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CRITICAL CARE

REVIEW

Clinical review: Optimal dose of continuous renal replacement therapy in acute kidney injury

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Abstract

Continuous renal replacement therapy (CRRT) is the preferred treatment for acute kidney injury in intensive care units (ICUs) throughout much of the world. Despite the widespread use of CRRT, controversy and center-specific practice variation in the clinical application of CRRT continue. In particular, whereas two single-center studies have suggested survival benefit from delivery of higher-intensity CRRT to patients with acute kidney injury in the ICU, other studies have been inconsistent in their results. Now, however, two large multi-center randomized controlled trials – the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network (ATN) study and the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study – have provided level 1 evidence that effluent flow rates above 25 mL/kg per hour do not improve outcomes in patients in the ICU. In this review, we discuss the concept of dose of CRRT, its relationship with clinical outcomes, and what target optimal dose of CRRT should be pursued in light of the high-quality evidence now available.

Introduction

Extracorporeal renal replacement therapy (RRT) has been used for the supportive treatment of acute kidney injury (AKI) for over 60 years. Whereas treatment methodologies have become increasingly sophisticated, the basic principles guiding the use of RRT have changed little. They aim at averting the immediately life-threatening consequences of severe renal dysfunction (acidosis, electrolyte imbalances, uremia, and fluid overload), preserving life, and allowing time for organ recovery to occur. Following these principles, one could argue that, as long as a minimum level of RRT is provided, the quality, quantity, and timing of RRT should not greatly affect outcome. However, considerable evidence that the development of AKI is independently associated with mortality now exists [1], suggesting that optimization of RRT could benefit survival. Until now, however, little evidence or consensus regarding the optimum delivery of RRT has existed, resulting in wide variations in clinical practice [2]. Furthermore, irrespective of intensity, the superiority of continuous renal replacement therapy (CRRT) over intermittent hemodialysis (IHD) for RRT in the intensive care unit (ICU) remains controversial, although there is increasing international consensus that initial therapy with CRRT is preferable in hemodynamically unstable patients [3-6]. Given that most patients critically ill with AKI do have hemodynamic instability, CRRT has become, worldwide, the dominant form of RRT for AKI in the ICU [2]. Furthermore, since a large majority of RRT treatments for AKI are now given in the ICU [7], CRRT is likely to be the most common modality for the initial treatment of AKI by RRT in the developed world.

As a continuous therapy, CRRT has the benefit of better mimicking normal renal function, while quantity of therapy delivered is more easily assessed and compared with endogenous renal function. Consequently, there has been continued interest in establishing the appropriate dose or intensity of this therapy. Two major multi-center randomized controlled trials (MC-RCTs) examining this question have now been performed: the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network (ATN) study [4] and the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study [8]. Together, these trials provide, for the first time, high-quality evidence to guide the prescription of CRRT in the ICU. This review examines the results from these and earlier studies to summarize our current understanding of the most appropriate dose of CRRT to deliver during AKI in critical illness.

Assessing dose of continuous renal replacement therapy

To compare differing intensities of RRT, some measure of quantity of blood cleansing is needed. Quantity or *dose* of

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RRT delivered is traditionally assessed by measuring clearance of urea (that is, the rate of plasma cleansing required to account for the rate of urea removal if the treatment separated all urea from the plasma processed). Such measurements are comparable to endogenous renal function assessed as glomerular filtration rate (GFR). Urea is chosen as an easily measured prototype for low-molecular-weight products of metabolism. While tubular reabsorption prevents urea clearance from being an accurate measure of kidney GFR, such concerns do not apply to extracorporeal blood purification. Measuring total urea in the dialysis or ultrafiltration effluent and continuous plasma urea concentration could allow calculation of clearance. However, this is cumbersome and approximations of dose are instead estimated from machine settings. This process is very easy for continuous therapies. For a small uncharged molecule such as urea, clearance during continuous hemofiltration (HF) is essentially equal to the ultrafiltration rate because the filter membrane negligibly impedes the passage of urea. Similarly, during continuous hemodialysis (HD), 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. Thus, provided that no pre-dilution is applied, in any HF, HD, or hemodiafiltration continuous therapy, the total clearance is approximately the total flow of fluid out of the dialyzer or filter (that is, the effluent flow rate).

