Timing, dose and mode of dialysis in acute kidney injury

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Purpose of review

In the past 3 years substantial progress has been made in the field of renal replacement therapy (RRT) for critically ill patients.

Recent findings

Two important multicenter randomized clinical trials have been recently published and extensively discussed: the randomized evaluation of normal versus augmented level (RENAL) replacement therapy study and the VA/NIH Acute Renal Failure Trial Network (ATN) study. The RENAL and ATN studies were designed to compare 'normal' or 'less intensive' renal support to an 'augmented' or 'intensive' therapy: both studies showed no benefit in outcomes by increases in intensity of RRT dose. The definition of 'normal dose' is now recommended in a range of 20–30 ml/kg per h for continuous therapies and/or thrice weekly intermittent hemodialysis. On the contrary, the complex issue of RRT optimal timing still remains uncertain and controversial.

Summary

Wide variations in clinical practice still require RRT for critically ill patients to be optimized. The ideal prescription does not exist; however, continuous hemofiltration at a dose of 30 ml/kg/h meets many requirements of optimal care. In order to shed some light in the issue of RRT timing, furthermore, in the near future a standardized and clinically relevant definition of 'early' RRT should be provided. Great expectations currently rely on the utilization of acute kidney injury severity classifications and on new biomarkers of renal function.

Keywords

acute kidney injury, dialysis dose, dialysis modality, hemofiltration, timing of renal replacement therapy

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Introduction

The broad definition of renal replacement therapy (RRT) identifies any form of artificial (extracorporeal or intracorporeal) blood purification: during the course of acute kidney injury (AKI), the lost 'renal homeostasis' (basically management of pH, electrolytes, nitrogen cycle waste products, and fluid balance) of critically ill patients should be artificially replaced. This apparently simple task, however, must include the prescription (and delivery) of an adequate schedule (intermittent or continuous) and amount (dose) of RRT, the choice of optimal materials (dialysis machine, membrane and vascular access), the exact timing of RRT start (early or late). Given the high mortality that still plagues AKI occurrence in the ICU [1], it is plausible to hypothesize that optimization of RRT is still far from being a reality. In particular, even if some evidence regarding the optimum delivery and timing of RRT has been produced, little consensus and wide variations in clinical practice are currently common [2]. This review will highlight the most recent evidence and debate on the issues of acute dialysis dose, mode and timing.

Dose and mode of renal replacement therapy

RRT prescription, as any other therapy posology, should depend on specific indications, clinical efficacy and side effects. Much controversy has characterized this concept in the past 10 years. RRT dose is the expression of how much dialysis should be prescribed in order to achieve a certain level of blood cleansing. In this light, RRT dose relies on patient clinical picture (catabolic rate, muscle mass, presence of pulmonary edema, fever, dysionemia, etc.), on the solute to clear (water, urea, electrolytes, cytokines) and, eventually, the final desired blood level of the target solute. The amount of delivered RRT, then, is a function of selected time schedule (continuous or intermittent), membrane type, modality (dialysis, hemofiltration or hemodiafiltration), extracorporeal circuit

blood flow and dialysis/replacement flow. Measuring total marker solute amount in the dialysate or ultrafiltration effluent and continuous plasma concentration of the same marker (typically urea) allows calculation of solute mass transfer and, eventually, clearance. However, dose can be estimated from easy calculations. This process is particularly easy for continuous veno-venous hemofiltration (CVVH) in which (small solute) clearance is essentially considered equal to the ultrafiltration rate (effluent to plasma concentration ratio of small solutes is close to one). Infusion of hemofiltration replacement solution as predilution will reduce effective dose by the degree to which the plasma is diluted. Similarly, during continuous veno-venous hemodialysis (CVVHD), when the dialysis flow rate is much slower than the blood flow rate, urea concentration in the dialysate will equilibrate with that in the plasma and clearance can be approximated by the dialysate flow rate. The above approximations have been shown to acceptably correlate with a more formal set of measurements of urea clearance [3], provided some caveats for higher dosages and longer treatments [4•]. Thus, the dose of continuous RRT (CRRT) is reported as effluent flow in milliliters per hour or milliliters per kilogram of body weight per hour. Most importantly, time spent off CRRT (downtime) due to circuit clotting, radiological investigations, and/or surgical procedures, can be substantial and can impact azotemic control [5]. The impact of these factors must be accounted for when prescribing therapy as it should foresee downtime and consequently slightly overestimate desired target dose. Finally, metabolites of higher molecular weight are significantly cleared (though not with a linear proportion like urea) only during hemofiltration. Other substances that significantly bind to plasma proteins may be relatively retained in the plasma. In these cases, changes in effluent flow rate may correlate poorly with changes in solute clearance. Thus, it should be remembered that effluent measures of dose, whereas reproducible and convenient, only give a broad and partial idea of blood cleansing during RRT [6•]. In particular, clearance of important substances (phosphate, amino acids, brain natriuretic peptide, etc.) [7,8] should be carefully considered when high-intensity treatments are prescribed.

