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Renal Replacement Therapy

REVIEW

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Anticipation of recovery of native renal function and liberation from renal replacement therapy in critically ill patients with severe acute kidney injury

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Abstract

Background: Renal replacement therapy (RRT) is used to manage critically ill patients with severe acute kidney injury (AKI-D), and it is undoubtedly life-sustaining for most patients. However, the prolonged unnecessary use of these techniques may be harmful. At present, no consensus guidelines provide specific recommendations for clinicians on when (optimal timing of discontinuation) and how (liberation or weaning) to stop RRT in intensive care unit (ICU) patients with recovering native kidney function.

Methods and results: Numerous variables such as clinical parameters, classical surrogate markers for glomerular filtration rate, novel biomarkers of kidney function and damage, and new imaging techniques in AKI-D have been described to predict successful discontinuation of RRT. Most available studies are limited by study design, heterogeneity of variable assessment and thresholds of biomarkers, and lack of prospective validation. At present, the decision on discontinuation of RRT in ICU patients is based on three clinical scenarios: (a) intrinsic kidney function (defined as spontaneous urine output > 500 ml/24 h, timed creatinine clearance > 15 to 20 ml/min) has adequately improved to match the demands and continued RRT is no longer consistent with goals of care (transition to intermittent RRT); (b) the acute illness that prompted RRT has improved; (c) the clinical practice of switching haemodynamic stable patients with persistent AKI-D from continuous RRTs to intermittent RRTs is variable, but de-escalation of RRT (frequency, dose) may facilitate mobilization and discharge of ICU patients.

Conclusions: The predictive ability of novel kidney biomarkers, surrogate markers of kidney function, and direct measurements of kidney function should be evaluated in future studies.

Keywords: Liberation from renal replacement therapy, Acute kidney injury, Critically ill patients, Assessment of renal recovery

Background

Recovery of sufficient kidney function after acute kidney injury requiring renal replacement therapy (AKI-D) is recognized as an important clinical determinant of patient-centred outcome, but it is unpredictable. Numerous risk factors for maladaptive renal repair processes have been identified and include patient-related factors (age, chronic kidney disease, proteinuria, specific comorbidity, high acuity of the precipitating illness (multiple organ failure), the aetiology, stage, and duration of AKI, post-insult exposure to therapeutic nephrotoxins or diagnostic use of nephrotoxins after onset of AKI as well as potentially the renal replacement therapy per se (membrane, intensity) [1–4].

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Defining renal recovery is far from straightforward due to the limitations of the criteria used to assess renal function. A good definition of renal recovery from AKI-D should include four main domains: inception (starting point of recovery), extent of recovery of renal function, timing (when recovery is assessed), and confounding factors [5]. Despite limitations, non-recovery of AKI-D (transition from AKI-D to end-stage renal disease) is best defined as persistent dialysis dependence, partial recovery as no need for RRT but failure to meet the criteria for complete recovery or a lower AKI stage, and complete recovery as absence of AKI criteria [2]. The investigators of the Artificial Kidney Initiation in Kidney Injury 2 (AKIKI2) defined renal function recovery in three different ways: (a) adequate diuresis (more than 1000 ml/day in the absence of diuretic therapy or more than 2000 ml/day with diuretic therapy and no resumption of RRT within 7 days after stopping RRT), (b) adequate urine output and spontaneous decrease in serum creatinine value and no re-institution of RRT within 7 days after stopping RRT, and (c) absence of any AKI KDIGO stages 1–3 [6].

The extent and the time pattern of recovery of intrinsic kidney function substantially affect the well-being and morbidity/mortality of unwell patients surviving an acute episode of AKI-D [2, 7]. The mortality rate of AKI-D survivors is higher than that of opponents without AKI-D, and a reverse correlation exists for a progressively high risk of death [8]. Patients who fail to recover sufficient renal function and require maintenance dialysis treatment have a shortened life span, a low quality of life, and succumb to numerous morbidities. Survivors with partial recovery of kidney function have an increased risk for progressive de novo CKD, morbidity, and mortality. Both the risk for premature death and transition to CKD were lowest in ICU patients with normal renal function prior AKI-D [9].

Predicting the probability of kidney recovery in an individual ICU patient after AKI-D is a dilemma faced by physicians, patients, and patients' families. Moreover, ICU patients with AKI-D may recover sufficient kidney function late, i.e. after weeks or even months (up to 1 year) of RRT. Determining which patients have a reasonable chance of renal recovery may guide decision-making such as transfer to nephrological ward, vascular access creation, discharge from the hospital, outpatient dialysis chair placement. It determines the frequency of follow-up and prevention of sequelae of prolonged unnecessary RRT (catheter-related infections, bleeding, haemodynamic instability, delayed renal recovery, and inappropriate drug dosing) [10].