The above approximations have been shown to correlate well with a more formal set of measurements of urea clearance [9]. Thus, the dose of CRRT is reported as effluent flow in milliliter per hour or milliliter per kilogram of body weight per hour. Infusion of HF replacement solution as pre-dilution will reduce effective effluent dose by the degree to which the plasma is diluted. Since this dilution effect is dependent on circuit blood flow, replacement fluid rate, and hematocrit, these factors have to be measured to correctly assess dose when pre-dilution is applied [9]. Most importantly, time spent off CRRT (circuit clotting, radiological investigations, and/or surgical procedures) can be substantial and can impact azotemic control [10]. The impact of these factors must be accounted for when prescribing therapy as it is the delivered and not the prescribed dose that will affect outcome. Finally, unlike urea, metabolites of higher molecular weight will interact significantly with the dialyzer membrane. Similarly, 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, while reproducible and convenient, do not measure all aspects of blood cleansing in CRRT.

Clinical variation in continuous renal replacement therapy dose

Prescribed and delivered intensities of CRRT vary widely. Two multi-center observational studies have documented CRRT dose in the ICU; in both studies, interquartile ranges for dose were large (15.3 to 27.7 mL/kg per hour in the BEST Kidney [Beginning and Ending Supportive Therapy for the Kidney] study [11] and 22.1 to 33.9 mL/kg per hour in the DO-RE-MI [Dose Response Multicentre International collaborative initiative] study [12]). As units participating in these studies were recruited by expression of interest, one can assume far wider variation and lower delivered doses in units without an interest in research and the provision of CRRT. Much of this variation in dose may be accounted for by the use of standard doses of CRRT unadjusted for weight. For example, in the DO-RE-MI study, patients receiving the lowest CRRT doses were 33% heavier than those receiving the higher doses [13]. This greatly confounds the interpretation of observational data on CRRT dose since weight is likely to have a complex causal relationship with outcome. Furthermore, even when used, weight estimation in the ICU can be highly error-prone and it is far from clear whether estimates of ideal body weight, pre-morbid weight, 'dry' weight, or actual body weight should be used [13].

Dose-response relationship in continuous renal replacement therapy

Prior to the ATN and RENAL trials, four single-center studies had prospectively examined the relationship between CRRT dose and survival in critical illness (Table 1). All of these trials were, however, relatively small and varied in geographical location, patient case mix, and mode of CRRT. In the first of these, Ronco and colleagues [14] randomly assigned 425 critically ill patients with AKI treated using continuous veno-venous hemofiltration (CVVHF) at a single center to ultrafiltration rates of 20, 35, or 45 mL/kg per hour. Survival 15 days after discontinuation of CRRT was significantly better in the highest- and intermediate-dose arms in comparison with the lowest-dose arm (58% and 57% versus 41%, respectively; $P < 0.001$). Three smaller randomized control trials subsequently examined RRT dose-response relationships in the ICU. Saudan and colleagues [15] randomly assigned 206 patients with AKI in a single-center trial comparing CVVHF (mean ultrafiltration rate of 25 ± 5 mL/kg per hour) with continuous veno-venous hemodiafiltration (CVVHDF) with the addition of a mean dialysate flow rate of 15 ± 5 mL/kg per hour to a similar mean ultrafiltration rate (24 ± 6 mL/kg per hour): survival rates after 90 days were 34% in the CVVHF group and 59% in the CVVHDF group ($P = 0.0005$), analyzed on an intention-to-treat basis. While higher-intensity therapy involved a