In clinical practice, the choice of RRT modality, continuous or intermittent, seems to play a minor role in terms of hard outcomes such as mortality, according to several observations and to a recent randomized controlled trial [9]: however, intermittent dialysis requires careful use in patients with impaired hemodynamic status. It must be remarked that most critically ill patients with AKI do have hemodynamic instability: hence, it can be stated that CRRT has become, worldwide, the dominant form of RRT for AKI in the ICU [10]. However, the choice of RRT modality should be based on the clinical status of the single patient such as his/her hemodynamic state, presence of important electrolyte or acid-base disturbances and bleeding risk but, above all, on local availability and expertise. As far as RRT dose is concerned, after about 10 years from the milestone trial that first suggested the possible impact of RRT intensity on patients' outcome [11], two multicenter clinical trials examined the issue of the optimal RRT dose in critically ill patients: the randomized evaluation of normal versus augmented level (RENAL) replacement therapy study [12] and the VA/NIH Acute Renal Failure Trial Network (ATN) study [13]. The RENAL and ATN studies were designed to compare 'normal' or 'less intensive' renal support to an 'augmented' or 'intensive' therapy: in particular, the RENAL study compared 25 ml/kg per h continuous veno-venous hemodiafiltration (CVVHDF) to 40 ml/kg per h and the ATN study 20 ml/kg per h CVVHDF or thrice weekly intermittent dialysis to 35 ml/kg/h CVVHDF or daily intermittent dialysis. Surprisingly, both studies showed no benefit in outcomes by increases in intensity of RRT dose, essentially confuting a large body of evidence coming from previous smaller trials. As a consequence, the definition of 'normal dose' is now recommended in a range of 20–30 ml/kg per h for continuous therapies and/or thrice weekly intermittent hemodialysis [14•]. It must be remarked that overt underdialysis might be harmful in critically ill patients with AKI [15]. In this light, the ATN and RENAL studies were rigorous clinical trials and minimized greatly the discrepancy between prescribed and delivered dose: as recently confirmed by the DOse REsponse Multicentre International (DoReMi) Collaborative Initiative, the difference between prescription and delivery of CRRT relies on therapy downtime (the amount of time the CRRT does not run in a 24-h period), clotting of the circuit (the cause of the majority of unexpected treatment stops), vascular access problems (that push clinicians to modify therapy settings) and prescription errors (some operators in the field of acute RRT do not really know how to correctly prescribe) [16•]. Hence, when in clinical practice, 20–25 ml/kg per h is prescribed during CRRT,

Key points

- Current evidence recommends a prescription of 20–30 ml/kg per h of continuous renal replacement therapy (RRT) or thrice weekly intermittent RRT.
- Hemodynamically unstable patients should preferably receive continuous RRT.
- There is still great uncertainty regarding the issue of RRT timing.
- Early RRT seems to be recommended only if specific comorbidities are present (i.e. respiratory failure, sepsis) provided adequate experience by operators.
- Further work has to be done on RRT timing definition and renal biomarkers validation.

consistently with those in the RENAL and ATN studies, the possibility of a significant reduction in dialysis dose delivery should be considered. In practice, clinicians need to over-prescribe RRT with a 25% safety margin, targeting 30–35 ml/kg per h in order to achieve the 'adequate' delivered dose [14•].

