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EDITORIAL COMMENTARY

Liberation from continuous kidney replacement therapy—is it an art or a science?

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Though the field of critical care nephrology has made huge inroads in the last 2 decades, due to a lack of practice-based recommendations, there still remains considerable variation in practice in the delivery of continuous kidney replacement therapy (CKRT) to critically ill children. This has been well-demonstrated by the recent survey of CKRT practices in pediatric intensive care units (PICUs) across Europe conducted by the critical care nephrology section of the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) [1]. This survey demonstrated a wide variation in current CKRT practice, including organizational aspects, education and training, prescription, and liberation from CKRT, in European PICUs. These variations add to the existing confusion regarding best practices in delivering CKRT safely and effectively to children admitted to the PICU. One controversy which often gets discussed is the timing of the initiation of CKRT in critically ill children. However, for the bedside clinicians and patients and their families, the question of when to stop or de-escalate CKRT is equally important and perplexing. In addition to clinical consequences, assessing kidney function to decide to stop CKRT has significant public health and cost-saving implications, especially in resource-limited settings.

According to the guidelines published by the Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, CKRT should be stopped when "it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care" [2]. However, the issue with these guidelines is that they are not specific enough for healthcare professionals to implement in their daily clinical practice. Assessment of recovery of kidney function to assess the timing of liberation from CKRT has always been a clinical challenge.

The 26th Acute Disease Quality Initiative (ADQI) meeting, dedicated to pediatrics in 2021, was conducted to develop expert-driven pediatric-specific recommendations on needed AKI research, education, practice, and advocacy. Group 4 of this meeting focused on the safe and effective delivery of kidney support therapy to critically ill children. The group identified timing and strategies for liberation from kidney support therapy as major challenges [3].

In this editorial commentary, we discuss the predictors of successful weaning/liberation from CKRT including the use of clinical, biochemical, and novel biomarkers; strategies used to liberate children from CKRT; patient management after liberation from CKRT; and follow-up of patients to look for the development of chronic kidney disease (CKD). We focus on continuous KRT and not on other modalities of kidney support therapy (KST)—peritoneal dialysis, intermittent hemodialysis, or prolonged intermittent renal replacement therapy (PIRRT), though liberation/de-escalation is equally important in these modalities as well.

In the European survey discussed above, we saw a wide variation in the current practice of deciding the timing of liberation from CKRT. Clinicians assess the resolution of underlying indications for which CKRT was initiated, hemodynamic status, the trajectory of fluid balance over time, variable amounts of native urine output while being on CKRT, and importantly multi-disciplinary evaluation of the patient's ability to sustain metabolic, acid–base, and hemodynamic milieu once a trial off CKRT has begun [4]. There are no set variables in predicting successful liberation from CKRT.

Though a number of studies in adult patients have explored these variables, there is an extreme paucity of data in the pediatric population where it is even more important to be precise about the duration of CKRT due to issues with

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vascular access, filter clotting, and technical expertise available for CKRT provision to smaller children.

Relevant studies

Wei et al. looked at the predictors of successful CKRT cessation in pediatric patients [5]. Successful discontinuation was defined as remaining off CKRT for at least 7 days. A higher proportion of patients who were unsuccessful at CKRT liberation had underlying cardiac disease, underwent cardiopulmonary bypass, or had an underlying oncologic disease. The 6-h and 24-h urine outputs prior to CKRT discontinuation were significant. Urine output in the 6 h prior to CKRT discontinuation in the success group had a median of 0.8 mL/kg/hr compared to 0.1 mL/kg/hr in the failure group. In the 24-h period, the urine output for the success group was 0.8 mL/kg/hr, while the failure group had a urine output of 0.2 mL/kg/hr. When categorizing urine output based on diuretic use status, only urine output without diuretics remained significant in both time periods. Their key finding was that urine output greater than 0.5 mL/kg/hr irrespective of diuretic administration in the 6-h period before CKRT discontinuation was a significant predictor with AUC 0.72. The authors must be commended for conducting this in-depth analysis of the variables which could reliably predict liberation from CKRT in critically ill children. The importance of the failure of successful liberation from CKRT is shown by the authors where patients who required CKRT re-initiation had a longer ICU length of stay (27.2 vs. 44.5 days) and higher in-hospital mortality (15.1% vs. 46.2%). The decision to liberate from CKRT too early (consequences of re-initiation of CKRT) or too late (implications of cost, resources, patient/family anxiety) is detrimental. Therefore, it is important to be able to reliably predict the timing of cessation or de-escalation of kidney support therapy.