Table 1. Randomized controlled trials comparing dose of continuous renal replacement therapy in the intensive care unit

Study	Type	Number	Comparison	Survival (measured at)	Comment
RENAL [8] 2009	MC-RCT	1,508	40 mL/kg per hour versus	55% (day 90)	
			25 mL/kg per hour	55% NS	
			Post-dilution CVVHDF		
ATN [4] 2008	MC-RCT	1,124	Pre-dilution CVVHDF 35 mL/kg per hour or 6/week SLEDD or 6/week IHD versus	46% (day 60)	Choice of CRRT/SLEDD versus IHD based on daily cardiovascular SOFA score.
			Pre-dilution CVVHDF 20 mL/kg per hour or 3/week SLEDD or 3/week IHD	48% NS	
Tolwani, *et al*. [17] 2008	SS-RCT	200	17 mL/kg per hour	49% (ICU or 30 days)	
			29 mL/kg per hour	56% NS	
			Pre-dilution CVVHDF (delivered doses)		
Saudan, *et al*. [15] 2006	SS-RCT	206	CVVHF: 1-2.5 L/hour versus	34% (day 90)	
			CVVHDF: 1-2.5 L/hour HF + 1-1.5 L/hour HD	59% $P = 0.0005$	
Bouman, *et al*. [18] 2002	2C-RCT	106	72-96 L/day early versus	74% (day 28)	Combined trial of dose and timing early versus late.
			24-36 L/day early versus	69% NS	
			24-36 L/day late	75% NS	
			CVVHF		
Ronco, *et al*. [14] 2000	SS-RCT	425	20 mL/kg per hour versus	59% (day 15)	Unorthodox mortality outcome (day 15 after CRRT).
			35 mL/kg per hour versus	43%	
			45 mL/kg per hour	42%	
			Post-dilution CVVHF	20 versus 35 or 45 $P < 0.002$	
				35 versus 45 NS	

2C-RCT, two-center randomized controlled trial; ATN, Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network; CRRT, continuous renal replacement therapy; CVVHDF, continuous veno-venous hemodiafiltration; CVVHF, continuous veno-venous hemofiltration; HD, hemodialysis; HF, hemofiltration; ICU, intensive care unit; IHD, intermittent hemodialysis; MC-RCT, multi-center randomized controlled trial; NS, not significant; RENAL, Randomized Evaluation of Normal versus Augmented Level; SOFA, Sequential Organ Failure Assessment; SLEDD, slow extended-duration daily dialysis; SS-RCT, single-center randomized controlled trial.

different modality, evidence suggests that solute clearances in continuous high-flux dialysis and CVVHF are quite similar [16], so this study is best regarded as investigating the effect of a dose increment.

On the other hand, two studies [17,18] that included 200 and 106 patients, respectively, failed to demonstrate any beneficial effects of increased CRRT intensity on patient survival or renal recovery. Similarly, in the prospective observational DO-RE-MI study [12], which included 338 patients undergoing CRRT for AKI in the ICU, higher-dose CRRT (defined as greater than 35 mL/kg per hour) was not associated with increased survival even after statistical adjustment for baseline characteristics (adjusted odds ratio for death 1.21, 95% confidence interval 0.66 to 2.21; $P = 0.537$). Disparity in these results, concerns over the inherent biases of single-center studies [19], and consequent uncertainty about the optimum dosing of CRRT in the ICU led to the initiation of the ATN and RENAL studies.

