Strategies for the optimal timing to start renal replacement therapy in critically ill patients with acute kidney injury

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Renal replacement therapy (RRT) is increasingly utilized to support critically ill patients with severe acute kidney injury (AKI). The question of whether and when to start RRT for a critically ill patient with AKI has long troubled clinicians. When severe complications of AKI develop, the need to commence RRT is unambiguous. In the absence of such complications but in the presence of severe AKI, the optimal time and thresholds for starting RRT are uncertain. The majority of existing data have largely been derived from observational studies. These have been limited due to confounding by indication, considerable heterogeneity in case mix and illness severity, and variably applied definitions for both AKI and for how "timing" was anchored relative to starting RRT. It is unclear whether a preemptive or earlier strategy of RRT initiation aimed largely at *avoiding* complications related to AKI or a more conservative strategy where RRT is started *in response to* developing complications leads to better patient-centered outcomes and health services use. This question has been the focus of 2 recently completed randomized trials. In this review, we provide an appraisal of available evidence, discuss existing knowledge gaps, and provide perspective on future research that will better inform the optimal timing of RRT initiation in AKI.

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Acute kidney injury (AKI) is a growing clinical challenge for health care providers.[1–3] AKI, even when mild, has been associated with incremental risk of short- and long-term complications, including chronic kidney disease,[4] major cardiovascular events,[5–7] sepsis,[8–10] gastrointestinal bleeding,[11] malignancy,[12] fracture risk,[13] and death.[14,15] In a subset of patients perceived to have severe AKI or those in whom clinical and/or metabolic complications related to AKI develop, renal replacement therapy (RRT) is often commenced.[1,16] Recent trends suggest the growing use of RRT in critically ill patients with AKI.[17–19] However, the dilemma of whether and when to start RRT for critically ill patients with AKI, in the absence of clearly urgent indications has been unclear and has long been a vexing clinical issue for intensivists and nephrologists.[20–22] This issue has been repeatedly identified as a high research priority in the fields of critical care and nephrology.[23–25]

In critically ill patients with life-threatening medically refractory complications of AKI (e.g., hyperkalemia, acidemia, fluid overload), there is little controversy about the role for urgent initiation of RRT (Table 1). However, recent observational data have suggested that the occurrence of these "conventional" indications for RRT in critically ill patients with AKI may be less commonly encountered and are generally not the most common primary triggers for starting RRT in routine intensive care unit (ICU) practice.[26–28] In these circumstances, RRT is likely started in response to absolute and expected trends in illness severity and nonrenal organ dysfunction, coupled with a subjective perception of benefit by providers (i.e., anticipation of worsening or the low likelihood of kidney recovery).[28]

The goals of RRT in ICU settings are to achieve and maintain fluid, electrolyte, acid-base, and uremic solute homeostasis along with facilitating additional supportive measures when indicated (i.e., nutritional support, medications, obligatory fluid intake, blood transfusions), while also to prevent overt life-threatening AKI complications from occurring or worsening. Importantly, given the delicate nature of kidney-organ interaction in critically ill states (i.e., kidney-lung, kidney-heart, kidney-brain), RRT might represent an additional important platform of multiorgan support by potentially limiting worsening nonrenal organ dysfunction that may be exacerbated by AKI and overt kidney failure (Table 2). Although these concepts are theoretically

Table 1 | Summary of absolute and relative indications and contraindications for starting RRT in critically ill patients with AKI

