by both nephrologists and critical care experts.[15] The National Institute for Health and Care Excellence in the United Kingdom recently issued a statement as part of its set of guidelines on AKI noting that, "A prospective study is needed of adult inpatients with acute kidney injury Acute Kidney Injury Network stages 2 and 3, who are likely to need renal replacement therapy within a given timeframe (eg, 72 hours), but have no urgent need for therapy."[16]

THE ARGUMENT IN FAVOR OF EARLIER RRT INITIATION

Irrespective of the definition that is applied, earlier initiation of RRT will confer more prompt control of acid-base status, electrolyte imbalances, and extracellular volume accumulation, as compared with a treatment strategy in which RRT is started later in the course of the patient's illness (Table 1). All conventional forms of acute RRT will mediate effective clearance of low-molecular-weight solutes, although it is unclear which of these is implicated in the toxicity of AKI. When convective modes of clearance are applied early, it is conceivable that larger molecules,

Table 1. The Advantages and Shortcomings of Earlier RRT Initiation in Acute Kidney Injury

Advantages	Shortcomings
More effective reversal of volume expansion, especially in diuretic-resistant patients	Exposure to complications associated with supplemental vascular access (both at time of insertion and thereafter)
Better control of electrolyte and acid-base status	Exposure to complications associated with RRT (eg, intradialytic hypotension, dysrhythmias, clearance of antibiotics)
Proactive clearance of toxic low- and middle-molecular-weight solutes	Higher cost, especially if patient was destined to recover kidney function
Avoidance of AKI-related emergencies (eg, cardiac dysrhythmias related to hyperkalemia)	