Timing of Kidney Replacement Therapy in Acute Kidney Injury

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AKI is a common complication with an increasing incidence and a higher risk of short- and long-term complications (1). Kidney replacement therapy (KRT) is often required in patients with severe AKI who develop clinical and/or metabolic complications. In the absence of clearly urgent indications, the decision when to initiate KRT in patients with AKI is challenging and remains a conundrum for clinicians. In the last few years, several clinical trials have examined different aspects of KRT, including the optimal dose, ideal modality, and most effective method of anticoagulation. However, the fundamental questions of whether and when to start KRT with AKI remain unanswered.

Theoretically, early KRT initiation should be advocated to facilitate better fluid balance, electrolytes, and acid-base homeostasis. Furthermore, it may putatively modulate inflammatory cytokine levels during inflammatory processes and serve to support organ function. However, KRT goes along with a higher risk of vascular access and dialysis-related complications, increased health care costs, and more bedside workload. These opposing considerations prompted the Kidney Disease Improving Global Outcomes (KDIGO) Consortium in 2012 to publish guidelines regarding the timing of KRT initiation in AKI. Two recommendations, both not graded, were to start KRT "emergently when life threatening changes in fluid, electrolyte, and acid-base balance exist" and that physicians should consider the "broader clinical context, the presence of conditions that can be modified with KRT, and trends of laboratory tests—rather than single BUN and creatinine thresholds alone—when making the decision to start KRT" (2). The second statement does not help clinicians to decide when to initiate KRT; however, it reflects clinical practice, where clinicians evaluate the overall condition of an individual patient rather than a single biochemical or physiologic parameter.

Until recently, available data on the initiation of KRT were largely derived from retrospective and observational studies, and only few randomized, controlled trials were available. A meta-analyses investigating this controversy has suggested that early KRT initiation in critically ill patients did not result in lower mortality (3). However, no conclusions can be drawn from this study, because the analysis has a poor methodological quality and significant heterogeneity among the included studies.

In a feasibility study including 100 patients, Wald *et al.* (4) investigated KRT initiation in patients with a moderate AKI (KDIGO AKI stage 2) and a positive damage biomarker (blood neutrophil gelatinase–associated lipocalin [NGAL] ≥400 ng/ml). In the "standard" group, KRT initiation was determined by classic indications, whereas in the "accelerated" arm, KRT was started within 12 hours of reaching the eligibility criteria. Although mortality was not the primary end point, there was no difference in mortality, and approximately 30% of patients randomized to standard treatment did not require KRT.

Recently, two randomized, controlled trials reported results of the timing of KRT initiation in critically ill patients with AKI. The Artificial Kidney Initiation in Kidney Injury (AKIKI) (5) multicenter trial included 620 patients in France; it compared a strategy of KRT initiation at KDIGO stage 3 (early) with that at KDIGO stage 3 and clinical indications (late) and was intended to show that a late start reduces mortality. The trial showed no difference in the primary outcome (60-day all-cause mortality). However, 49% of patients randomized to late KRT initiation never received it due to recovery of kidney function or death. A *post hoc* analysis showed that, when patients in the late group treated with KRT were analyzed separately, mortality was significantly higher in the late group in comparison with the early group.

The Early Versus Late Initiation of KRT in Critically Ill Patients with AKI single-center trial in Germany (6) compared KRT initiation at KDIGO AKI stage 2 (early group) with initiation at KDIGO AKI stage 3 (late group). In this study, an inclusion strategy that combined clinical criteria of AKI progression with a damage biomarker (NGAL>150 ng/ml) was used to mitigate the chance of including patients who would recover spontaneously from AKI without requiring KRT. In contrast to the AKIKI trial, the early group showed a lower 90-day all-cause mortality (primary end point). Almost all patients in the late group had developed AKI stage 3, and only 5% spontaneously recovered from AKI without requiring KRT. Because there were no differences in baseline characteristics and setting of AKI between the two groups, it is reasonable to expect that the early group would also

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have developed a disease progression similar to the late group. However, the use of NGAL resulted in the exclusion of very few patients.

