Indications for and Timing of Initiation of KRT

Marlies Ostermann [iD],[1] *Sean M. Bagshaw,*[2] *Nuttha Lumlertgul,*[1,3,4] *and Ron Wald*[5,6]

Abstract

KRT is considered for patients with severe AKI and associated complications. The exact indications for initiating KRT have been debated for decades. There is a general consensus that KRT should be considered in patients with AKI and medically refractory complications ("urgent indications"). "Relative indications" are more common but defined with less precision. In this review, we summarize the latest evidence from recent landmark clinical trials, discuss strategies to anticipate the need for KRT in individual patients, and propose an algorithm for decision making. We emphasize that the decision to consider KRT should be made in conjunction with other forms of organ support therapies and important nonkidney factors, including the patient's preferences and overall goals of care. We also suggest future research to differentiate patients who benefit from timely initiation of KRT from those with imminent recovery of kidney function. Until then, efforts are needed to optimize the initiation and delivery of KRT in routine clinical practice, to minimize nonessential variation, and to ensure that patients with persistent AKI or progressive organ failure affected by AKI receive KRT in a timely manner.

Correspondence:
Prof. Marlies Ostermann, Department of Critical Care, King's College London, Guy's & St. Thomas' NHS Foundation Trust, Westminster Bridge, London SE1 7EH, United Kingdom. Email: Marlies.Ostermann@gstt.nhs.uk

Introduction

KRT is an integral component of organ support in modern critical care. It encompasses different modalities, including continuous, intermittent, and hybrid techniques, and also, acute peritoneal dialysis. In general, KRT is most often considered in patients with severe AKI and associated complications such as severe metabolic acidosis, uremia, severe electrolyte and metabolic derangements, and/or fluid accumulation. Despite its name, KRT only facilitates the removal of excess fluid, a limited array of endogenous and exogenous waste products, and electrolytes and provides restoration of base buffer. KRT does not replace any other intrinsic functions of the kidneys (*i.e.*, reabsorption of amino acids, production of erythropoietin, activation of vitamin D, regulation of the renin-angiotensin system, and metabolic functions). For this reason, it has been argued that the term "kidney support" may be more appropriate than KRT (1). Lastly, because of the nonselective nature of clearance, important micronutrients and medications may be removed during KRT.

Indications

Defining the intent and goals of kidney support therapy is a key consideration when deciding to commence KRT. The exact indications for initiating KRT have been debated for decades (1–3). There is general consensus that KRT should be considered in patients with AKI and medically refractory complications ("urgent indications"), thereby preventing or mitigating the deterioration of nonkidney organ function and death (Table 1). However, the exact criteria and thresholds for metabolic acidosis, hyperkalemia, or severe pulmonary edema vary widely in clinical practice.

"Relative indications" are more common but defined with less precision (Table 1). Although serum creatinine and urine output are routinely used as markers of AKI severity, they are inadequate indicators of kidney function and do not reliably distinguish patients who will develop an urgent need for KRT from those who will recover kidney function without KRT. This is compounded by the fact that the precise molecules that mediate the toxicity and the attributable harm of AKI are not known (4). In fact, there is no unique parameter to accurately identify patients with a clear indication for KRT who will benefit from this escalation in organ support (1). Thus, the interpretation of relative indications varies across patient case mix and intensive care unit (ICU) settings and among clinicians, resulting in heterogenous clinical practice. Fluid overload is a common indication for KRT but poorly defined in the literature. Some studies suggested to use a 5% or 10% increase in body weight as criteria for fluid overload (5,6). However, this approach is limited by the fact that an increase in fluid balance may occur with the appropriate treatment of intravascular hypovolemia. A rising cumulative fluid balance may indicate fluid accumulation but does not necessarily equate to fluid overload. Furthermore, different patients with similar creatinine values or degrees of fluid accumulation may have different indications for KRT due to differences in acute and chronic comorbidities and concomitant therapies. For instance, there are no clear guidelines for KRT initiation in patients treated with extracorporeal membrane oxygenation (ECMO) or extracorporeal carbon dioxide removal (ECCO2R) (7,8). Nonetheless, patients for