Absolute indications (in the absence of contraindications to RRT)	• Refractory hyperkalemia (e.g., K^+ >6.5 mmol/l, rapidly increasing, or cardiac toxicity) • Refractory acidemia and metabolic acidosis (e.g., pH ≤7.2 despite normal or low arterial pco_2) • Refractory pulmonary edema due to fluid overload (i.e., diuretic resistant) • Symptoms or complications attributable to uremia (e.g., bleeding, pericarditis, encephalopathy) • Overdose/toxicity from a dialyzable drug/toxin
Relative indications (in the absence of life-threatening complications of AKI)	• Limited physiologic reserve to tolerate the consequences of AKI • Advanced nonrenal organ dysfunction worsened or exacerbated by excessive fluid accumulation (i.e., impaired respiratory function) • Anticipated solute burden (i.e., tumor lysis syndrome, rhabdomyolysis, intravascular hemolysis) • Need for large volume fluid administration (i.e., nutritional support, medications, or blood products) • Severity of the underlying disease • Concomitant accumulation of poisons or toxic drugs that can be removed by RRT (i.e., salicylates, ethylene glycol, methanol, metformin)
Relative contraindications	• Futile prognosis • Patient receiving palliative care • High likelihood of nonrecovery of renal function in patient who is not a candidate for long-term dialysis

AKI, acute kidney injury; CKD, chronic kidney disease; RRT, renal replacement therapy.
Adapted from Papazian L, Forel JM, Gacouin A, et al. (Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363:1107–1116).[61]

appealing, RRT is associated with potential complications related to both the procedure itself and the need for a dedicated vascular access. As a result, a compelling case may be made for the conservative use of RRT whereby RRT is only started when a life-threatening complication evolves. Ultimately, the controversy surrounding this topic has been stimulated by the absence of high-quality evidence to inform practice. This has contributed to practice variation in the timing of initiation and the use of RRT among critical care units and among individual providers.[27,29–32] The lack of strong evidence to guide care has likely contributed to inconsistent and suboptimal quality of care.

In this concise review, we aim to critically appraise current and recently published evidence focused on when to start RRT for ICU patients with AKI, highlight prevailing knowledge and evidence care gaps, provide perspective on existing clinical practice guidelines, and discuss ongoing clinical studies.

Interaction of RRT and outcome

RRT, along with mechanical ventilation, vasoactive therapy, and nutritional support, is one of the defining life-sustaining technologies in contemporary critical care. Although a smaller proportion of critically ill patients receive RRT compared with other forms of organ support, its use has progressively expanded.[1,17–19] The addition of RRT to the ongoing support of a critically ill patient contributes to an increase in the complexity and costs of care; however, temporal trends in recent decades have shown modest improvements in short-term mortality among those who receive RRT.[17]

There is fundamental debate about whether RRT may influence patient outcomes or whether, as a supportive therapy in the setting of high illness severity, it is largely a surrogate for the impact of critical illness on outcome. Circumstantial evidence has suggested that receipt of any RRT *per se* may be independently associated with mortality among ICU patients with AKI.[29,33,34] These studies compared outcomes among patients with AKI who received or did not receive RRT. These data likely have methodological limitations commonly encountered in observational studies such as fundamental differences in the populations studied (i.e., case mix, illness severity), residual confounding by indication, and

Table 2 | Benefits and drawbacks of earlier RRT in the absence of conventional indications among critically ill patients with AKI

Benefits	Drawbacks
Avoidance and/or early control of fluid accumulation and overload	Need for and complications associated with dialysis catheter insertion (i.e., bleeding, pneumothorax, bloodstream infection)
Avoidance and/or earlier control of acid-base derangement	Need for and complications associated with anticoagulation regimens
Avoidance and/or earlier control of electrolyte/metabolic derangement	Risk of iatrogenic episodes of hemodynamic instability that may exacerbate AKI and impede kidney repair/recovery
Avoidance and/or earlier control of complications of uremia	Risk of excess loss of unmeasured micronutrients and trace elements
Avoidance of unnecessary or excessive diuretic exposure	Risk of excess clearance or subtherapeutic levels of vital medications (i.e., antimicrobials, antiepileptics)
Immunomodulation and clearance of inflammatory mediators	Unnecessary exposure to RRT in patients who have a high likelihood of kidney recovery with conservative management
"Unloading" or "resting" stressed and/or damaged kidneys	Increased bedside workload for providers, resource use, and direct health costs

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