This narrative review aims to discuss the available literature on current approaches to anticipate recovery of kidney function from acute kidney injury and to propose recommendations for front-line physicians on when (optimal timing) and how (liberation or weaning) RRT could be safely discontinued in critically ill patients with AKI-D.

Current practice of RRT discontinuation on anticipation of renal recovery

The 2012 Clinical Practice Guidelines for Acute Kidney injury of the Kidney Disease Improving Global Outcomes (KDIGO) organization recommend that "RRT should be discontinued when it is no longer required, because intrinsic kidney function has recovered to the point that it is adequate to meet patients need" [11]. However, these guidelines are based on expert opinions and lack detailed guidance for when and how clinicians should assess candidates for successful discontinuation of RRT.

There are currently no established guidelines for discontinuation of RRT in unwell patients with AKI-D. As no randomized controlled trial (RCT) to date has evaluated the optimal timing of discontinuation, the factors determining the decision to stop RRT, or the effects of success or failure of liberation on primary or secondary patient outcomes remain unclear. This situation is in contradiction to that related to acute lung injury and mechanical ventilation for which there are multiple multicentre randomized trials and international consensus guidelines outlining ventilator treatment strategies and liberation/weaning parameters [12].

Currently, practices of RRT discontinuation depend on centre policy, vary from early (fast track approach) to late (wait and see approach) cessation of RRT, and result in a high rate of unsuccessful attempts [13]. Utilizing the 24-h urinary creatinine excretion rate, a small study encompassing a total of 54 ICU patients receiving IHD reported successful weaning in 26 out of 54 patients (48%). Twenty-one patients needed a second attempt, and 7 patients more than 2 attempts [14]. Whether or not unsuccessful discontinuation causing re-occurrence of acute uraemia or reinstitution is by itself harmful has not been thoroughly examined. Observational studies found, however, that AKI-D patients with failure to stop RRT may have longer ICU or hospital stay, less chance of kidney recovery among survivors [13, 15], and a higher short-term mortality [16, 17] than successfully discontinued patients.

Criteria for cessation of RRT in critically ill patients with AKI-D

Readiness for de-escalation

The complex decision to discontinue RRT in critically ill patients with AKI-D is based on two clinical scenarios: a) intrinsic kidney function has adequately improved to meet demands and continued RRT is no longer

consistent with the goals of care and b) the acute illness that prompted renal support has improved.

There is consensus that the assessment of the clinical status of the patients should be conducted at least daily to determine whether the patient meets criteria to move forward with the liberation process. The criteria should include (a) resolution of the precipitating cause of AKI-D; (b) improvement in multi-organ failure; (c) haemodynamic stability; (d) need for volume removal does not exceed daily urine output; (e) absence of electrolyte imbalance refractory to medical management; and (f) sufficient intrinsic kidney function capable of maintaining acid base and metabolic homoeostasis.

Anticipation of recovery of intrinsic renal function

Nephrologists/intensivists start RRT when confronted with life-threatening complications of acute uraemia. However, there is a wide variation in the minimum severity of indications prompting discontinuation of RRT in critical ill patients. Many factors modify these decisions, such as, age, comorbidity, illness severity, or administration of drugs.

A survey of US nephrologists treating AKI-D patients found that the most common criteria to stop dialysis were resolution of oliguria (51%), resolution of volume overload (29%), improvement in serum creatinine (27%), and resolution of hyperkalaemia (21%) [18].

Score systems to predict AKI-D recovery

Numerous scores encompassing laboratory results, patients' characteristics, or features of AKI, alone or in combination, have been used to predict successful RRT liberation from AKI-D.

Wang et al. performed a meta-analysis of 10 observational studies to evaluate routine laboratory parameters as predictors of successful weaning in AKI-D. Not surprisingly, the authors noted that surrogate parameters of renal function such as urine output, urinary urea and creatinine excretion rate, and serum creatinine as well as parameters of electrolyte (serum potassium) or acid–base homoeostasis (serum bicarbonate, pH) were significantly associated with weaning success [19]. Other tools for prediction of renal recovery from AKI-D encompass patient-related factors (age, higher SOFA score) or AKI-D-associated factors (duration of renal support, a diuresis < 400 ml and not increasing spontaneously or responding adequate to diuretic challenge, presence of hypervolemia and degree of azotaemia) [16, 17, 20, 21].