Table 1. Potential indications for KRT in the setting of AKI

Level of Indication	Clinical Scenario
Urgent indication	• Severe metabolic acidosis refractory to medical treatment • Pulmonary edema • Uremic complications (pericarditis, encephalopathy, bleeding) • Severe hyperkalemia refractory to medical treatment • Intractable fluid overload coupled with organ dysfunction • Concomitant intoxication with a dialysable drug or toxin
Relative indication	• Progressive and/or persistent AKI (sCr >3× baseline and/or profound oliguria) • Severe nonkidney organ dysfunction worsened by AKI • Worsening trajectory of critical illness

sCr, serum creatinine.

whom ECMO or ECCO2R is required are very sensitive to fluid accumulation and may have a lower threshold to start KRT as compared with patients with similar metabolic parameters but not receiving ECMO/ECCO2R.

Correction of AKI-mediated metabolic acidosis is a recognized reason for starting KRT. The indication for KRT in other types of metabolic acidosis, other than those associated with the ingestion of certain toxic alcohols, is less clear. Levraut *et al.* (9) compared lactate clearance during KRT with endogenous kidney clearance. They showed that the median filter lactate clearance was 24.2 ml/min compared with the median endogenous lactate clearance of 1379 ml/min, confirming the negligible effect of KRT on lactate removal (<3%). Thus, the reduction of lactate concentration during KRT usually reflects an improvement in patients' hemodynamic status and correction of the factors that mediated the lactic acidosis. Similarly, although ketones are removed during KRT, the treatment of severe ketoacidosis consists of management of the underlying condition.

The emergency management of severe hyperkalemia includes KRT, but the exact potassium threshold and factors that influence the risk of mortality (*e.g.*, serum potassium threshold and comorbidities) are uncertain (10). Serum potassium concentrations of >6.5 mmol/L refractory to medical management and electrocardiogram manifestations of cardiac toxicity (regardless of serum potassium level) have been recommended as triggers for initiation of KRT, but robust evidence is lacking.

Similarly, hyperammonemia with cerebral edema is a major contributing cause of mortality in patients with liver failure, but there is no consensus or firm guideline for the implementation of KRT with the express reason of removing ammonia (11). Lastly, the decision to consider KRT should be made in conjunction with other forms of organ support therapies and important nonkidney factors, including the patient's preferences and overall goals of care (Figure 1).

Strategies to Anticipate the Need for Kidney Replacement Therapy

There is an ongoing search for tools that identify patients who will likely progress to receive KRT. As an alternative to the current approach of determining the indication for KRT, it has been proposed that KRT is indicated when the kidneys no longer have the capacity to meet the metabolic

and fluid demands placed on them (12–14). This "demand capacity" concept acknowledges the dynamic nature of critical illness and the interactions between different organ functions and therapies, and it emphasizes the importance of using an individualized approach on the basis of the severity of the acute illness and the patient's kidney capacity. However, the exact methods for determining "kidney demand and capacity" and specific components that affect decision making are still under investigation (14).

The standardized furosemide stress test to interrogate tubular cell function has been proposed as a practical bedside tool to anticipate the risk of AKI progression, including the likelihood of the patient requiring KRT (1,15–17). The methodology of the furosemide stress test is on the basis of the fact that furosemide gains access to the tubular lumen by active secretion *via* the human organic anion transporters 1 and 3 in the proximal convoluted tubule. Once in the tubular lumen, furosemide inhibits luminal active chloride transport throughout the thick ascending limb of Henle. The furosemide stress test consists of a single dose of intravenous furosemide (1.0 mg/kg for loop diuretic–naïve patients and 1.5 mg/kg for those who had prior loop diuretic exposure) and replacement of urine output milliliter for milliliter each hour with an isotonic solution for 6 hours to minimize the risk of hypovolemia (18). Patients must not be hypovolemic before undertaking any type of furosemide challenge, and volume replacement is not mandatory in patients who are felt to be volume

Figure 1. | **Factors affecting the initiation of KRT in the intensive care unit (ICU).**

expanded (18). A urine output of >200 ml in 2 hours after furosemide administration is considered an indicator of preserved renal tubular function (17). A multicenter pilot study confirmed that the furosemide stress test could be used to screen patients with AKI at high risk for KRT (15). Only 14% of patients with a positive furosemide stress test ultimately received KRT, whereas 78% of nonresponders randomized to a standard KRT initiation strategy received KRT or died ($P<0.001$).