The ATN and RENAL studies were large, multi-center randomized controlled trials investigating the effects of RRT dose on survival and were conducted in ICUs throughout the US and in Australia and New Zealand, respectively (Table 2). The ATN study [4] randomly assigned critically ill adults with AKI that required RRT to high-intensity or low-intensity RRT. High-intensity therapy consisted of pre-dilution CVVHDF to provide a total effluent flow rate of 35 mL/kg per hour or six sessions of IHD per week [4]. Low-intensity therapy consisted of CVVHDF to provide a total effluent flow rate of 20 mL/kg per hour or thrice-weekly IHD. A very small number of patients received slow extended-duration dialysis six or three times weekly in the high-intensity and low-intensity groups, respectively, in centers where CRRT was not available [4]. Within treatment groups, patients were allocated to CRRT or IHD when their cardiovascular Sequential Organ Failure Assessment (SOFA) score was 3 or 4 and received IHD if

Table 2. Comparison of patient populations in VA/NIH ATN and RENAL studies

	VA/NIH ATN study	RENAL study
Number	1,124	1,508
Age, years	59.7	64.5
Percentage of males	70.6%	64.6%
CKD classification[a]		
0-2	61.0%	68.6%
3a	21.1%	9.7%
3b	11.0%	10.4%
4	Excluded	11.3%
5	Excluded	Excluded
Sepsis	63.0%	47.9%
Mechanical ventilation	80.6%	73.9%
Illness severity score	APACHE II: 26.4	APACHE III: 102.4
Total SOFA score (respiratory, cardiovascular, liver, coagulation)	7.55	7.40
Modalities of RRT	CVVHDF, SLEDD, or IHD	CVVHDF
RRT prior to randomization	64.3% (only patients who had undergone fewer than two sessions of IHD or SLEDD or less than 24 hours CRRT were included)	0% (patients with prior RRT excluded)
Commenced on CRRT	69.7%	100%
CRRT mode	Pre-dilution CVVHDF	Post-dilution CVVHDF
CRRT high-dose effluent target	35 mL/kg per hour	40 mL/kg per hour
CRRT low-dose effluent target	20 mL/kg per hour	25 mL/kg per hour
Time from ICU admission to first study RRT	6.7 days	2.1 days
Urea at study enrolment	23.8 mmol/L	24.2 mmol/L
Achieved dose of CRRT (high dose)	27.1 mL/kg per hour[b]	33.4 mL/kg per hour
Achieved dose of CRRT (low dose)	17.5 mL/kg per hour[b]	22 mL/kg per hour
Mean daily urea on CRRT (high dose)	11.7 mmol/L	12.7 mmol/L
Mean daily urea on CRRT (low dose)	16.8 mmol/L	15.9 mmol/L
Daily fluid balance on therapy	+130 mL	–20 mL
Survival at day 60	47.5%	Not reported
Survival at day 90	Not reported	55.3%
Percentage of survivors dependent on RRT		
At day 28	45.2%	13.3%
At day 60	24.6%	Not reported
At day 90	Not reported	5.6%

[a]Where baseline renal function was not available, patients are assumed to have normal baseline renal function. [b]Dose was corrected for pre-dilution at median blood flow and replacement rates. APACHE, Acute Physiology and Chronic Health Evaluation; CKD, chronic kidney disease; CRRT, continuous renal replacement therapy; CVVHDF, continuous veno-venous hemodiafiltration; ICU, intensive care unit; IHD, intermittent hemodialysis; RENAL, Randomized Evaluation of Normal versus Augmented Level; RRT, renal replacement therapy; SLEDD, slow extended-duration daily dialysis; SOFA, Sequential Organ Failure Assessment; VA/NIH ATN, Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network.

their cardiovascular SOFA score was not more than 2. However, patients receiving only CRRT switched to IHD if their cardiovascular SOFA score was 0 or 1 for more than 24 hours. CRRT was provided to 69.7% of patients as their initial therapy [20]. Switching between modalities occurred at similar rates in high-intensity and low-intensity groups [20]. Among patients who survived to day 60, 84.2% received IHD at some stage during their ICU stay [20]. Given the controversies in dose comparison between treatment modalities and the use of IHD in many patients, the ATN trial might best be described as a test of maximization of intensity of RRT within current US practice rather than a direct test of a dose-response relationship for CRRT.