Liu et al. looked at a cohort of 1135 adult patients with AKI requiring CKRT over a period of 10 years [6]. Successful CKRT liberation and KRT-free survival at hospital discharge were observed in 20% and 35% of patients, respectively. Mean hourly urine output within 12 h before liberation, mean serum creatinine value within 24 h before liberation, cumulative fluid balance from ICU admission to liberation, CKRT duration before liberation, and the requirement of vasoactive agents within 24 h before liberation were the independent variables associated with liberation from CKRT.

A systematic review and meta-analysis performed by Katulka et al. looked at the clinical and biochemical parameters that can potentially predict the successful discontinuation of KRT [7]. The authors included 3 different types of variables—physiologic variables (urine output before CKRT), biochemical measures of glomerular filtration rate (serum creatinine, serum urea), and newer kidney biomarkers (cystatin C, serum neutrophil gelatinase-associated lipocalin (NGAL)). Urine output prior to discontinuation of KRT was the most-studied variable with pooled analysis showing a sensitivity of 66.2% and specificity of 73.6% for urine output to predict successful KRT discontinuation. However, different studies have used different urine output thresholds to predict discontinuation from CKRT; therefore, the authors could not recommend any optimal urine output threshold. The clinical scoring model developed by Baeg et al. to predict successful discontinuation from CKRT included urine output ≥ 300 mL/day on day 1 and adequate blood pressure, serum potassium < 4.1 mmol/L, and BUN < 35 mg/dL (12.5 mmol/L) on the discontinuation day [8].

In order to predict which patients will successfully come off CKRT (complete liberation from CKRT), it is important to understand the underlying etiology or indication for which CKRT was initiated. An issue that needs discussion is the liberation of kidney support therapy in patients who are started on CKRT for non-kidney indications (non-AKI indications)—acute liver failure, acute on chronic liver failure, inborn errors of metabolism, intoxications, etc. Will the standard variables evaluated in children with AKI hold true in this patient cohort as well? Children with acute liver failure are initiated on CKRT for hepatic encephalopathy, hyperammonaemia, and metabolic abnormalities [9]. The endpoints for CKRT in these patients are either achieving successful liver transplantation or spontaneous liver regeneration. Therefore, some variables like urine output and serum creatinine cannot be used in these clinical conditions. Hence, predictors of liberation from CKRT have to be used in the context of the underlying disease for which CKRT was initiated. This was demonstrated by Wei et al. in their manuscript as well where they demonstrated that children with certain underlying aetiologies had a higher failure rate than others (cardiac, oncology).

In addition to using clinical and biochemical parameters, the use of novel kidney biomarkers (cystatin C, NGAL, IL-18, IL-6, and serum osteopontin) can help predict successful liberation from CKRT. However, their use is still not well-established, as the current data on biomarkers in predicting successful liberation from CKRT come from small, observational studies, with significant heterogeneity in their definitions of successful liberation, weaning criteria, the timing of measurement of biomarkers, and threshold values [10].

In addition to the timing and prediction of successful liberation from CKRT, there remains a wide variation in the practice adopted by clinicians to trial patients off CKRT, as found in the European survey. The use of diuretics, though not recommended by KDIGO, is widely used either as a bolus dose or a bolus dose followed by infusion. However, there are conflicting results on the ability of diuretics to

enhance the predictive capability of urine output as a predictor marker of successful liberation from CKRT. Although some literature on adult supports the increase of urine output following the use of furosemide to successfully predict liberation or de-escalation from CKRT, a large study from Uchino et al. suggested that the use of diuretics may decrease the accuracy of urine output as a predictive marker [11]. However, there is no data in pediatrics to guide clinicians for or against the use of diuretics in achieving successful liberation from CKRT [11, 12].

Administration of fluids, nutrition, and medications during a trial off CKRT need to be vigilantly managed especially when there is incomplete kidney recovery. One needs to closely monitor the clinical, acid–base, electrolyte, and fluid status following cessation of CKRT and consider re-initiating CKRT in case of hyperkalemia, acidosis, uremic symptoms, and rise of toxins (non-kidney indications). Multidisciplinary management in these patients with the pharmacist, dietician, and nephrology and intensive care colleagues is strongly recommended. Figure 1 demonstrates a suggested guide for practicing clinicians to trial a patient off CKRT.