Since critically ill patients are subject to several risk factors for organ injury (surgical intervention, trauma, rhabdomyolysis, hemodynamic instability, organ hypoperfusion, bacteremia and endotoxemia, sepsis and septic shock), several authors have hypothesized that selected subgroups of the critically ill might benefit from some extracorporeal blood purification, according to the 'humoral theory of sepsis' (soluble substances that circulate in blood and participate in the generation of the different disorders of MODS [17•]). In the ATN trial, there was no benefit from higher dose in any subgroup, including sepsis and vasopressor requirement. When the post-hoc analysis was focused, in the RENAL study, to the subgroup of septic patients, there was only a tendency to lower mortality with the higher intensity approach [odds ratio (OR) 0.84, 95% confidence interval (CI) 0.62–1.12]. However, animal models, which have suggested beneficial effects of CRRT on the severity of systemic inflammatory responses, employed very high dose therapy (greater than 50 ml/kg per h) initiated very early in the course of illness (prior to overt renal dysfunction) [18]. Dose–response studies of conventional CRRT, such as the ATN and RENAL trials, were not intended to examine the multiorgan protective effect of CRRT. It must be remarked that delivery of doses of CVVH in excess of 50 ml/kg per h is complex, presenting a number of clinical and technical challenges. Interestingly, a recent systematic review including 12 randomized trials comparing high versus standard-dose CRRT (>30 versus <30 ml/kg per h, seven trials), intermittent hemodialysis (three trials), or sustained low-efficiency dialysis (one trial) (daily versus alternate day, or by target biochemistry) [19•] found no effect of high-dose RRT on mortality (risk ratio 0.89, 95% CI 0.77–1.03), even in the subgroup of septic patients. According to these authors, there is a high-medium level of evidence that high-dose RRT does not improve patient survival in AKI patients, with or without sepsis. An in-depth further review of extrarenal blood purification techniques would go beyond the scope of this article. It is worth noting, however, that the evolution of extracorporeal renal support has been paralleled by the design of new extracorporeal circuits and modalities (adsorbent cartridges, extracorporeal liver support, increased application of extracorporeal membrane oxygenation, new machines for cardiac [20] and/or pulmonary support [21] and, finally, the development of specific lung support strategies for extracorporeal decapneization [22]). In the context of multiorgan failure, hence, the terms extracorporeal blood purification and multiorgan support have been conceived, with more specific indications and potentially improved efficacy with respect to 'traditional' high-dose RRT.

Timing of renal replacement therapy

Even if the debate on RRT dose has not been definitely ended yet, it is now clear that a 'best practice region' exists and acute dialysis should be prescribed accordingly [6•]. Nevertheless, it is now also clear that ml/kg/h are not sufficient *per se* to provide substantial changes in the poor outcome of AKI patients. Another fundamental aspect of RRT delivery other than 'how much' is 'when'. Should clinicians wait for frank anuria or unequivocal signs of uremia or fluid overload before starting an extracorporeal therapy or should the treatment be indicated proactively? Are there reliable indices helping the operators to choose RRT timing? Back in 2001, the Acute Dialysis Quality Initiative (ADQI) workgroup defined some 'absolute' indications for RRT that, however, came after a consensus statement, not from specific clinical data (given below) (www.adqi.org).

Absolute indications for starting RRT:

(1) Uremic complications, for example encephalopathy, pericarditis, bleeding.
(2) Serum urea at least 36 mmol/l (100 mg/dl).
(3) K+ at least 6 mmol/l and/or ECG abnormalities.
(4) Mg at least 4 mmol/l and/or anuria/absent deep tendon reflexes.
(5) Serum pH 7.15 or less.
(6) Urine output less than 200 ml/12 h or anuria.
(7) Diuretic-resistant organ edema (i.e. pulmonary edema) in the presence of AKI.