However, such severity of illness scores was developed to predict renal recovery in small cohorts of patients and are not very helpful in individual patients [22]. Generally spoken, current predictive models have low discrimination, missing calibration statistics, are at risk of bias, and show limited clinical applicability. There is a need for studies that prospectively collect relevant data of intrinsic renal function recovery in large cohorts and then proceed to validate findings in external data sets.

Timing of RRT cessation by markers of kidney function and damage

Numerous surrogate markers of kidney function (changes in serum creatinine, changes in eGFR, kinetic GFR, urine output, urinary creatinine excretion rate, urinary urea excretion rate, and timed creatinine clearances), a raising number of novel biomarkers of kidney damage (neutrophil gelatinase-associated lipocalin, kidney injury molecule 'Linterleukin 6 and interleukin 18, urinary markers of cell cycle arrest) and of kidney function (cystatin C), or circulating markers of hypervolemia due to kidney dysfunction (NT-proBNP, osteopontin) have been assessed to identify patients for whom RRT may be successfully discontinued. However, available traditional or novel markers of kidney recovery are limited by study design (retrospective analyses, small sample size, definition of successful RRT discontinuation), variable heterogeneity, and lack of prospective validation of the cut-offs [23, 24].

Spontaneously increasing urine output and decreasing serum creatinine concentrations may herald the beginning of renal recovery. The predictive value of urine output, prior or after discontinuation of RRT, has been examined in numerous studies. However, recent meta-analyses found a pooled sensitivity of 66.2% and specificity of 73.6%. The thresholds of urine output ranged from 191 to 1720 ml/day. The authors graded the overall certainty of evidence regarding this parameter as very low [23].

Another strategy is to use enhanced urinary output and sodium excretion. This may allow optimal timing of RRT liberation, and a negative fluid balance may reduce the risk for restart of RRT. The reported predictive effect of a diuretic challenge was variable. Some studies described a decrease in the predictive ability of urine volumes after diuretics, and other reports described superior discrimination following administration. There was a wide range in the cut-off values ranging from 125 to 2330 ml/day. The effect of the exposure to diuretics administration (furosemide bolus/infusion, thiazides, etc.) on the predictive ability of augmented urine output remains uncertain [23]. Van der Voort and colleagues demonstrated an excellent clinical performance of the furosemide stress test with an AUROC of 0. 84 for assessing renal recovery [25]. While the authors did not show performance of specific cut-off values of urine output for the 4-h collection after a 24-h infusion of furosemide, they did provide interquartile ranges for each group. A cut-off value of

333 ml/24 h appears to produce a test with potential predictive utility for liberation from RRT.

The KDIGO AKI Guidelines state that the creatinine clearance remains the best clinical surrogate marker of renal function, and it should be measured, when possible, in AKI. However, neither the RIFLE, AKIN nor KDIGO classification system estimates actual creatinine clearance. Physicians caring for critically ill AKI-D patients should be aware of pitfalls in urinary creatinine clearance measurements and avoid misinterpretation of recovering renal function. Timed creatinine clearance calculations in unwell AKI-D patients mostly require an indwelling urethral catheter. Improper urine samples lead to underestimation of renal function. Determination of urinary creatinine clearance can be more challenging in AKI-D patients receiving IRRT, compared to patients treated with CRRT, due to fluctuations of serum creatinine in the intra-, post-, and interdialytic period (dose-dependent reductions in raised small solute levels during the session, post-dialytic rebound of serum creatinine starting at the end of the session as well as the interdialytic serum creatinine rise). However, standard equations for estimation of creatinine clearances are not accurate in the presence of unstable serum creatinine levels. Therefore, native renal function of AKI-D patients treated with IRRT—as assessed by timed creatinine clearance—can only be estimated during the interdialytic period on non-dialysis days. The problem of fluctuations in serum creatinine concentrations is much easier to address in AKI-D patients treated with CRRT, where steady-state creatinine concentrations are usually achieved at a prescribed dose. Finally, because of quite variable creatinine tubular secretion, urinary creatinine clearance systematically overestimates measured GFR, particularly at low GFR levels. Despite these constraints, few small cohort studies, collecting urine at 2 h, 6 h, or 24 h, have shown that urinary creatinine clearances between 11 and 20 ml/min are useful surrogate markers for native kidney function and for decision-making regarding liberation from RRT (Table 1) [26–28].

