Intensive Care Med
https://doi.org/10.1007/s00134-024-07463-y

EDITORIAL

When is the optimal time to stop continuous renal replacement therapy in children?

Shaegan Irusen[1], Antoine Schneider[2] and Michael Joannidis[3*]

Continuous renal replacement therapy (CRRT) is applied to 5–20% of critically ill patients and represents the main supportive therapy in severe acute kidney injury (AKI) [1, 2]. In the past two decades, several key questions related to CRRT have been addressed: the dose, rate of fluid removal, anticoagulation and the timing for initiation. High quality studies have provided clues as to how to approach most of these issues to allow for uniformity across intensive care units and dialysis units. On the other hand, the question of CRRT cessation has merely been raised and needs further exploration. Correctly timing the termination of CRRT has major implications: unnecessary CRRT increases costs, workload for healthcare staff and patients' length of stay. Conversely, failed weaning from CRRT might expose patients to recurrent fluid overload, inadequate metabolic control and might, therefore, hinder recovery. In the absence of high quality data, clinicians are left without due guidance at the bedside and practice appears to greatly vary across sites [3].

This issue is even more relevant in children for whom little data on CRRT management is available. In this population, most CRRT modalities are not readily available and peritoneal dialysis (PD) often remains the primary kidney replacement modality in many centres, especially in resource-limited regions [4]. Only large, academic centres can provide "conventional" CRRT to children. Furthermore, vascular access and extra-corporeal circuit volume represent major challenges in the paediatric population. Expertise, dedicated staff, and devices are required, particularly in low body weight patients. In this population, early therapy cessation appears particularly desirable; however, criteria associated with successful liberation remain unknown.

In this issue of Intensive Care Medicine, Stenson and colleagues report data from the Worldwide Exploration of Renal Replacement Outcomes Collaboration in Kidney Disease (WE-ROCK) cohort across 32 international centres [5]. They aimed to identify factors predicting successful liberation and any potential associations between liberation, morbidity and mortality. In more than 600 children and young adults, they found that higher vasoactive-inotropic scores (VIS), paediatric logistic organ dysfunction scores at CRRT initiation, higher urine output (UO) prior to CRRT initiation and shorter CRRT duration were associated with successful liberation. A subset of patients who received a diuretic challenge to augment diuresis prior to liberation also had higher chance of successful liberation if responding with increased UO.

It is remarkable that approximately 46% of the reported paediatric patients actually failed their first attempt, reinforcing the urgent need for better criteria for stopping CRRT. Underlying kidney disease seems to plays a dominant role for AKI and for its recovery in children as seen previously in data reported from adult patients in various settings [6, 7]. Patients who were unsuccessfully liberated had a roughly two fold higher rate of renal comorbidities whereas the absence of renal comorbidities nearly doubled the chance for successful liberation in the multivariate analysis [5].

The observed association of higher VIS support and clinical severity with successful discontinuation of CRRT in the present study is thought provoking. The authors have postulated that these patients could be more responsive to resuscitative efforts and, hypothetically, more amenable to improvement in organ perfusion and recovery of kidney function [5]. It is also conceivable that severe metabolic acidosis and presumption of

*Correspondence: michael.joannidis@i-med.ac.at
[3] Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria
Full author information is available at the end of the article

decreased vasopressor response triggered initiation of CRRT at a lower stages of AKI with a potentially higher renal reserve. The fact that VIS at time of discontinuation was not different between the two cohorts any more may further support the hypothesis that targeted resuscitation is crucial to successful CRRT cessation. It also indicates that successful weaning from inotropes and vasopressors may indeed be a prerequisite to successful liberation from CRRT.