Numerous novel biomarkers have been found to be associated with the receipt of KRT, but the quality of existing evidence does not support using them when deciding whether to initiate or withhold KRT (1,19,20). Limitations include the use of different cutoff values in published reports, the lack of standard analysis methods, and confounding by acute and chronic comorbidities (21). In a meta-analysis of 41 studies including over 15,000 patients, the pooled areas under the receiver operating curve (AUROCs) for urine and blood neutrophil gelatinase–associated lipocalin for the prediction of KRT were 0.72 (95% confidence interval [95% CI], 0.64 to 0.80) and 0.76 (95% CI, 0.71 to 0.80), respectively, whereas serum creatinine and cystatin C had pooled AUROCs of 0.76 (95% CI, 0.73 to 0.80) and 0.77 (95% CI, 0.73 to 0.81), respectively (19). Urine biomarkers IL-18 and cystatin C and the product of the cell cycle arrest markers tissue inhibitor of metalloproteinases–2 and insulin-like growth factor-binding protein 7 ([TIMP-2]x[IGFBP7]) showed pooled AUROCs of 0.67 (95% CI, 0.61 to 0.73), 0.72 (95% CI, 0.58 to 0.87), and 0.86 (95% CI, 0.79 to 0.93), respectively. Some of the limitations for biomarker-based predictions are the variable cutoffs used in studies, reliance on single measurements, and confounding by underlying comorbidities and clinical conditions. Recently, new biomarkers of persistent AKI were identified (22). Data on their role in determining the indication and timing of KRT are awaited.

When to Start Kidney Replacement Therapy in AKI: The Crux of the Debate

The core of the debate surrounding the optimal timing for KRT initiation revolves around whether and when to commence KRT in individuals with severe AKI who lack urgent indications for KRT (Table 1). Stated differently, does the preemptive initiation of KRT have a role in the management of patients with severe AKI, manifesting only as depressed GFR and/or oligoanuria, and without any other complications associated with AKI? Preemptive KRT initiation may seem intuitively attractive as a means of proactively modulating volume excess, maintaining acid-base homeostasis, and affecting the removal of conceivably toxic (but as of yet unidentified and, hence, unmeasurable) molecules that accumulate in the setting of AKI. On the other hand, a strategy of structured KRT deferral would entail close surveillance and reserve deployment of KRT to when more severe and medically refractory AKI-associated complications arise. This approach incorporates a window of opportunity to observe for evidence of kidney recovery. The delay in KRT initiation, and in some cases, the complete obviation of the need to start KRT will reduce exposing patients to the risks of KRT while potentially conserving resources.

Clinical Trials Comparing Kidney Replacement Therapy Initiation Strategies in AKI

Prior to 2016, clinical trials exploring KRT initiation in AKI were too small to evaluate patient-important clinical outcomes (23–25). Observational studies tended to support earlier KRT initiation but were likely to be confounded by indication bias (26–28). Publication of the Early versus Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients with Acute Kidney Injury (ELAIN) trial in 2016 heralded a series of larger trials with the potential of informing clinical practice (29) (Table 2). ELAIN was a single-center trial that recruited 231 patients predominantly admitted to the ICU after cardiac surgery who had stage 2 AKI, a plasma neutrophil gelatinase–associated lipocalin >150 mg/ml (a surrogate for tubular injury), and one of the following: sepsis, need for BP support, evidence of congestion, and/or some manifestation of nonkidney organ dysfunction. Patients were randomized to early KRT initiation, which entailed the initiation of KRT within 8 hours of randomization, or a strategy in which KRT was delayed until progression to stage 3 AKI, escalation of serum urea to >36 mmol/L, hyperkalemia, hypermagnesemia, or edema refractory to diuresis. All patients in the early arm received KRT as did nearly all patients (91%) in the delayed arm, mostly triggered by progression to stage 3 AKI. The primary outcome, 90-day all-cause mortality, was significantly lower among patients in the early arm (39% versus 55% in the delayed arm; hazard ratio, 0.66; 95% CI, 0.45 to 0.97). Early KRT initiation also conferred a reduction in the duration of mechanical ventilation and length of stay in the ICU. One year of follow-up of the ELAIN cohort demonstrated that the advantages of earlier KRT initiation were maintained (30). Notably, major adverse kidney events, comprising death, dialysis, or GFR decline, were lower among patients who were initially randomized to early KRT initiation. Of note, the ELAIN trial had a fragility index of three, meaning that some combination of three fewer deaths in the delayed group or three more deaths in the early group would have resulted in a loss of statistical significance with regard to the primary outcome.

