RRT treatment for AKI: is more always better?

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Hippocratic Oath: Primum non nocere
Thomas Sydenham (1624–89)

Acute kidney injury (AKI) is an increasingly common condition, occurring in up to 25% of critically ill patients admitted to the intensive care unit (ICU) [1]. It is associated with significant morbidity and up to 60% in-hospital mortality in its most severe form, necessitating renal replacement therapy (RRT) [2].

In the absence of effective pharmacological therapy, the treatment of patients with AKI is predominantly supportive, managing haemodynamic and volume status, correcting electrolyte and acid–base disturbances, providing adequate nutrition and adjusting drug doses. In patients with sustained, severe renal failure, RRT is indicated for the management of volume overload, hyperkalaemia, acidosis and symptoms of uraemia while awaiting the recovery of kidney function. Most clinicians are convinced that RRT is life saving and not starting RRT will lead to death in severely ill AKI patients, but data are lacking to support this opinion. Conservative treatment for AKI has only been considered as the treatment option for less severe patients. In recent years, several controlled studies [3–7] and meta-analysis [8–10] showed similar benefit with continuous and intermittent dialysis modalities. Critics of the published studies, however, pointed to different shortcomings in these studies [11, 12]. However, hard data remain absent or conflicting regarding when to start dialytic therapy and what constitutes the appropriate dose [13].

In 2011, the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI was developed, aiming to assist practitioners caring for adults and children at risk for or with AKI [14]. They recommend to initiate RRT emergently when life-threatening changes in fluid, electrolyte and acid–base balance exist. Continuous RRT (CRRT) and intermittent RRT (IRRT) are considered as complementary therapies, but they suggest using CRRT, rather than standard IRRT, for haemodynamically unstable patients. The dose of RRT to be delivered should be prescribed before starting each session of RRT. KDIGO recommend delivering a Kt/V of 3.9/week when using IRRT or extended RRT and an effluent volume of 20–25 mL/kg/h for CRRT. This will usually require a higher prescription of effluent volume.

Numerous modalities of RRT can be used in the treatment of patients with AKI. These include various modalities of intermittent haemodialysis (IHD), of CRRT, ‘hybrid’ modalities such as sustained low-efficiency dialysis (SLED), that combine aspects of both conventional IHD and CRRT, and peritoneal dialysis. Although there are many arguments favouring the use of continuous therapies in critically ill patients with AKI [15], the predominance of current evidence does not support a benefit of CRRT compared with IRRT. Nonetheless, the use of CRRT versus IRRT remains a subject of ongoing controversy, in particular because studies of modality must select a patient population in which both modalities are considered safe. Thus, the results can probably not be generalized to all patients.

Three systematic reviews analysed the published literature and concluded that the applied modality of RRT does not have a major impact on survival or recovery of kidney function [8–10]. In a Cochrane review, Rabindranath et al. [8] identified 15 randomized, controlled trials that compared CRRT with intermittent therapies, with a total of 1550 patients. They concluded that CRRT offered no survival benefit over intermittent therapy as assessed by in-hospital mortality [relative risk (RR) 1.01; 95% confidence interval (CI) 0.92–1.12] or ICU mortality (RR 1.06; 95% CI 0.90–1.26). Moreover, the recovery of kidney function was not better in patients treated with CRRT. In a systematic review, Pannu et al. [9] identified 30 randomized, controlled trials and 8 prospective cohort studies. In the seven studies that compared continuous with intermittent therapy, with a total of 918 patients, the relative mortality risk associated with CRRT was 1.10 (95% CI 0.99–1.23). There was no difference between modalities regarding long-term dialysis dependence. In the third meta-analysis, Bagshaw et al. [10] identified nine randomized, controlled trials with a total of 1403 patients. They found an equal mortality comparing CRRT with intermittent therapy [odds ratio (OR) 0.99; 95% CI 1.78–1.26]. Regarding the recovery of kidney function, 8.5% (26 of 306) of patients remained dialysis-dependent at hospital discharge with no difference in recovery by modality (OR 0.76; 95% CI 0.28–2.07).

Three additional studies were not included in the aforementioned meta-analyses [7, 16, 17]. Two reached another conclusion regarding the recovery of kidney function. Uchino et al. [16] analysed the recovery of kidney function in the 1218 patients who received RRT in the observational Beginning and Ending Supportive Therapy for
the Kidney (BEST Kidney) study and Bell et al. [17] from the Swedish Intensive Care Nephrology Group (SWING) reported on outcomes of 2202 ICU patients in Sweden who underwent RRT for AKI. In BEST, the OR for dialysis independency was 3.3 (95% CI 1.8–6) and in SWING 2.6 (95% CI 1.5–4.3). These observational studies have a number of important limitations making the interpretation of the results complicated by the inability to adjust completely for baseline factors like pre-existing kidney disease, severity of underlying and comorbid diseases.