In comparison, 1,508 critically ill adults meeting predetermined criteria for the initiation of RRT in the RENAL study [8] were randomly assigned to post-dilution CVVHDF with an effluent flow of 40 mL/kg per hour or 25 mL/kg per hour. All patients received CRRT as their first mode of RRT; only a small proportion of patients (approximately 7%) received IHD later in their ICU stay, and this proportion was similar to that of patients who remained dependent on dialysis at day 90. A small number of patients requiring an extended period of post-ICU RRT accounted for the higher *mean* duration of RRT (11.5 ± 18.0 days and 13.0 ± 20.8 days in the two treatment groups) despite a duration of study treatment of only 5.9 ± 7.7 and 6.3 ± 8.37 days. The RENAL study thus constitutes a more direct measure of the relationship between intensity of CRRT and survival.

Both studies failed to detect any reduction in mortality associated with a more intensive RRT. In addition, no significant differences in mortality rates were observed between high-intensity and low-intensity treatment in pre-specified subgroups in either study. These subgroups included patients with sepsis and those requiring vasopressors. These results now provide definitive evidence that an increase of CRRT dose beyond conventional effluent flow rates of 25 mL/kg per hour is not beneficial for unselected ICU patients with AKI. Importantly, both the ATN study and the RENAL study demonstrated that the prescribed dose is typically 10% to 15% less than the delivered dose in these patients, presumably because of treatment downtime. This observation is important because downtime may be longer outside of the environment of a clinical trial and clinicians seeking to replicate these outcomes will need to account for this in their prescription. In contrast to the within-trial comparisons, important differences between overall survival and recovery of renal function in the ATN and RENAL studies can be highlighted (Table 2). These differences do not detract from the consistent primary results within the trials and may be accounted for by differences in population and case mix. However, they also suggest that other aspects of RRT provision, such as timing of therapy [21] and prevalence of IHD, may impact outcomes and should be the subject of further study [3].

After the publication of the above pivotal trials, it was speculated that the relationship between CRRT dose and survival is at a plateau between 20 and 40 mL/kg per hour but that lower or much higher doses could be associated with worse outcomes (Figure 1) [22]. Certainly, there is now little incentive to use doses of greater than 25 mL/kg per hour in unselected ICU patients. It may be speculated that individual patients might benefit from differing doses of CRRT; however, there was no suggestion that specific groups benefited in subgroup analysis of the ATN and RENAL trials, indicating that identification of such patients may be difficult. Similarly, different target doses of CRRT may be sufficient at various stages of critical illness, but this question has not been examined in prospective randomized controlled trials.

The absence of improved survival with dose increment above 20 mL/kg per hour should not be taken as an indication that assessment of dose is irrelevant, and lower intensities still will suffice. It can be reasonably presumed that some relationship for increasing survival with intensity of therapy exists as one increases intensity from no therapy to a greater level of therapy, with a plateau response occurring at or before 20 to 25 mL/kg per hour. It seems unlikely that this plateau is occurring much before a dose of 20 mL/kg per hour. In the DO-RE-MI study [12], patients in the second tertile of dose (23.6 to 30.9 mL/kg per hour) had the lowest mortality, with an adjusted odds ratio for death of 0.67, compared with doses of less than 23.6 mL/kg per hour, but this trend was far from statistically significant ($P = 0.196$).

Historically, introduction of CRRT into the ICU led to improved survival when compared with previous use of thrice-weekly conventional IHD or acute peritoneal dialysis (PD) [23]. In this setting, use of CRRT led to improved azotemic control in comparison with the historical cohort, suggesting that increased survival may have been partly associated with delivery of a higher standardized dose of therapy. Similarly, a randomized control trial of CVVHF versus acute PD in patients with falciparum malaria or sepsis [24] demonstrated that CVVHF (mean prescribed dose of 19 mL/kg per hour) was associated with improved survival over continuous PD (2-L exchanges with 30-minute dwell time) (mortality of 15% versus 47%; $P = 0.005$). While modality-related factors undoubtedly played a role in these results, the rate of decline in creatinine was twice as fast in those treated with CVVHF in comparison with those treated with PD, suggesting that the dose of small-molecular clearance delivered may have, in part, determined outcome.

