

# Timing of Renal Replacement Therapy in Acute Kidney Injury: Shedding New Light on an Old Controversy

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## Abstract

Critically ill patients with severe acute kidney injury (AKI-D) require renal replacement therapy (RRT) increasingly. However, the optimal timing of initiation of RRT for non-life-threatening indications of AKI remains unknown. There is a debate as to whether different philosophies of RRT initiation (early vs. delayed) confer a survival benefit. Lowering the threshold for RRT initiation, however, inevitably leads to more critically ill patients receiving unnecessary RRT. The relevant proportion of nonprogressing early stage AKI patients with spontaneous kidney recovery is a matter of severe concern because RRT has potentially lethal complications and is expensive. Moreover, these patients should be excluded from randomized trials. The furosemide stress test in critically ill patients with early stages of AKI serves as a novel tubular function test to identify those patients with severe and progressive AKI-D. Future trials to validate findings of a promising pilot study are warranted.

**Keywords:** Acute kidney injury, furosemide stress test, renal replacement therapy

## INTRODUCTION

Renal replacement therapy (RRT) is increasingly used in critically ill patients with severe acute kidney injury (AKI-D). The goals of RRT have remained the same over seven decades: first, to replace those aspects of excretory kidney function that affect other vital organs with as little disruption as possible and second to allow functional recovery of the kidneys and other vital organs. RRT can prevent the occurrence of life-threatening complications of oligo-anuric AKI (hyperkalemia, pulmonary edema, or acidemia) and may limit worsening of other (distant) organ dysfunctions. RRT is necessary to provide additional therapeutic interventions (nutrition, medications, and blood transfusions).

Untreated severe AKI in critically ill patients is associated with higher mortality (approaching 100%). However, despite the dramatic evolution of technologies for RRT and multiple advances in intensive care medicine, a recent meta-analysis of worldwide AKI epidemiology (765 studies) showed that the global mortality of critically ill patients with AKI-requiring RRT was still as high as 46%. Conventionally, AKI has been viewed as an “innocent bystander,” a marker for the severity of the underlying acute illness. Today, AKI has become an independent protagonist in acute illness, even if the increase

in serum creatinine concentration was small (0.3 mg/dl). Underdosing of RRT is associated with increased mortality. Increasing the dose of RRT above the required level does not reduce mortality. AKI influences mortality of critically ill patients through means that are not reversed by the conventional timing of RRT.<sup>[1,2]</sup>

## Indications to commence renal replacement therapy in critically ill patients with acute kidney injury-D

There are several absolute indications when initiation of RRT is considered lifesaving, namely volume overload unresponsive to diuretic therapy, severe hyperkalemia with cardiac compromise, or severe metabolic acidosis refractory to medical management, life-threatening uremic manifestations. However, these indications are not always present, and RRT is often initiated preemptively well before the development of these complications of severe AKI. The concept of prophylactic RRT describes the initiation of AKI before nitrogen waste products reach some arbitrary predefined blood concentrations,

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regardless of the presence of absolute indications. There is no proof that the widely used concept of prophylactic RRT might be associated with a survival benefit.

### Current practice of timing of renal replacement therapy in acute kidney injury-D

In noncritically ill patients with normuric AKI, it is currently believed that it is beneficial to avoid RRT as long as possible. However, the situation is very different for intensive care unit (ICU) patients with AKI. RRT is generally viewed as a type of organ support rather than a detoxification procedure in these patients. Early initiation of RRT is already daily practice in ICU patients with AKI. Plausible reasons to support earlier initiation of RRT include improved volume control, quicker control of acid-base, and electrolyte homeostasis accelerated removal of small- and middle-sized molecules, avoidance of morbidity associated with a “wait for a complication” approach. Earlier initiation of RRT in critically ill patients with AKI, however, lacks a scientific basis, when looking at studies comparing “early” versus “delayed” RRT.<sup>[2-4]</sup> The lack of a consensus on accepted nonlethal indications has led to the substantial variability of RRT performance in ICU patients across the world. At present, the provision of RRT in AKI patients is strongly affected by empiricism, patient characteristics (age, severity of illness, and comorbid diseases) or local institutional practices and resources.

The dilemma to define “early” and “delayed.” There has been no consensus on how best to define timing related to RRT initiation in AKI.

Published studies have used physiologic measures (urine output), biochemical parameters (urea, creatinine, and potassium), time relative to AKI onset, time related to hospital or ICU admission, and time related to the development of AKI complications. However, the terms “early” and “delayed” are unprecise. The onset of AKI is known only for a few subsets of AKI patients (postcardiac surgery AKI and contrast media-induced AKI). Currently, there is no consensus that a more quantitative characterization of RRT timing should be used, such as the RIFLE classification or AKIN staging system, number and severity of comorbid diseases (severity scores), rate of biochemical changes (trends), or the pace of clinical evolution of the patient (illness trajectory).