The observation of UO both at CRRT initiation and discontinuation to be a robust primary predictor of successful liberation is more intuitive and is consistent with prior observations [8]. In a meta-analysis by the DOnE RRT group, UO had a pooled sensitivity and specificity of 66.2% and 73.6% to predict successful CRRT liberation in adults [9]. In a paediatric cohort, a urine output greater than 0.5 ml/kg/h in the 6 h prior to cessation of CRRT was predictive of a positive outcome [10]. Finally, in a single centre retrospective study, UO and serum creatinine prior to liberation, cumulative fluid balance whilst admitted and RRT duration were independent predictors of successful discontinuation [11]. Several "new" biomarkers been investigated with regard to prediction of sustained discontinuation of CRRT in adults [3]. Low urinary neutrophil gelatinase-associated lipocalin levels at cessation of continuous venovenous hemodiafiltration (CVVHDF) predicted successful liberation with an AUC (Area Under The Curve) ROC (Receiver Operating Characteristics) curve of 0.81 similar to urinary output in a multicentre prospective study [12]. Serum cystatin C was also found to be an independent predictor for successful weaning of CRRT [13]. Whether any of these biomarker might help in decision-making for discontinuation in paediatric patients will require further investigations.

Duration of CRRT was another factor associated with successful CRRT liberation. This is an association also reported amongst adult patients [14]. However, the duration of CRRT is always a parameter, which can only be obtained post-hoc and thus does not really help in decision-making, even if this finding may tell us that probability for successful liberation decreases the longer the patient is on CRRT.

Stenson et al. [5] do raise questions that clinicians are confronted with when managing patients with severe AKI. Their data do suggest that aggressive fluid removal might be associated with lower chances of CRRT liberation. However, although a similar amount of fluid was removed in patients who could be liberated and those who could not, the latter had a faster rate of fluid removal. This is consistent with prior observations where aggressive ultrafiltration may be associated with increased mortality due to coronary hypoperfusion, rarely seen in paediatric patients, and mycocardial ischaemia, gut hypoperfusion with bacterial translocation and cardiac arrhythmias [15]. The authors acknowledge that further evaluation of patient admission diagnosis, critical care scores, CRRT timing, rates of fluid removal and balances need to be examined in follow up studies.

Quite expectedly prolonged CRRT was associated with longer intensive care unit stay, dialysis dependency at 90 days and mortality [5, 10, 11]. This finding highlights the relevance of the research question and should prompt further prospective studies. Acute care nephrologists and intensivists base their decision to cease CRRT on anticipated pathophysiology, underlying the admission diagnoses, fluid balances and recovery of residual renal function. At the moment the most easily available sign for recovery during CRRT is increasing UO. More evidence gleaned from well-constructed research is needed to support these clinical criteria to liberate patients from CRRT. Whereas less CRRT may be more, the right time to stop still remains an open question.

Author details
[1] Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa. [2] Service de Médecine Intensive Adulte (SMIA), Centre Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon, 46, 1011 Lausanne, Switzerland. [3] Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria.

Funding
None.

Declarations

Conflicts of interest
SI reports no COI. AS reports receiving research grants from B Braun Avitum and speaking honorarium from B Braun Avitum and Fresenius Medical Care outside the submitted work. MJ has received honoraria or research support from Baxter Healthcare Corp, AM-Pharma, CLS Behring, Fresenius, Takeda and Novartis.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 6 March 2024 Accepted: 23 April 2024
Published online: 13 May 2024

References

1. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, Honoré PM, Joannes-Boyau O, Joannidis M, Korhonen AM, Lavrentieva A, Mehta RL, Palevsky P, Roessler E, Ronco C, Uchino S, Vazquez JA, Vidal Andrade E, Webb S, Kellum JA (2015) Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 41:1411–1423
2. Peters E, Antonelli M, Wittebole X, Nanchal R, François B, Sakr Y, Vincent JL, Pickkers P (2018) A worldwide multicentre evaluation of the influence of deterioration or improvement of acute kidney injury on clinical outcome