The contrasting results from these two trials have spurred significant debate; however, they are not comparable, because they had different study designs, inclusion criteria, patient populations, and definitions of "early" and "late" KRT initiation. These trials highlight the fact that timing of KRT initiation is a very complex decision process involving the considerations of the clinical course of the patient and different clinical variables. Additionally, physician actions for initiating KRT are conditioned by the availability of personnel and equipment and personal biases that reflect prevailing local patterns of care. Recently, a small single-center study showed that the implementation of a clinical decision algorithm for initiating KRT may improve outcomes in patients with AKI (7). The algorithm provided recommendations to clinicians for deciding when to start or withhold dialysis on the basis of clinical parameters and patient comorbidities. Patients who were treated according the algorithm had lower in-hospital mortality (43% versus 63%; $P<0.01$) and 60-day mortality (46% versus 68%; $P<0.01$). However, in this study, physicians were more likely to accept recommendations to withhold rather than initiate dialysis, reflecting a strong preference for avoiding KRT. Our current approach anchoring the decision to initiate KRT solely on parameters of kidney dysfunction has been shown to be inadequate. Currently available biomarkers cannot be used to guide decision making on when to initiate KRT. The furosemide stress test, evaluating the urine volume at 2 hours after a standardized dose of furosemide, is a promising approach to test structural-functional relationships. The furosemide stress test was predictive of patients who progressed to a higher stage of AKI severity, and it was shown to be effective in identifying patients who require KRT (8). However, more research is needed to identify biomarkers and decision support systems to help physicians personalize KRT timing on the basis of individual patient need. These decision support systems need to discriminate patients who have a high likelihood to develop a deterioration of AKI and may benefit from earlier KRT initiation from those who have a high likelihood of rapid recovery of kidney function and do not need KRT.

A key area is to recognize the role that KRT plays in organ support independent of kidney functional change. In critical illness, the underlying disease process adds a significant demand on underlying organ functional capacity that is magnified as multiple organs are affected (9). This mismatch of demand and capacity is further influenced by the process of care (*e.g.*, fluid resuscitation could be used as a dynamic quantitative measure to determine when organ support is needed). In line with this, the Acute Disease Quality Initiative (ADQI) workgroup recently suggested that a more personalized approach can be developed on the basis of dynamic assessments of different clinical parameters that reflect the mismatch of demand and capacity (10). It is assumed that the kidneys have a limited capacity. Therefore, KRT initiation should be triggered by kidney's ability to meet the demands being placed on them. A raising demand induces an imbalance and may lead to dysfunction of other organs. KRT should be considered in situations where a significant gap between functional capacity of the kidney and demand exists or is anticipated. If demand is high (*e.g.*, septic shock), KRT should also be considered at lower stages of AKI. In contrast, if the fluid and metabolic demands are low, KRT may not be necessary, even in a patient with AKI stage 3. It remains to be seen whether a robust system can be constructed on the basis of this conceptual framework and tested in clinical trials. Three large multicenter, randomized, controlled trials are ongoing that will definitely add knowledge to this important unanswered clinical question. As we await these trial results, we suggest that it is not necessary to wait for conventional indications to consider KRT; rather, the choice should be on the basis of ongoing assessments of the patient anticipating the course in the absence of KRT. Reasonable rationales for starting KRT are avoidance of fluid accumulation, provision of space to accommodate nutritional and medication needs, maintenance of acid-base and electrolyte control, and abrogation of the interaction between the kidney and other organs. We recommend moving away from considering KRT timing for an individual patient as early or late; rather, the focus should be on making KRT timely for each patient to improve outcomes.

The evidence for KRT initiation in critically ill patients with AKI is relatively weak, and guideline statements are very unspecific. Recently published trials provided contrasting results. The ADQI workgroup recently suggested that the decision to initiate KRT should be individualized and on the basis of the demand-capacity concept. Continued research in this area is needed to reduce variation in timing of KRT initiation.

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