Treatement with CRRT was associated with greater dialysis independency among survivors. Lins et al. [7] reported the results of a multicentre, randomized clinical trial of CRRT versus IRRT (extended daily dialysis for 4–6 h) in 316 patients. There was no difference in mortality or renal recovery between the treatment groups.

There are scant data of comparative outcome studies in AKI including other modalities of RRT, such as peritoneal dialysis, or other forms of haemofiltration. In this issue of the journal, Škofic and colleagues [18] compared mortality and recovery of kidney function with intermittent high-volume pre-dilution on-line haemofiltration with standard IHD in a prospective, randomized, controlled, single-centre clinical study of critically ill adult patients with AKI. In 273 patients, they found no difference in mortality, recovery of kidney function or need for dialysis support.

This study adds to the growing body of literature that suggests that there is no strict benefit for mortality or recovery of one RRT modality over another. Co-morbidities and other factors like a higher degree of fluid overload at RRT initiation predicts worse renal recovery at 1 year as was very recently shown [19].

Some authors cautioned that there are many weaknesses in the design and conduct of the individual trials, including an absence of blinding, lack of standardized criteria for initiation of RRT, high crossover rates, lack of power, selection bias and disregard of differences in disease severity [10–12]. One of the reasons for these weaknesses is the difference in populations studied. This is partially related to difficulties in acquiring written informed consent in critically ill ICU patients, leading towards selection bias in favour of less severe patients and limiting the possibility to generalize study results [20]. In the Škofic et al. study in this issue [18], written informed consent was not required as inclusion criterion. This allowed more extensive and uniform enrolment of the most severely ill patients. It would be very difficult however to generalize this approach from an ethical point of view. Probably, it will also not be approved by many ethical committees.

It can be concluded that intermittent, continuous and hybrid techniques should likely be considered as complementary, and not competing techniques. Selection of modality should be based upon local expertise and availability of staff and equipment, except for some selected patient groups, where other factors may prevail.

Early, single-centre, randomized clinical trials suggested that more intensive RRT is associated with improved outcomes [21, 22]. In the study by Ronco et al. [21], CRRT at 35 and 45 mL/kg/h was associated with improved survival when compared with CRRT at 20 mL/kg/h. A study with intermittent dialysis demonstrated that daily haemodialysis was associated with decreased mortality and more rapid recovery of kidney function than alternate-day dialysis [22]. However, more recently, two large, multicentre randomized controlled trials assessing the effect of different intensities of RRT on mortality in severe AKI [23, 24] have not demonstrated a survival benefit for more intensive compared with less intensive RRT, nor a significant difference in rates of recovery of renal function. The Acute Renal Failure Trial Network (ATN) study was a large, multicentre, randomized clinical trial to assess the impact of intensity of renal support in AKI [23]. A total of 1124 patients were enrolled. The rate of death from any cause by Day 60 was 53.6% with intensive therapy and 51.5% with the less-intensive approach. Furthermore, there were no significant differences in in-hospital mortality, duration of RRT, recovery of renal function or non-renal organ failure. These equivalent outcomes occurred despite the fact that there were more episodes of hypotension, hypophosphataemia, and hypokalaemia in the intensive-therapy group. A second large, multicentre, randomized clinical trial of dialysis dosage in AKI was completed in Australia and New Zealand [24]. In the RENAL study, 1508 patients with AKI were randomly assigned to continuous venovenous haemodiafiltration at an effluent flow of either 25 or 40 mL/kg/h. At 90 days, mortality (44.7%) was the same in each group. In addition, the incidence of patients who continued to receive RRT at 90 days was similar with both dialysis doses.

The trial in this issue of the journal [18] was not a comparison between different doses of the same treatment modality, but between high-volume haemofiltration and standard IHD. However, high-volume haemofiltration is supposed to confer beneficial effects, particularly in patients with sepsis or other systemic inflammatory response syndromes, owing to enhanced clearance of inflammatory mediators, involved in the development of multiple organ failure [25]. The results suggest that dialysis dose is similar in both modality groups, but the authors mention correctly that small solute clearance alone cannot adequately reflect dialysis efficiency. The actual importance of these benefits is uncertain, given the absence of a difference in survival. It may also result in the removal of beneficial anti-inflammatory mediators and, in addition, the extracorporeal clearance of these mediators is low relative to the rates of generation and endogenous clearance.

A recent meta-analysis that included 12 randomized or quasi-randomized clinical trials demonstrated no benefit with high-intensity therapy [26]. High-dosage RRT included CRRT with effluent flow rates of ≥30 mL/kg/h, or at least six sessions per week of IHD or sustained low-efficiency dialysis. Standard-dosage therapies included CRRT with effluent flow rates of <30 mL/kg/h, or two to four sessions per week of IRRT. There was no benefit of high-intensity therapy regarding 90- or 60-day mortality (RR 0.89; 95% CI 0.77–1.03) or dialysis dependence (RR 1.15; 95% CI 0.92–1.44).