Further research in the field of AKI led to the possibility to assess not only the presence but also the severity of AKI: the RIFLE (Risk, Injury, Failure, Loss of Function, End Stage Renal Disease) classification was proposed by the ADQI group either as a definition, intended to establish the presence or absence of the clinical syndrome of AKI in a given patient or situation, and to describe the severity of this syndrome [23,24]. RIFLE was not originally designed to predict mortality or adverse outcomes, nor to trigger standardized therapeutic interventions. However, it seemed logical to assume that more severe disease should result in worse outcome. In the presence of severe AKI and/or rapidly deteriorating kidney function (towards 'F' level), RRT initiation should be considered, particularly if there was failure to respond to initial therapy [2]. However, the decision of if, and when, to initiate RRT in critically ill patients with mild-to-moderate AKI (i.e. RIFLE category R/I) is often the most challenging. It is important to recognize that the decision to initiate RRT in these patients should

be 'dynamically' tailored on each case and not strictly rely on a single indication. The presence of one or more mitigating factors, such as rapidly worsening AKI and/or overall severity of illness, severe sepsis, and reduced renal reserve, would push us to consider RRT in earlier stages of AKI. Primary diagnoses associated with high catabolic rates (e.g. septic shock, major trauma, burn injury) or those likely to place considerable demand on kidney function (i.e. gastrointestinal bleeding, rhabdomyolysis) should be identified in the context of potential need for early initiation of RRT. Critically ill patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) receiving lung-protective ventilation may intentionally develop respiratory acidosis due to permissive hypercapnia [25]. Co-existent and/or evolving AKI in these patients will significantly impair capacity for kidney bicarbonate regeneration to buffer systemic acidemia. Earlier RRT may prove beneficial in these patients prior to the development of severe acidemia, worsening ARDS and/or volume overload. A positive fluid balance and overt clinical fluid overload, when refractory to medical therapy (i.e. diuretics), is also an important circumstance in which RRT initiation may prove beneficial. In critically ill patients, fluid overload may be under-recognized as an important contributor to morbidity and mortality [26]. Longer duration of mechanical ventilation, weaning failure, delayed tissue healing, and cardiopulmonary complications have all been associated with fluid overload [27]. RRT initiation should therefore be considered an important therapeutic measure for the prevention (and not only the treatment) of refractory fluid overload. A clinical algorithm has been recently proposed in order to guide clinicians from 'conventional' indications (which in most cases might be seen as 'rescue therapies') to proactive RRT initiation [28].

In clinical practice, however, even if a general agreement exists that a survival benefit is provided by early initiation of RRT, it remains a quite difficult choice being essentially based on arbitrary thresholds [29•]: is an 'early' start when the very first AKI signs and symptoms are temporally close or referred to a milder severity of the disease? Again, how is timing from ICU admission (that possibly corresponds to the initiation of events finally leading to kidney dysfunction) considered? Third, how does the 'early/late' distinction take into consideration AKI cause, the presence of multiorgan failure or other elements triggering the indication to extrarenal RRT? In this light, it seems unlikely to compare an RRT for an 'F' RIFLE class AKI soon after an emergency department admission in a trauma patient and an RRT for an 'R' level in an advanced phase of multiple organ dysfunction syndrome in a long-stay patient with pneumonia: the different clinical pictures underling these two dialytic prescriptions do not reliably identify an 'early' or 'late' treatment. The detractors of anticipated initiation of RRT, furthermore, claim that some 'early patients' might also recover renal function with conservative treatment alone without being subjected to unnecessary risks [30]. A significant body of literature on this aspect of AKI management is lacking. A recent meta-analysis on early versus late initiation of RRT in critically ill patients with AKI showed that the overall methodological quality of the 15 included studies was poor [31•]. According to these authors, early RRT, compared with late therapy, was associated with a significant improvement in 28-day mortality (OR 0.45, 95% CI 0.28–0.72). However, this conclusion is based on heterogeneous studies of variable quality and only two randomized trials: there are clearly insufficient data to determine absolute indications and optimal timing for initiation of RRT in patients with AKI. Interestingly, heterogeneity also relied on the disparate definitions used to detect early and late treatments in different studies: 'early' patients in some studies might have been considered 'late' by other authors. RIFLE classes were utilized as RRT timing markers in a recent analysis of patients affected by postabdominal surgery AKI [32]: late dialysis, identified with a higher RIFLE classification severity, had a death hazard ratio of 1.846; other factors independently associated with risk of dying were old age (hazard ratio 2.090), cardiac failure (hazard ratio 4.620), pre-RRT SOFA score (hazard ratio 1.152). However, another retrospective observation in the context of septic AKI, in which 'no AKI' or 'R' in a simplified RIFLE classification were used as markers of timely dialysis, could not demonstrate significant benefits of early RRT [33•]. In a recent interesting retrospective analysis in 1847 critically ill patients with AKI patients requiring RRT, Ostermann and Chang [34] evaluated the relationship between biochemical, physiological and comorbid factors at time of RRT start and ICU mortality. Multivariate analysis showed that at time of initiation of RRT, independent risk factors for ICU mortality were, among others, mechanical ventilation (OR 6.03), oligoanuria (OR 1.6), age (OR 1.03), serum urea (OR 1.004) and cardiovascular failure (OR 1.3). A higher pH at initiation of RRT was independently associated with a better outcome. Failure to correct acidosis and development of more organ failure within 48 h after initiation of RRT were also associated with an increased risk of dying in ICU. The message of this research seems to remark that RRT should be commenced for AKI critically ill patients before organ failure and metabolic derangements have reached the slippery threshold of irreversibility. An interesting and controversial part of the study remarked that survivors tended to have, at RRT start, lower urea and higher creatinine levels. This finding further supports that the decision when to start RRT for AKI should be guided more by associated dysfunction of other organ systems, urine output and serum pH rather than absolute serum creatinine and/or urea levels. It is clear that creatinine is not an ideal biomarker for decision on RRT