By analogy, in the setting of end-stage renal disease, while doses of thrice-weekly IHD above an equilibrated Kt/V (eKt/V) of greater than 1.16 have not been associated with improved outcomes [25], observational data have shown that an eKt/V of less than 1.05 is linearly associated with decreased survival in patients with end-stage renal disease [26,27]. Thrice-weekly IHD with an eKt/V of 1.05 provides azotemic control similar to that of approximately 11 mL/kg per hour of CRRT, according to the peak concentration method of dose comparison [28], and somewhat more if time-averaged urea concentration [29] is used as a comparator. It seems unlikely that the critically ill will have a lower requirement for RRT in comparison with stable HD patients. These considerations, therefore, suggest that we should not tolerate doses of CRRT in critically ill patients near the inflexion point

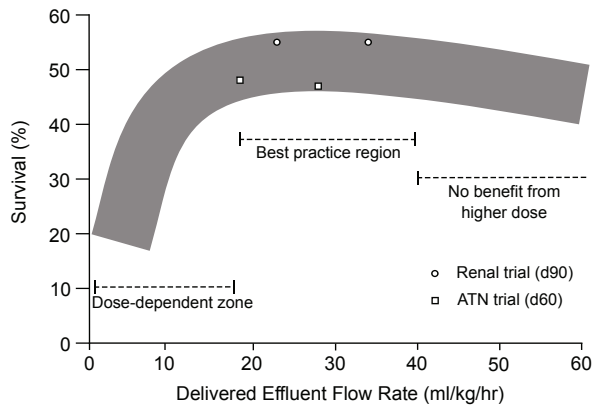

Figure 1. Possible relationship between delivered dose of continuous renal replacement therapy and survival, with results from the ATN and RENAL trials illustrated. ATN doses are corrected for pre-dilution. These studies indicate a plateau response at the dose ranges examined. To reproduce these results, clinicians will need to prescribe continuous renal replacement therapy doses above the lower target dose in the trial protocols (20 or 25 mL/kg per minute) as larger periods of filter downtime can be expected outside a clinical trial environment. Below this best-practice region, survival is likely to be dose-dependent; however, the exact nature of this relationship has not been formally determined. Doses above the best-practice region are unlikely to be beneficial to unselected patients and could potentially be harmful. ATN, Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network; RENAL, Randomized Evaluation of Normal versus Augmented Level. Adapted from [18].

of the dose-response relationship seen in the chronic HD population. Collectively, all of the observations provide strong circumstantial evidence that CRRT doses of less than 20 mL/kg per hour are likely to be harmful and should be avoided. Thus, to guarantee outcomes similar to those seen in the ATN and RENAL studies and to have confidence that an effective dose of CRRT has been delivered, clinicians should prescribe 20 to 30 mL/kg per hour on the basis of body weight at time of commencement of CRRT and ensure that excessive periods off of treatment are not compromising dose delivered. Notably, international surveys [11,12] have reported that, even now, a significant minority of patients receive treatment intensities of less than 20 mL/kg per hour and may be suboptimally treated. If RRT doses are increased by adoption of these targets, clinicians should be aware that adjustments in drug (most importantly, antibiotic) dosing may be required to allow for increased clearances.