Future research

The inability to transition from CKRT in a timely manner may have negative impacts on patient outcomes especially with emerging data on the effectiveness of the ICU liberation bundles. Therefore, the goals of early mobilization/rehabilitation and CKRT need to align with each other. This might mean complete liberation with no requirement of any KST or transition to intermittent modalities like intermittent hemodialysis or giving set periods of time off CKRT in which rehabilitative care can be provided. Therefore, variables to predict complete independence from CKRT or transition to other modalities of KST will be extremely helpful to plan resource use and family counseling. Similarly, defining variables to predict liberation from CKRT for non-kidney conditions need to be defined. Any suggested algorithm for an attempt to liberate patients should consider a combination of patient-related clinical factors, biochemical factors, and biomarkers. Future research should focus on the determination and validation of urine output thresholds especially in children of varying ages and sizes, and the evaluation of additional clinical and biochemical/biomarker parameters in multivariate models to enhance predictive accuracy to reduce unnecessary dependence on CKRT with its associated morbidity and cost. Two ongoing pilot randomized trials in adult patients—Promoting Kidney Recovery After Acute Kidney Injury Receiving Dialysis (Recover-AKI, ClinicalTrials.gov NCT04948476) and Liberation from Acute Dialysis (LIBERATE-D, ClinicalTrials.gov NCT04218370)—have been designed to test the feasibility of applying objective criteria that must be satisfied to make a clinical decision whether to stop or continue KRT. Focused efforts to address these gaps in knowledge need to

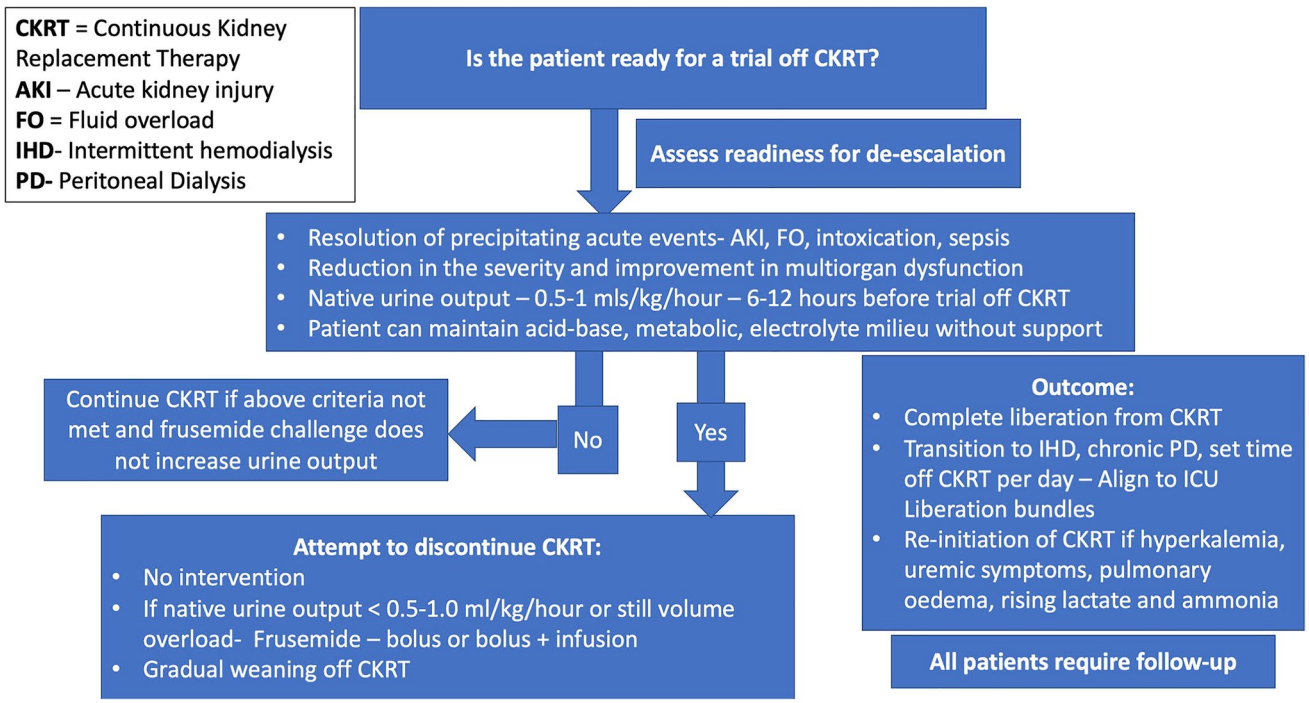

Fig. 1 Suggested algorithm for an attempt for liberation/de-escalation from CKRT

be undertaken by the pediatric AKI-dedicated platforms like the Acute Disease Quality Initiative (ADQI) and the Critical Care Nephrology section of ESPNIC.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest The author declares no competing interests.

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