in critically ill patients with and without sepsis at ICU admission: results from The Intensive Care Over Nations audit. Crit Care (Lond, Engl) 22:188
3. Boyer N, Perschinka F, Joannidis M, Forni LG (2023) When to discontinue renal replacement therapy. What do we know? Curr Opin Crit Care 29:559–565
4. Wald R, Beaubien-Souligny W, Chanchlani R, Clark EG, Neyra JA, Ostermann M, Silver SA, Vaara S, Zarbock A, Bagshaw SM (2022) Delivering optimal renal replacement therapy to critically ill patients with acute kidney injury. Intensive Care Med 48:1368–1381
5. Stenson EKA, Alobaidi R, Bottari G, Fernandez S (2024) Factors associated with successful liberation from continuous renal replacement therapy in children and young adults: analysis of the Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease. Intensive Care Med. https://doi.org/10.1007/s00134-024-07336-4
6. James MT, Grams ME, Woodward M, Elley CR, Green JA, Wheeler DC, de Jong P, Gansevoort RT, Levey AS, Warnock DG, Sarnak MJ (2015) A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. Am J Kidney Dis 66:602–612
7. Mayerhofer T, Perschinka F, Klein SJ, Peer A, Lehner GF, Bellmann R, Gasteiger L, Mittermayr M, Breitkopf R, Eschertzhuber S, Mathis S, Fiala A, Fries D, Strohle M, Foidl E, Hasibeder W, Helbok R, Kirchmair L, Stogermuller B, Krismer C, Heiner T, Ladner E, Thome C, Preuss-Hernandez C, Mayr A, Potocnik M, Reitter B, Brunner J, Zagitzer-Hofer S, Ribitsch A, Joannidis M (2023) Incidence, risk factors and outcome of acute kidney injury in critically ill COVID-19 patients in Tyrol, Austria: a prospective multicenter registry study. J Nephrol 36:2531–2540
8. Daverio M, Cortina G, Jones A, Ricci Z, Demirkol D, Raymakers-Janssen P, Lion F, Camilo C, Stojanovic V, Grazioli S, Zaoral T, Masjosthusmann K, Vankessel I, Deep A, Critical Care Nephrology Section of the European Society of P, Neonatal Intensive C (2022) Continuous kidney replacement therapy practices in pediatric intensive care units across Europe. JAMA Netw Open 5:e2246901
9. Katulka RJ, Al Saadon A, Sebastianski M, Featherstone R, Vandermeer B, Silver SA, Gibney RTN, Bagshaw SM, Rewa OG (2020) Determining the optimal time for liberation from renal replacement therapy in critically ill patients: a systematic review and meta-analysis (DOnE RRT). Crit Care (Lond, Engl) 24:50
10. Wei EY, Vuong KT, Lee E, Liu L, Ingulli E, Coufal NG (2023) Predictors of successful discontinuation of continuous kidney replacement therapy in a pediatric cohort. Pediatr Nephrol (Berlin, Germany) 38:2221–2231
11. Liu C, Peng Z, Dong Y, Li Z, Andrijasevic NM, Albright RC Jr, Kashani KB (2021) Predicting successful continuous renal replacement therapy liberation in critically ill patients with acute kidney injury. J Crit Care 66:6–13
12. Komaru Y, Oguchi M, Sadahiro T, Nakada TA, Hattori N, Moriguchi T, Goto J, Shiga H, Kikuchi Y, Negi S, Shigematsu T, Kuriyama N, Nakamura T, Doi K (2023) Urinary neutrophil gelatinase-associated lipocalin and plasma IL-6 in discontinuation of continuous venovenous hemodiafiltration for severe acute kidney injury: a multicenter prospective observational study. Ann Intensive Care 13:42
13. Kim CS, Bae EH, Ma SK, Kim SW (2018) A prospective observational study on the predictive value of serum cystatin C for successful weaning from continuous renal replacement therapy. Kidney Blood Press Res 43:872–881
14. Shawwa K, Kompotiatis P, Sakhuja A, McCarthy P, Kashani KB (2022) Prolonged exposure to continuous renal replacement therapy in patients with acute kidney injury. J Nephrol 35:585–595
15. Murugan R, Kerti SJ, Chang CH, Gallagher M, Clermont G, Palevsky PM, Kellum JA, Bellomo R (2019) Association of net ultrafiltration rate with mortality among critically ill adults with acute kidney injury receiving continuous venovenous hemodiafiltration: a secondary analysis of the randomized evaluation of normal vs augmented level (RENAL) of renal replacement therapy trial. JAMA Netw Open 2:e195418