The Artificial Kidney Initiation in Kidney Injury (AKIKI) investigators randomized 620 critically ill patients at 31 centers in France with stage 3 AKI who were receiving concomitant vasopressor and/or ventilatory support with serum urea <40 mmol/L and no other acute indications for KRT initiation (31). Participants in the early KRT arm were to receive KRT within 6 hours of meeting criteria for stage 3 AKI, whereas those in the delayed arm only commenced KRT if oligoanuric AKI persisted for >72 hours, serum urea surpassed 40 mmol/L, or another AKI-related emergency supervened. The trial population was composed mostly of patients with medical reasons for ICU admission, and approximately 80% had sepsis. Nearly all patients in the early arm received KRT, with a median time of 4.3 hours after documentation of AKI stage 3. In the delayed arm, approximately half of the patients received KRT (median time from randomization
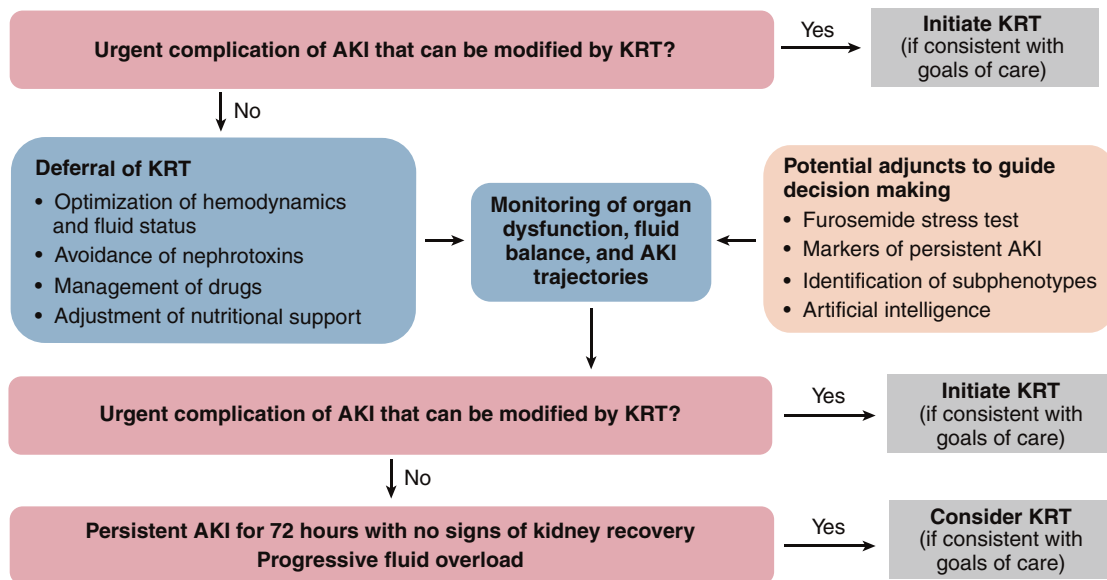
Figure 2. | Algorithm to guide KRT initiation.

was 57 hours), and the most common triggers were oligoanuria and serum urea >40 mmol/L. The primary outcome of 60-day mortality did not differ between the two KRT initiation strategies (49% versus 50% in the early and delayed groups, respectively). There were no differences in any other prespecified outcomes.

The Initiation of Dialysis Early versus Delayed in the Intensive Care Unit (IDEAL-ICU) trial compared early and delayed KRT initiation strategies in patients with stage 3 AKI complicated by septic shock in 29 French ICUs (32). Those in the early arm started KRT within 12 hours of meeting AKI criteria, whereas those in the delayed arm commenced KRT only in the setting of an AKI emergency or after 48 hours if kidney recovery had not occurred. The trial was stopped early after 488 patients (56% of the planned recruitment target) were enrolled. Nearly all participants in the early arm commenced KRT a median of 8 hours from AKI diagnosis. In the delayed arm, 62% of participants received KRT, mostly triggered by mandated initiation of KRT at 48 hours but with no ostensible AKI-related emergency. Mortality at 90 days was not different (54% versus 58%; $P=0.38$) between the two strategies.