Special circumstances

A number of authors have hypothesized that subgroups of the critically ill, particularly those with sepsis or multi-organ failure, might benefit from a more intensive CRRT. It is thought that removal of circulating pro- and anti-inflammatory mediators might blunt systemic derangement of immune responses in severe critical illness [30,31]. In the ATN and RENAL trials, there was no benefit from higher dose in any subgroup, including sepsis and vasopressor requirement. However, animal models [32-34], 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 hour) initiated very early in the course of illness (prior to overt renal dysfunction). Dose-response studies of conventional CRRT, such as the ATN and RENAL trials, were not intended to examine these pleiotropic effects of CRRT in critical illness. A detailed discussion of this topic is beyond the scope of this review; however, as such immune-modulating effects are often cited as a rationale for dose adjustment of CRRT in severe sepsis, it is pertinent to briefly discuss the current evidence base for such use of high-intensity CRRT in carefully selected patients.

Very-high-volume CRRT has been examined in uncontrolled clinical trials and case series with suggestion of benefit [35-39]. As removal of middle-molecular-weight mediators was desired, purely convective therapy (HF) was used in most of these studies. Very-high-volume HF has been defined as a dose of greater than 50 mL/kg per hour [40], although many studies have used higher doses. In practice, delivery of doses of CVVHF in excess of 50 mL/kg per hour is complex, presenting a number of clinical and technical challenges [40] that may account for the lack of high-quality clinical trial data to confirm or refute a benefit. An MC-RCT, the IVOIRE (High Volume in Intensive Care) study, examining the use of high-volume versus intermediate-dose CRRT (70 versus 35 mL/kg per hour for 96 hours in patients with septic shock and moderate kidney injury) has recently stopped recruiting as interim analysis revealed lower-than-expected mortality in all patients, rendering the planned study size (480 patients) insufficiently powerful to prove an effect on survival [41]. Interest has thus focused on other methods of blood purification – including coupled plasma filtration with bioadsorption [42] or hemofiltation using high-cutoff point (greater than 50 kDa) membranes [43,44] – that may be easier to clinically implement. As yet, the adjunctive uses of CRRT and related technologies for the treatment of severe sepsis and multi-organ failure remain experimental and are subject to ongoing trials. However, given the complexity of these treatments and the diverse patient population, direct proof of survival benefit may be difficult to obtain and surrogate endpoints such as vasopressor requirements and organ failure scoring may form the basis of practice recommendations in the future.

Conclusions

The ATN and RENAL studies have now established an upper limit of intensity for CRRT. In addition, they found

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no evidence to suggest that any specific subgroups would benefit from higher doses of RRT, refuting previous smaller studies [14]. The findings of these studies, however, do not imply that the estimation of dose is unimportant. A dose-response relationship is likely at lower treatment intensities (that is, less than 20 mL/kg per hour), and a significant minority of patients still receive treatment intensities less than this [11,12]. Given the likelihood of a dose-response relationship somewhere below 20 mL/kg per hour, delivery of doses lower than this should be avoided [22]. To ensure outcomes similar to those seen in the ATN and RENAL trials, clinicians should also prescribe CRRT on the basis of patient body weight to the established effluent flow rate target of 20 to 25 mL/kg of body weight per hour.

Abbreviations

AKI, acute kidney injury; ATN, Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network; CRRT, continuous renal replacement therapy; CVVHDF, continuous veno-venous hemodiafiltration; CVVHF, continuous veno-venous hemofiltration; DO-RE-MI, Dose Response Multicentre International collaborative initiative; eKt/V, equilibrated Kt/V; GFR, glomerular filtration rate; HD, hemodialysis; HF, hemofiltration; ICU, intensive care unit; IHD, intermittent hemodialysis; MC-RCT, multi-center randomized controlled trial; PD, peritoneal dialysis; RENAL, Randomized Evaluation of Normal versus Augmented Level; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment.

Competing interests

RB was lead author of the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study and has received consulting fees from Gambro (Stockholm, Sweden), Biosite (San Diego, CA, USA), Abbott Diagnostics (Abbott Park, IL, USA), and Philips Medical Systems (Andover, MA, USA) and grant support from Fresenius Kabi (Bad Homburg, Germany), Bard (Covington, GA, USA), Pfizer Inc (New York, NY, USA), and Gambro. JRP and AS declare that they have no competing interests.

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