timing: it can result normal in case of RRT for fluid overload (which decreased creatinine levels due to hemodilution) [35•] and of early kidney damage. In this light, new biomarkers will hopefully improve the performance of creatinine, urea and RIFLE [36].

In this delicate and difficult debate, a recent provocative observation from Stuivenberg Hospital Acute Renal Failure (SHARF) project, showed that RRT patients had a higher mortality (43 versus 58%) as well as a longer ICU and hospital stay compared to patients treated with conservative approach (volume, electrolyte, acid-base homeostasis and specific drug management without dialysis) [37••]. A higher mortality in the RRT group was confirmed after multiple adjustments and the authors concluded that the higher mortality expected in AKI patients receiving RRT versus conservative treatment can not only be explained by a higher disease severity in the RRT group: early RRT, in this context, would result as definitely detrimental.

Regardless of current conflicting (and mostly retrospective) literature, RRT remains an important therapeutic and supportive measure and is commonly used in clinical practice. It is possible that uncertainty about the ideal circumstances in which to initiate RRT and for what indications will keep causing a large variation in clinical practice between clinicians and across institutions and countries. However, experience on 'early' RRT prescription is rapidly growing even outside specific referral centers, together with treatment safety. At this point of critical care nephrology, as far as further standardized definitions, literature and wide consensus will be provided, operators should establish RRT timing case by case, basing on patients' AKI severity, presence of comorbidities and other organ failures and locally available techniques and devices.

Conclusion

RRT dose and timing remain two crucial (though not exclusive) aspects of renal replacement optimization during AKI. Recent literature provided consistent data on RRT dose: the experience accumulated so far would seem to recommend a prescription of 20–30 ml/kg per h of continuous RRT (regardless of modality) in hemodynamically unstable patients. Thrice-weekly RRT for hemodynamically stable patients would meet the standard of optimal care in centers delivering intermittent therapies. The near future will hopefully shed some light in the issue of RRT timing that is currently lacking due to the extreme uncertainty and variability about the concept of 'early' RRT. Great expectations currently rely on the utilization of new biomarkers of renal function. At the moment, intense training, the availability of clear institutional RRT protocols, local recommendations and, finally, the availability of a dedicated multidisciplinary RRT team that took care of RRTs technical (yet fundamental) aspects might help in overcoming the lack of a strict timing indication.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 666–667).

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