In a systematic review and meta-analysis, Jun et al. [2] assessed the effect of different intensities of RRT on all-cause mortality and renal recovery in AKI patients. Eight trials were identified between 1950 and 2009 which
provided data on 3841 patients and 1808 deaths. More intense RRT (35–48 mL/kg/h or equivalent) had no overall effect on the risk of death (RR 0.89, 95% CI 0.76–1.04, P = 0.143) or recovery of renal function (RR 1.12, 95% CI 0.95–1.31, P = 0.181) compared with less-intensive regimens (20–25 mL/kg/h or equivalent). In both reviews, there was significant trial heterogeneity.

Moreover, data are missing on possible negative effects of high-dose RRT on electrolyte balance leading to hypophosphataemia, on nutrition or on adequate drug levels like those of antimicrobial drugs. This issue should be addressed in further studies.

Rather than implying that the dosage of RRT does not matter in critically ill patients with AKI, these results reinforce the need to better understand the effects of treatment modalities, doses, timing and variability in this high-risk population. As the delivered dosages of RRT in the ATN study [23] may have exceeded the threshold above which further increases do not lead to improved outcomes, this finding suggest that careful attention needs to be paid to the actual delivered dosage of therapy. Probably, there is a threshold dosage above which additional dialysis is not of benefit, but attention must be paid to ensure that patients receive adequate therapy. Specifically during CRRT interruptions of treatment must be minimized. During IHD, frequent measurement should be performed to ensure the delivery of a minimum Kt/V urea of at least 1.2 per treatment, as in the ATN study. In AKI, the accuracy of Kt/V is however compromised by a variable increase in urea generation and a complex relationship between uraemic toxins and total body water.

Furthermore, it should not be forgotten that patient care needs to be individualized and more intensive therapy may be required for the treatment of some complications like hyperkalaemia, metabolic acidosis or extreme hypercatabolism.

The indications for and optimal timing of initiation of RRT in patients with AKI remain uncertain. Although there is little debate that some emergency situations like severe volume overload, hyperkalaemia, metabolic acidosis and uraemic manifestations such as pericarditis represent clear indications for therapy initiation, many physicians begin renal support ‘prophylactically’ in response to progressive uraemia or oliguria. Two studies focussed on the timing of initiation of RRT and clinical outcomes. Using data from the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study, an observational study of critically ill patients with AKI in 54 ICUs across 23 countries, Bagshaw et al. [27] compared outcomes of patients who initiated dialysis ‘early’ or ‘late’ using several measures of timing. There was no difference in crude or adjusted mortality between the early and late groups. This study highlights some of the difficulties with observational studies of timing of dialysis initiation. Interpretation of study results is highly dependent on the definitions used for ‘early’ and ‘late’, which vary widely across studies.

In some patients, early start of renal support may improve outcome. However, early initiation may expose other patients unnecessarily to the risks of RRT [13]. The AKI Network, reviewing the evidence in this field, stated that ‘the indications for RRT must be viewed within the context of the patient’s entire clinical condition with most indications being relative and only a small number of absolute indications’ [28].

Moreover, we must not forget that our first duty as a physician is to help and at least not harm our patients. So waiting somewhat longer for spontaneous renal recovery before starting RRT could possibly avoid the risks of a more harmful treatment. Arguments for this statement are scarce and conservative treatment for AKI has so far only been considered as the treatment option for less severe patients. It was never considered as a meaningful alternative treatment, worthwhile to be included in research projects comparing outcome in different treatment modalities for AKI. In a cohort study of 1303 AKI patients [29] consecutively admitted to the ICU, Elseviers et al. could confirm that mortality is equal in patients treated with IRRT or CRRT. However, prognosis was significantly worse in those receiving RRT compared with conservative treatment and this difference remained significant after correction for the severity of disease and in different subgroup analysis. Moreover, more intensive treatment has an incremental cost without a significant increase in quality of life [30]. In a very recent Australian study, Schneider et al. [31] identified 195 consecutive patients admitted to their institution who developed RIFLE-F AKI over a 3-year period and did not receive RRT, and compared their characteristics and outcomes with those of RIFLE-F RRT-treated patients. About one-third of critically ill patients with severe (RIFLE-F) AKI did not receive RRT. One-third of these patients died in hospital. The timing of the deaths and their underlying causes did not suggest that a broader application of RRT would have changed patient outcomes.

Based on these observations and on recent experiences in other fields of medicine like chronic renal failure, diabetes and hypertension, showing that more intensive treatment does not lead to better outcomes, it is important to stress the need to re-consider the value of careful monitoring and conservative treatment as a valid and independent option in the treatment of AKI. Whenever an RRT modality is needed, the different modalities have to be seen as complementary methods and the most appropriate choice must be guided by local experience and by the individual needs of the patient.

So, the final message should be to avoid ‘over’-treatment that probably causes harm and certainly does not benefit our AKI patients.

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References

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