Early systematic reviews, including largely observational studies and few randomized trials, concluded that early initiation of RRT in critically ill patients may be associated with a survival benefit.<sup>[5-7]</sup> These conclusions were not unexpected. Most studies were susceptible to bias and confounding factors such as retrospective design, posthoc secondary analyses, small sample size, heterogeneities in the study populations (age, illness severity, and comorbidities) variations in the definitions of AKI and in the timing or thresholds for starting RRT.

More recently, several randomized trials have been reported that focused on timing strategies for the initiation of RRT in critically ill patients with AKI. Recent meta-analyses including

RCTs found out in unison that early initiation of RRT for ICU patients with AKI was not associated with decreased overall mortality or a delayed renal recovery rate.<sup>[8-11]</sup> The RCTs have – without doubts – vastly improved the quality and quantity of evidence regarding the optimal timing of RRT initiation in critically ill patients with AKI. However, these trials have not resolved the dilemma of discrepant results. The trial Artificial Kidney Initiation in Kidney Injury (AKIKI) – an open-label multicenter trial – did not show a survival advantage in the delayed arm and 60 days’ mortality was comparable between the two groups. In addition, there was no difference in RRT dependence at 60 days.<sup>[12]</sup> The ELAIN trial (effect of early vs. delayed initiation of RRT on mortality in critically ill patients with AKI) is an open-label single-center trial. In the early arm significantly lower mortality, shorter duration of RRT, or mechanical ventilation and length of hospitalization were observed.<sup>[13]</sup> Notably, only 51% of the patients allocated to the delayed arm of the AKIKI trial commenced RRT. In contrast, almost all patients in the late arm of the ELAIN study reached a trigger for RRT initiation (in most cases KDIGO Stage 3).

Physicians using or advocating early RRT initiation must accept the reality that a significant proportion of critically ill patients may never have to start RRT because of spontaneous kidney recovery. However, there are currently no clinical or laboratory prediction tools to determine the factors leading to the recovery of renal function without RRT. Further studies are warranted to guide implementation of large-scale trials for the timing of RRT initiation.

### New strategies for optimal timing to start renal replacement therapy in critically ill patients with acute kidney injury

Clinicians have limited tools to try to predict which patient with early-stage AKI will progress to more severe stages. Chawla *et al.* investigated the ability of the furosemide stress test (FST) which uses intravenous administration of furosemide (1 or 1, 5 mg/kg) and measurement of the ensuing urine output to predict the development of AKIN Stage III in 77 critically ill patients with early-stage AKI. The ideal cutoff for predicting AKI progression during 2 h following FST was a urine volume of <200 ml (100 ml/h). The FST urine output outperformed novel biomarkers for prediction of progressive AKI, the need for RRT and in-hospital mortality. This promising pilot study by Chawla *et al.*, obviously needs confirmation and prospective extension to multiple study sites and a larger number of participants.<sup>[14,15]</sup>

### Furosemide stress test guiding initiation of renal replacement therapy

Lumlertgul *et al.* conducted a multicenter prospective, open-label, two-group pilot trial to determine whether the FST could be used to screen patients at high risk for RRT and to determine the feasibility of this test to exclude low-risk patients from enrolment in trials of RRT timing.<sup>[16]</sup> The FST was performed in 162 patients. FST nonresponsiveness was defined

by urine output <200 ml in 2 h after intravenous furosemide (1 mg/kg in furosemide naive patients and 1, 5 mg/kg in previous furosemide users). Among 118 FST nonresponsive patients, there were 98.3% in the early RRT arm and 75% in the standard RRT arm who received RRT. The authors observed no differences in the 28-day mortality, or 7 days' fluid balance or RRT dependence.

## CONCLUSIONS

The optimal timing to initiate RRT for acute kidney injury remains uncertain. Earlier RRT holds the risk of unnecessary RRT-related complications, increased bedside workload, and health-care costs. The FST represents a novel dynamic functional assessment of tubular function and appears to have good predictive capacity to identify those patients who will progress to advanced stages of AKI. The FST is feasible and seems well tolerated in critically ill patients with early AKI. However, patients should be euvolemic before furosemide challenge, and volume replacement is mandatory in patients who are not obviously volume overloaded. Future large-scale studies to validate the findings of Lumlertgul *et al.*, are warranted.

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## Conflicts of interest

There are no conflicts of interest.

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