Novel Kidney biomarkers correlating with renal cell injury or function could potentially predict renal recovery. Studies in critically ill patients with AKI-D have shown that lower initial levels of kidney specific biomarkers or decreasing levels of kidney specific biomarkers over time indicate a more likely recovery of kidney

Table 1 Readiness for RRT liberation or de-escalation

Assessment of ICU patients in anticipation of recovery of native kidney function from AKI-D
Clinical scenarios
Evidence of stabilization of clinical status
Resolution of the precipitating insults
Reduction in the acuity of the underlying disease and improvement in multi-organ dysfunctions (Haemodynamic stability, mechanical ventilation)
Natural improvement in kidney function (spontaneous increase in urine output > 400 ml/day)
Adequate capacity to maintain metabolic, electrolyte, acid–base homoeostasis and to manage obligatory fluid requirements by conservative management of AKI
Additional considerations
Discharge from the ICU
Physiotherapy and mobilization of the patient
Logistic capabilities of the institution (staffing, nurses, availability of bedside IRRT)
Additional diagnostic measures to predict successful discontinuation of RRT
Timed creatinine clearance (> 15 ml/min)
Spontaneously decreasing serum creatinine
Positive furosemide challenge, and/or urine output > 2300 ml/day on diuretics
Attempt to discontinue RRT
Liberation versus weaning
Critical appraisal of the attempt
Morbidity and mortality due to inadequate resolution of AKI
Morbidity and mortality of transition to IRRT
Re-institution of RRT
Success/failure of the attempt
Success: no further dialysis for 7 days
Failure: re-institution of RRT within 7 days of the attempt to stop RRT

RRT renal replacement therapy, *AKI* acute kidney injury, *AKI-D* acute kidney injury requiring dialysis, *ICU* intensive care unit, *IRRT* intermittent renal replacement therapy

function [29]. Plasma cystatin C, urinary NGAL, and urinary markers of cell cycle arrest appear to have a promising predictive ability. Xie et al. found that the risk of ineffective discontinuation of CRRT (less than 7 days) was nearly 5 times higher in patients with urinary biomarkers of cell cycle arrest than in biomarker-negative patients [30]. The authors concluded that urinary markers of cell cycle arrest can serve as an auxiliary biomarker for the identification of renal function recovery.

At present, the accuracy of the novel markers of kidney function and kidney damage markers for sufficient recovery of renal function cannot be determined. There is a need for prospective validation of candidate biomarkers to predict successful replacement therapy discontinuation.

Prospective AKI trials have used timed creatinine clearance (combined with other surrogate markers of kidney function) to define renal recovery. In the Veterans Affairs National Institutes of Health Acute Renal Failure Trial Network (ATN Trial), patients with a 6-h creatinine > 20 ml/min were trailed off RRT, whereas patients with a creatinine clearance < 12 ml/min had RRT continued [31]. In the Early vs Delayed Initiation of Renal Replacement Therapy on mortality in critically ill patients with acute kidney injury trial, RRT was discontinued; if renal recovery defined by creatinine clearance > 20 ml/min occurred. Regrettably, rates for successful discontinuation/weaning were not reported [32].

Imaging techniques and prediction of RRT discontinuation

Non-radioactive exogenous techniques (inulin, iohexol) for GFR measurements are very cumbersome and are therefore not applicable in a clinical setting.

Radioactive GFR markers (e.g. 125 I-iothalamate and 51 Cr-EDTA) have been used in conjunction with a radiation detector real-time GFR. However, the downside of using such techniques is the low availability and the high costs, difficulties in repeating the measurements, and the need to transport the patient for the study [33].

The visible fluorescent injectate (VFI)-based approach allows for the rapid determination of GFR at the bedside while maintaining patient safety and measurement accuracy and reproducibility. Measurements of GFR in patients with chronic kidney disease (stages 2, 3, and 4) required three 0.5 ml blood samples drawn over 3 h utilizing the VFI-based approach, but 5 samples taken over 6 h utilizing Iohexol-based GFR measurements [34]. Data obtained from ICU patients with resolving AKI-D are limited, and no definitive interferences can be made from the available data.

The Doppler-based renal resistance index (RI), which is a simple, rapid, non-invasive, and repeatable marker, could be promising to distinguish transient from persistent AKI-D in critically ill patients. A small prospective observational study assessed the performance of the Doppler RI in diagnosing persistent AKI-D [35]. The area under the RI ROC curve was 0.91. The RI was 0.71 in the no-AKI-D group and 0.71 in the transient and 0.82 in the persistent AKI-D group. The progress in contrast-enhanced ultrasound (CEUS) gives the opportunity to assess kidney microcirculation at the bed side in the ICU. However, CEUS is still an experimental tool [36].

Whether or not these imaging methods should be employed as screening in those critically ill patients with AKI-D where surrogate or biomarkers are suggestive of renal function recovery remains to be determined. Most studies focused more on the differentiation between transient and persistent AKI-D and on recovery of renal function than on their predictive value for successful RRT cessation [37].