The Standard versus Accelerated Initiation of Renal Replacement Therapy in AKI (STARRT-AKI) trial addressed the question of optimal timing for KRT initiation at 168 sites in 15 countries (33). The trial population comprised individuals with stage 2 or 3 AKI who lacked any objective indications for impending KRT initiation and had a significant background of preexisting CKD or suspicion for an AKI etiology other than acute tubular necrosis. Patients with a high likelihood of experiencing imminent kidney recovery and thus, unlikely to ever receive KRT if randomized to the standard arm of the trial were excluded. In addition, those individuals perceived to require immediate KRT initiation were excluded, thereby ensuring that the trial population included only patients in whom there was a fundamental dilemma regarding the optimal time of KRT initiation. Although in the accelerated arm, participants were to commence KRT

within 12 hours of meeting eligibility criteria, the standard arm of STARRT-AKI differed markedly from the delayed strategies in ELAIN, AKIKI, and IDEAL-ICU. Specifically, clinicians were discouraged to initiate KRT unless the patient developed severe hyperkalemia, profound metabolic acidosis, or severe hypoxemia attributed to fluid overload. However, there was no mandate to initiate KRT under these circumstances if these complications could be managed through non-KRT means, nor was there a deadline by which KRT needed to be started. For patients with persistent AKI 72 hours after randomization, clinicians had the option to initiate or defer KRT at their discretion.

The trial recruited 3019 patients, of whom 2927 were included in the primary modified intent-to-treat analysis (1465 in the accelerated arm and 1462 in the standard arm). There was a predominance of patients with a medical reason for ICU admission; the majority had sepsis, and a substantial minority had preexisting CKD. KRT was commenced in 97% of those allocated to the accelerated arm at a median of 6 hours from meeting all eligibility criteria. In the standard arm, KRT was deployed in 62% of patients a median of 31 hours from full eligibility being attained. All-cause mortality was no different between the two arms of the trial. There was also no evidence of a survival difference in prespecified subgroups, including in patients with and without sepsis and preexisting CKD, surgical versus medical patients, and patients with a higher severity of illness. However, the receipt of KRT at 90 days among surviving patients was more common in the accelerated arm (10% versus 6% in the standard arm; risk ratio, 1.74; 95% CI, 1.24 to 2.43). Adverse events, specifically KRT-induced hypotension and hypophosphatemia, were more common in participants allocated to the accelerated arm.

Lingering Questions and Need for Further Research

Uncertainty remains regarding the duration for safe KRT deferral in the presence of persistent AKI. A "wait and see"

Table 2. Summary of randomized controlled trials evaluating timing of KRT initiation in critically ill patients with AKI

Parameter	Early versus Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients with Acute Kidney Injury Trial	Artificial Kidney Initiation in Kidney Injury Trial	Initiation of Dialysis Early versus Delayed in the Intensive Care Unit Trial	Standard versus Accelerated Initiation of Renal Replacement Therapy in AKI Trial	Artificial Kidney Initiation in Kidney Injury 2 Trial
Setting	Single center; Germany	31 centers; France	29 centers; France	168 centers; 15 countries	39 centers; France
Population	n=231 (95% surgical patients, 47% cardiac surgery)	n=620 (80% medical patients)	n=488 (100% septic shock)	n=2927 (67% medical patients)	n=278 (58% medical patients)
Preexisting CKD, %	41	10	16	44	12
Early KRT criterion	KDIGO stage 2 (within 8 h) plus NGAL >150 ng/ml plus ≥1 risk factor[a]	KDIGO stage 3 (within 6 h) plus receiving vasopressors ± MV	RIFLE failure (within 12 h) plus within 48 h of vasopressor initiation	KDIGO stage 2 or 3 (within 12 h)	—
Delayed KRT criterion	KDIGO stage 3 (within 12 h); urgent indications; BUN >36 mmol/L	Urgent indications; BUN >40 mmol/L; oliguria >72 h	Urgent indications 48 h after randomization in the absence of kidney recovery	KRT discouraged unless urgent indications; persistent AKI ≥72 h[b]	KDIGO stage 3 and receiving vasopressors ± MV plus oliguria >72 h or BUN 40–50 mmol/L (within 12 h)
More delayed KRT criterion	—	—	—	—	Urgent indications; BUN >50 mmol/L
Time to KRT initiation from eligibility (early versus delayed),c median (QR)	6 h (4–7) versus 25.5 h (18.8–40.3)	2 h (1–3) versus 57 h (25–83)[d]	7.6 h (4.4–11.5) versus 51.5 h (34.6–59.5)	6.1 h (3.9–8.8) versus 31.1 h (19.0–71.8)	44 h (23–66) versus 94 h (59–130)
% received KRT	100 versus 91	98 versus 51	97 versus 62	97 versus 62	98 versus 79
KRT modality	CVVHDF	IHD or CKRT	IHD or CKRT	IHD or CKRT	IHD or CKRT
SOFA score at enrollment	16±2	11±3	12±3	12±4	12±4
Cumulative fluid balance at randomization	6.8 L (early) versus 6.3 L (delayed)	NA	3.2 L/d (early) versus 3.2 L/d (delayed)	2.6 L (early) versus 2.8 L (delayed)	NA
Mortality	90 d; 39% versus 64%; HR, 0.66; 95% CI, 0.45 to 0.97	60 d; 49% versus 50%; HR, 1.03; 95% CI, 0.82 to 1.29	90 d; 58% versus 54%; HR, 1.08; 95% CI, 0.90 to 1.30[e]	90 d; 44% versus 44%; RR, 1.00; 95% CI, 0.93 to 1.09	60 d; 44% versus 55%; HR, 1.65; 95% CI, 1.09 to 2.50[f]
KRT dependence	At day 90; 54% versus 39%; OR, 0.55; 95% CI, 0.32 to 0.93	At day 60; 2% versus 5%; RR, 0.53; 95% CI, 0.20 to 1.41[e]	At day 90; 2% versus 3%; RR, 0.83; 95% CI, 0.28 to 2.46[e]	At day 90; 10% versus 6%; RR, 1.74; 94% CI, 1.24 to 2.43	At day 60; 4% versus 2%; RR, 2; 95% CI, 0.19 to 8.25[e]
Other outcomes	Shorter KRT duration, MV duration, and hospital stay in the early group	More CRBSI in the early group (10% versus 3%)		Higher adverse events in the early group (23% versus 17%)	KRT-free days at 28 d; 12 versus 10 d (P=0.93)

KDIGO, Kidney Diseases Improving Global Outcomes; NGAL, neutrophil gelatinase–associated lipocalin; QR, quartile range; CVVHDF, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis; CKRT, continuous KRT; SOFA, Sequential Organ Failure Assessment; NA, not available; HR, hazard ratio; 95% CI, 95% confidence interval; RR, risk ratio; OR, odds ratio; CRBSI, catheter-related bloodstream infection.

[a]Severe sepsis, vasopressor use, fluid overload, or progression of other organ dysfunction.

[b]The decision to initiate KRT was left to the clinician's discretion.

[c]Related only to patients who received KRT.

[d]Time from randomization to KRT. The median time from eligibility to KRT was 4.3 hours in the early KRT arm but not available in the primary publication in the delayed arm.

[e]Calculated. Not provided in primary publication.

[f]Adjusted by the Simplified Acute Physiology Score III, MV, catecholamine infusion, sepsis status, and time between intensive care unit admission and AKI.

approach will undoubtedly reduce the exposure to KRT and could also translate into a potentially reduced burden of long-term dialysis dependence and, possibly, lower health resources utilization. However, a delayed approach will also prolong the exposure to the consequences of AKI, including uremia, acidosis, and fluid overload. The median times to KRT initiation in the delayed arms of AKIKI, IDEAL-ICU, and STARRT-AKI were 57, 51, and 31 hours, respectively. As such, the findings of these trials may not be applicable to patients with protracted unresolving AKI that lasts beyond 3–4 days. The efficacy and safety of prolonged KRT deferral were examined in the AKIKI-2 trial (34). Patients with stage 3 AKI that persisted for 3 days without any intervening AKI-related emergencies were randomized to either commence KRT under conditions that reflected the delayed arm in the AKIKI trial or subjected to further KRT deferral such that KRT was only commenced if serum urea exceeded 50 mmol/L or an AKI-related emergency arose ("more delayed" KRT initiation). The trial recruited 278 patients across 39 sites in France. The primary outcome of KRT-free days through day 28 was not different in both treatment arms (10 versus 12 days in the delayed and very-delayed groups, respectively; $P=0.93$). Of concern, in a prespecified adjusted analysis, 60-day mortality was higher in the very-delayed arm compared with the delayed arm (55% versus 44%, respectively; $P=0.07$) (35).