Definitions of successful liberation from RRT in AKI-D

Commonly used definitions of a successful attempt to discontinue RRT in critically ill patients with resolving AKI-D use an extended period free from further RRT.

Successful renal recovery to dialysis independence at 28 days has been defined by a patient receiving no RRT by 28 days. This time point has been chosen in RCTs because it is the furthest time point from randomization where data can be obtained from the greatest number of patients.

Sustained renal recovery to dialysis independence has been defined by a patient receiving no RRT for 7 days.

Successful cessation of RRT has been defined by no need to have dialysis for at least 14 days.

A minimum 90-day frame for renal recovery has been used to assess renal outcome in survivors of AKI-D discharged from hospital in accordance with the KDIGO guidelines which define chronic kidney disease as a persistent decline in kidney function lasting more than 90 days [38].

Cessation of RRT in critically ill patients with AKI-D: liberation or weaning

In critical care patients, one of the goals of clinicians is to discontinue the patient from RRT as soon as possible to allow recovery of native kidney function and to avoid RRT associated untoward effects.

At present, there are no standardized recommendations of the optimal method (weaning or liberation) for discontinuation the renal support due to lack of evidence. The strategy of stopping RRT must thus be individualized in each patient. Whether or not RRT discontinuation is best achieved by gradually reducing the level/duration

per session, frequency or by complete liberation (no RRT) is unknown. Undoubtedly, the process of weaning may prolong total duration of RRT. However, whether the risks of early liberation from RRT may outweigh the risk of prolonged RRT remains unknown.

Transition from an initial RRT modality to another modality later during AKI-D is common in clinical practice. The main reasons for switching are changes in the clinical condition (haemodynamic stability, recovery of intrinsic kidney function) or adverse events. RCTs reported wide variations in the rate of transition. In an RCT comparing CRRT and IHD, 26% of critically ill patients with AKI-D switched from initial CRRT to IHD and 21% transitioned from initial IHD to CRRT [39]. Higher rates of transition were noted in another RCT [40], in which 21% of the patients assigned to IHD switched to CRRT and 46% of the patients who were randomized to CRRT changed to IHD later during persistent AKI-D. The authors reported that transition from IHD to CRRT occurred earlier (mean time 4.4 days) compared with the switch from CRRT to IHD (mean time 6.2 days). The main reason for early transition of IHD to CRRT was haemodynamic instability. In the more recent Elain study (early versus late initiation of RRT), 34% of critically ill patients with AKI-D switched from CRRT to intermittent RRT (26% SLED, 2% IHD, 6% IHD and SLED) [32].

The Acute Dialysis Quality Initiative proposed a schema to guide the appropriate transition of RRT based on the limited existing data [41]. If the demand to capacity ratio improves, it is prudent to consider de-escalation to a RRT modality, that allows mobilization of the patient, earlier discharge from the ICU and places less strain on costs and resources [42]. Undoubtedly, the risks of transition may be lower in CRRT patients with serum creatinine levels closely to delayed exposure to intermittent RRT (IRRT) until at least 24 h after stopping administration of vasopressor agents [43].

When dialysis is weaned, discontinued, or patients are transitioned to another RRT, there is a need to adapt drug dosing regimens (such as antibiotics) according to differences in pharmacokinetics and pharmacodynamics of the drugs [44]. Moreover, the switch of AKI-D patients to intermittent techniques may be associated with electrolyte imbalances [45] and more intradialytic hypotensive episodes and increased mortality [46]. Finally, patients with ESRD due to nonrecovery from AKI-D must be transitioned to IHD or CAPD prior to hospital discharge.

Conclusions

Currently, standardized indices are non-existent for the discontinuation of RRT in critically ill patients with AKI-D. The decision to discontinue RRT in this subgroup of patients is complex and requires considerations of the patient's clinical condition, degree of native kidney function recovery, and ongoing need for RRT.

At present, spontaneously increasing urine output, a creatinine clearance of 15–20 ml/min, and a progressive decline in serum creatinine in the context of steady state in CRRT patients or a delayed increase in serum creatinine during the dialysis free interval in patients treated with IRRT are considered significant predictors of renal recovery.

Larger research studies are needed addressing this topic for the identification of renal recovery predictors, and for uniform consensus for cessation of RRT.

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The author meets the International Committee of Medical Journal Editor`s criteria for authorship for this article, takes responsibility for the integrity of the work, and has given his approval for the final version of the article to be published. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
This narrative review is based on previously conducted studies and does not contain any study with participants or animals performed by the author. It uses publicly accessible data as evidence. Institution approval and patient consent were not necessary.

Consent for publication
The manuscript does not contain data from any individual person.

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