There have been systematic efforts to standardize the initiation and delivery of KRT in routine clinical practice to minimize nonessential variation and to ensure that patients with persistent AKI or progressive organ failure affected by AKI receive KRT in a timely manner. A recent study conducted in ICUs at the Brigham and Women's Hospital illustrated the deployment of a Standardized Clinical Assessment and Management Plan (SCAMP) for critically ill patients with AKI (36). SCAMP provided defined criteria for KRT initiation, which comprised a series of specific indications (pH <7.2, potassium >6.5 mmol/L, toxin ingestion, massive anasarca, $FiO_2 >0.7$, urine output <100 ml/24 h, and/or overt uremic symptoms). SCAMP and a "sham" were applied in alternative periods over 1 year. Biochemical criteria at the time of KRT initiation were similar in both groups, suggesting a possible carryover effect from SCAMP to sham periods. Patients exposed to both strategies had a comparable likelihood of receiving KRT, and mortality was no different between both groups. However, ICU and hospital length of stay were shorter among patients exposed to the SCAMP intervention. In addition, KRT was utilized less frequently in the SCAMP-exposed patients as compared with the sham-exposed patients whose clinical prognosis was characterized as futile.

There are ongoing attempts to more precisely identify subphenotypes of AKI better, including patients with a high risk of progression to persistent AKI and CKD (37–39). Clinical judgment concerning the need for or avoidance of KRT may be complemented further by additional tools to stratify the risk, including the furosemide stress test, markers of persistent kidney injury, technologies enabling continuous measurement of GFR, and advances in artificial intelligence and digital health (40,41). In combination, these tools may enable the early identification of patients with progressive AKI in whom KRT may not be avoidable as well as the identification of patients who are likely to recover kidney function without needing KRT. Integration of these tools into clinical practice will be the subject of future research.

Finally, clinicians treating critically ill patients with AKI should consider the possibility that initiation of KRT might confer marginal benefits in some patients. The debate concerning futility includes the challenges of how to define it, but also touches upon questions of physicians' professional authority versus patients' rights and autonomy in deciding to withhold treatment (42). Despite these inherent difficulties, clinicians can take an active role in promoting discussion about futility in circumstances where clinical impression and objective parameters indicate that the prospects for a meaningful recovery are minimal (43). In case of uncertainty about the benefits of KRT or a patient's wishes, a time-limited trial of KRT with agreed goals of treatment, clear timelines for review, and agreed criteria for continuing or stopping KRT is a potential option (44). During time-limited trials, medical decision making is an ongoing process, and it accounts for changes in the patient's clinical status and reassessment of prognosis (44).

The balance of evidence from recently completed clinical trials indicates that immediate initiation of KRT in the absence of a pressing AKI-related emergency does not lead to a meaningful improvement in clinical outcomes (Figure 2). Moreover, this approach carries important risks. Better data are needed to inform the thresholds for KRT initiation when AKI is unresolving. An enhanced understanding of the molecules that mediate the toxicity of AKI as well as validation of novel biomarkers may enable the deployment of KRT in a more precise fashion.

Author Contributions

M. Ostermann conceptualized the study; S.M. Bagshaw, N. Lumlertgul, M. Ostermann, and R. Wald wrote the original draft; and S.M. Bagshaw, N. Lumlertgul, M. Ostermann, and R. Wald reviewed and edited the manuscript.

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AFFILIATIONS

[1]Department of Critical Care, King's College London, Guy's & St. Thomas' Hospital, London, United Kingdom

[2]Department of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta and Alberta Health Services, Edmonton, Alberta, Canada

[3]Division of Nephrology and Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

[4]Department of Nephrology, Center of Excellence in Critical Care Nephrology, Chulalongkorn University, Bangkok, Thailand

[5]Division of Nephrology, St. Michael's Hospital and the University of Toronto, Toronto, Ontario, Canada

[6]Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada