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REVIEW

Dose of continuous renal replacement therapy for acute kidney injury in critically ill patients

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Abstract

Continuous renal replacement therapy (CRRT) is commonly used for critically ill patients with acute kidney injury (AKI). Despite two decades of clinical research, the optimal CRRT dose remains uncertain. Early studies suggested benefits of high-intensity therapy; however, subsequent multicentre randomised clinical trials (RCTs) have demonstrated no survival advantage of effluent rates above 25 mL/kg/h, thereby establishing the current "standard dose" of 20–25 mL/kg/h recommended by guidelines. This narrative review synthesises current knowledge on the concept of CRRT dose, including physiologic principles of solute control, historical evolution of dosing strategies, distinctions between prescribed and delivered dose, and the potential adverse consequences of excessive clearance. Although standard dosing is based on achieving small-solute clearance, clinical practice varies widely, with some intensive care units (ICUs) delivering substantially lower doses, *i.e.*, 13–16 mL/kg/h, without apparent harm. Excessive clearance increases the risk of hypophosphatemia, nutrient loss, altered drug exposure, and potentially delayed renal recovery, which are collectively described as dialytrauma. Experimental and clinical observations have renewed interest in permissive azotaemia, proposing that moderate urea levels may facilitate renal repair. In parallel, real-world data have revealed significant global heterogeneity and have suggested that the minimum effective dose may be lower than traditionally assumed. Three ongoing RCTs are evaluating whether lower-intensity regimens are feasible, safe, and beneficial. Accordingly, the debate has shifted from "high *vs.* standard" to "standard *vs.* low". The results of the ongoing clinical trials will likely redefine optimal CRRT dosing and inform future international guidelines and clinical practice.

Keywords

Acute kidney injury; Renal replacement therapy; Dialysis dose; Dialytrauma; Kidney recovery; Permissive azotaemia

1. Introduction

Acute kidney injury (AKI) is a common complication in critically ill patients, occurring in 40%–57% of intensive care unit (ICU) admissions [1–4]. Severe AKI often requires renal replacement therapy (RRT), and approximately 9%–13% of ICU patients require RRT support [1–3]. Severe AKI requiring RRT carries as high mortality as 40%–50%, and survivors are at risk for progression to chronic kidney disease [5]. Continuous renal replacement therapy (CRRT) offers better hemodynamic stability, more intense fluid management, and steady acid-base control than intermittent dialysis by providing slow, continuous solute and fluid removal. Given these advantages, CRRT is widely utilised as an essential supportive therapy for ICU patients when conservative measures fail.

This review focuses on CRRT dose in the context of renal indications for AKI and does not address extrarenal applications of CRRT, such as cytokine adsorption or toxin removal.

1.1 The concept of "dose" in CRRT

CRRT prescription determines the intensity or "dose" of the therapy required for adequate solute clearance. In the context of CRRT, the dose is defined by the effluent flow rate (usually normalised to the patient's body weight in mL/kg/h), which serves as a surrogate for solute clearance. This effluent comprises the sum of the dialysate outflow, replacement fluids, and any net ultrafiltration (fluid removal) volume. A higher effluent rate generally increases the clearance of waste solutes like urea and creatinine. However, the optimal CRRT dose remains controversial. Underdialysis might lead to inadequate metabolic control, whereas excessive dialysis could theoretically cause harm by removing beneficial solutes or inducing hemodynamic instability; a concept sometimes referred to as "dialytrauma" or CRRT-associated trauma [6]. Over the past two decades, the question of how much CRRT dose is necessary and safe has evolved from a "more is better"

philosophy to a recognition that more is not always better [7, 8], and that aggressive treatment may impede renal recovery [9]. There is now a growing interest in a strategy for permissive azotemia [10], where a lower intensity of RRT is tolerated, allowing blood urea nitrogen to rise to moderate levels, with the expectation of intrinsic renal recovery.

1.2 Current guidelines and variability

Based on evidence from landmark trials that will be discussed below, the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 AKI guidelines [11] recommend an effluent dose of 20–25 mL/kg/h for CRRT. This target ensures adequate solute clearance while avoiding the risks and costs of overly intensive therapies. In clinical practice, a prescription of 25 mL/kg/h is usually chosen to achieve a delivered dose of 20 mL/kg/h, accounting for therapy interruptions (downtime) [12, 13]. Nonetheless, global practice varies widely [14]. Observational data revealed that typical CRRT doses in western ICUs cluster around 15–25 mL/kg/h [15], whereas in some regions, such as Japan, the average prescribed dose is much lower, around 10–15 mL/kg/h [16], limiting practical dose to about half the western average. Importantly, observational outcomes in Japan have shown comparative survival with these lower-intensity regimens, raising the question of whether the widely recognised "standard" dose [17] may itself be higher than necessary for many patients.

1.3 Aim of this review

Here we provide a narrative review of CRRT dosing in critically ill patients with AKI, focusing on the scientific rationale, evolution of dosing strategies, key evidence from clinical studies, real-world practice patterns, and implications for patient outcomes. We elaborate on the recent literature, including early observational studies and the latest trials. The literature was identified through targeted searches of major databases, including PubMed and Clinicaltrials.gov covering studies published up to October 2025. Study selection was guided by clinical and contextual relevance, rather than by formal systematic review. We highlight how the field is shifting from the debate of "high *vs.* standard" dose [17] towards a new question: "standard *vs.* low" dose: how low can we go without compromising efficacy? The results of ongoing randomised clinical trials (RCTs) are eagerly awaited and have the potential to reshape clinical practice in the coming years.

2. Definition and measurement of CRRT dose

In CRRT, the dose is most commonly quantified using the effluent flow rate, which is expressed as mL/kg/h of the effluent volume removed from the circuit. This effluent comprises all fluid exiting the CRRT filter, namely, the spent dialysate in continuous venovenous haemodialysis (CVVHD), replacement fluid plus ultrafiltration in continuous venovenous haemofiltration (CVVH), or a combination thereof in hemodiafiltration (CVVHDF). Effluent flow is a convenient single metric because, under steady-state conditions, it approximates the clearance of small, water-soluble toxins, such as urea, by the system. For example, an effluent dose of 25 mL/kg/h approximately correlates with a urea clearance that would achieve a Kt/V of 1.0 per day [18], where Kt/V is the dialysis dose index used in chronic dialysis. It is unclear whether this extrapolation of CKD practice, *i.e.*, 25 mL/kg/h, is beneficial for patients with AKI in the ICU [18]. It should also be noted that the effluent volume is a surrogate for solute clearance and assumes a near-complete equilibration of solute concentrations between the blood and dialysate or replacement fluid. In practice, factors such as membrane efficiency and saturation can cause small deviations [12], but effluent volume remains the standard index for CRRT dosing in clinical protocols.

2.1 Prescribed *vs.* delivered dose

An important distinction exists between the prescribed effluent rate and the actual dose delivered to the patient. Interruptions in CRRT due to filter clotting, circuit changes, diagnostic procedures, or other ICU interventions can significantly reduce the delivered dose relative to the prescribed dose. Studies have indicated that the delivered CRRT dose is typically only 75%–90% of the prescribed dose, meaning that a prescription of 25 mL/kg/h might yield an actual clearance of 20 mL/kg/h [13, 19]. Pre-dilution haemofiltration by adding replacement fluid before the filter also affects delivered clearance because it dilutes the blood solute concentration, thereby lowering the extraction ratio. For example, in prefilter replacement mode, one may need to prescribe a slightly higher effluent rate to achieve the same solute clearance as that in a purely diffusive mode. To account for these factors, the guidelines recommend aiming for a higher end of the 20–25 mL/kg/h range in the prescription, thereby ensuring that the patient reliably receives at least 20 mL/kg/h.

2.2 What high-dose CRRT loses

High-dose or high-intensity CRRT clears more solutes, but may also lead to unintended consequences, such as electrolyte disturbances, including hypophosphatemia [7], loss of nutrients, or, more critically, removal of medications [20]. In a recent study by Roberts *et al.* [20], meropenem and piperacillin/tazobactam dosing regimens were developed and validated using data from 179 patients in 12 countries who underwent RRT in the ICU. The study reported that the meropenem and piperacillin/tazobactam doses required to achieve effective unbound concentrations for empirically treating key organisms were dependent on the RRT dose. They provided a nomogram for antibiotic regimens under various RRT settings and the presence of oliguria or anuria, in which CRRT doses were classified as 1.5 L/h, 2.5 L/h, 3.5 L/h [20]. They reported that the optimal antibiotic regimens differed according to the presence of oliguria, as the appropriate antibiotic regimens depended on urine output; thus, consideration of an adequate CRRT dose must be placed in context.

In addition, rapid reductions in plasma osmolarity during high-dose CRRT may precipitate neurological complications, particularly when severe hypernatremia or marked uraemia is corrected too rapidly. Such rapid osmotic shifts can increase the risk of cerebral oedema and neurological dysfunction,

underscoring the need for cautious control of solute and sodium removal when high doses are prescribed. Furthermore, high-dose CRRT generally requires higher blood flow rates, which may impose catheter-related and haemodynamic constraints and accentuate platelet decline.

Conversely, low-dose CRRT may be associated with an increased risk of circuit-related complications, including reduced filter life and challenges with anticoagulation, particularly when blood flow or anticoagulation strategies are constrained, as discussed later.

2.3 Methods of measuring dose

Experts from the Acute Disease Quality Initiative (ADQI) Consensus Group have proposed a dynamic prescription of CRRT, adjusting the CRRT dose to account for variability in solute control over clinical courses, using urea as a surrogate marker for solute control [21].

There is also interest in calculation formulas and models that use urea-based approaches to achieve a more precise dose assessment during CRRT [22]. However, these approaches are still being evaluated. For routine practice, clinicians should ensure that the delivered dose is monitored, and downtime is minimised to improve dose delivery [23]; for example, using an appropriate anticoagulation strategy to secure adequate filter life [24]. High-fidelity protocols and nursing training have been shown to reduce unplanned CRRT interruptions, thereby narrowing the gap between prescribed and delivered dose [25].

3. Historical evolution of CRRT dosing

As CRRT became more widespread in the 1990s and early 2000s, clinicians sought to identify an optimal therapeutic dose that would improve patient outcomes. Drawing on observations from chronic dialysis, in which higher urea clearance is associated with lower mortality in end-stage renal disease, higher-intensity CRRT was hypothesised to improve survival in AKI. Ronco *et al.* [26] conducted a landmark single-centre trial in 2000 to evaluate different CRRT doses. In the trial, 425 ICU patients with AKI were randomised to three effluent rates: 20 mL/kg/h, 35 mL/kg/h, or 45 mL/kg/h of continuous haemofiltration. The results showed a clear benefit of more intensive therapy: the mortality rate was 58% in the low-dose (20 mL/kg/h) group compared with 41% in the highest-dose group. The trial concluded that the effluent rate should be at least 35 mL/kg/h for critically ill patients [26]. Around the same time, smaller studies also suggested benefits of intensive RRT. Schiffl *et al.* [27] reported improved survival with daily versus alternate-day of intermittent haemodialysis in patients with acute renal failure. Extrapolating these findings, many centres in the early 2000s adopted high-volume haemofiltration protocols aimed at effluent rates in the 35–45 mL/kg/h range, particularly in the context of sepsis, based on the theory that aggressive clearance of inflammatory cytokines might improve outcomes.

3.1 No added benefit of high dose

The high-dose paradigm was soon challenged by larger multicentre RCTs with rigorous study designs. The Australian/New Zealand RENAL Trial [7] and the U.S. The Veterans Affairs/National Institutes of Health (VA/NIH) ATN Study [8] were pivotal in this regard. The ATN Study enrolled over 1100 ICU patients with AKI and compared an intensive RRT strategy, which included an effluent rate of 35 mL/kg/h for CRRT or daily intermittent haemodialysis, with a less-intensive strategy, which included an effluent rate of 20 mL/kg/h for CRRT or intermittent dialysis every other day [8]. At the 60-day follow-up, there was no difference in mortality between the intensive and less-intensive groups (53.6% *vs.* 51.5%) and no difference in renal function recovery [8]. Similarly, the RENAL trial randomised 1508 patients to receive CRRT at 40 mL/kg/h *vs.* 25 mL/kg/h [7]. Mortality at 90 days was similar (44.7% *vs.* 44.7%), and there were no differences in ICU length of stay or RRT dependence among survivors. The notable differences were observed in biochemical parameters; the intensive group experienced more episodes of hypophosphataemia (65.1% *vs.* 54.0%), indicating that higher clearance can result in the loss of essential solutes. These two high-quality trials provided strong evidence that escalating CRRT dose above 25 mL/kg/h yielded no survival benefit [7, 8]. In fact, these findings suggested a plateau of efficacy: once a threshold of adequate small-solute clearance is reached, further dose escalation does not improve outcomes. Prowle *et al.* [17] conceptualised this as a “dose–response” curve that flattens out in the 20–25 mL/kg/h range. Doses above this threshold may confer no added advantage and could even be detrimental by introducing more complications or resource burdens. Secondary analyses of the ATN trial reported that more intensive RRT was associated with a longer duration of mechanical ventilation [28], possibly related to excessive phosphate loss and a lower likelihood of renal recovery [29, 30].

3.2 High-volume hemofiltration in sepsis

In addition to general AKI, there has been interest in ultra-high CRRT doses for septic shock, commonly referred to as high-volume haemofiltration (HVHF), with effluent rates >60–100 mL/kg/h intended to remove inflammatory mediators. Early uncontrolled series reported haemodynamic improvements with HVHF in septic patients [31–33]; however, the IVOIRE trial comparing 70 mL/kg/h with 35 mL/kg/h in septic AKI found no improvement in 28-day mortality or organ function with the higher dose [34]. This finding further supports the hypothesis that more intense clearance does not lead to improved clinical outcomes in patients with AKI. By the mid-2010s, the focus had shifted away from high-dose therapy. International guidelines, including KDIGO 2012 [11], formally recommended against the use of effluent rates exceeding 25–30 mL/kg/h.

3.3 "Standard" dose (20–25 mL/kg/h) and new questions

As discussed above, two observations have sustained ongoing debate: (1) Actual delivered doses are often lower than intended owing to downtime, raising concern that some patients may be underdialysed even with “standard” prescriptions [11–13, 18]. (2) In some settings, substantially lower CRRT

doses (10–20 mL/kg/h) are routinely used without worse outcomes. Several observational studies have reported comparable survival in patients with AKI treated with approximately 15 mL/kg/h on average [15, 16]. These findings suggest that the minimum effective dose of CRRT may be lower than the currently accepted standard, at least in some populations, and that the dose-response curve may flatten out at a lower range (Fig. 1).

Given that intensive RRT may hypothetically remove factors that support patient recovery or impose stress on the kidney [10], one could legitimately ask: Have we been overdialysing some patients? This question gave rise to the biologically plausible hypothesis of permissive azotaemia, well-described by Maynar Moliner *et al*. [6], which proposes that tolerating higher urea levels might facilitate renal recovery by avoiding unnecessary "dialytrauma" to the patient. Accordingly, attention has shifted towards defining the lower limits of CRRT dosing that still ensure patient safety.

4. Physiological rationale and consequences of dose variation

The physiological rationale for increasing the effluent dose of CRRT is that the removal of solutes, such as urea and creatinine, becomes more efficient. However, this effect reaches a plateau because of diffusion limitations and membrane conditions [13]. Clearance of middle molecules, such as β_2-microglobulin and cytokines, relies primarily on convection and is theoretically determined by the membrane cutoff and pore size distribution [35].

While a higher effluent dose may result in faster toxin clearance and acid–base and electrolyte control [36], it may also increase the removal of useful solutes, including antibiotics, vitamins, and micronutrients [6]. Such losses can lead to nutritional and pharmacological imbalances [20], and may even delay renal recovery through excessive clearance, which was referred to as "dialytrauma" [6, 10].

The concept of permissive azotaemia originated from observations in an experimental study by Zager *et al*. [37]. Using a mouse model, they reported that post-ischaemic azotaemia acts as a brake, slowing the progression of post-ischaemic kidney injury [37]. They induced a stepwise azotaemia milieu using a unilateral ischaemic injury model by varying the duration of contralateral kidney ischaemia and observed a correlation between the degree of initial azotaemia and the preservation of the injured kidney mass 2 weeks later [37]. Under the most severe azotaemic conditions, the injured kidney size was better preserved than that observed in controls [37]. This preservation was attributed to an early reduction in proximal tubule cell dropout and subsequent maintenance of

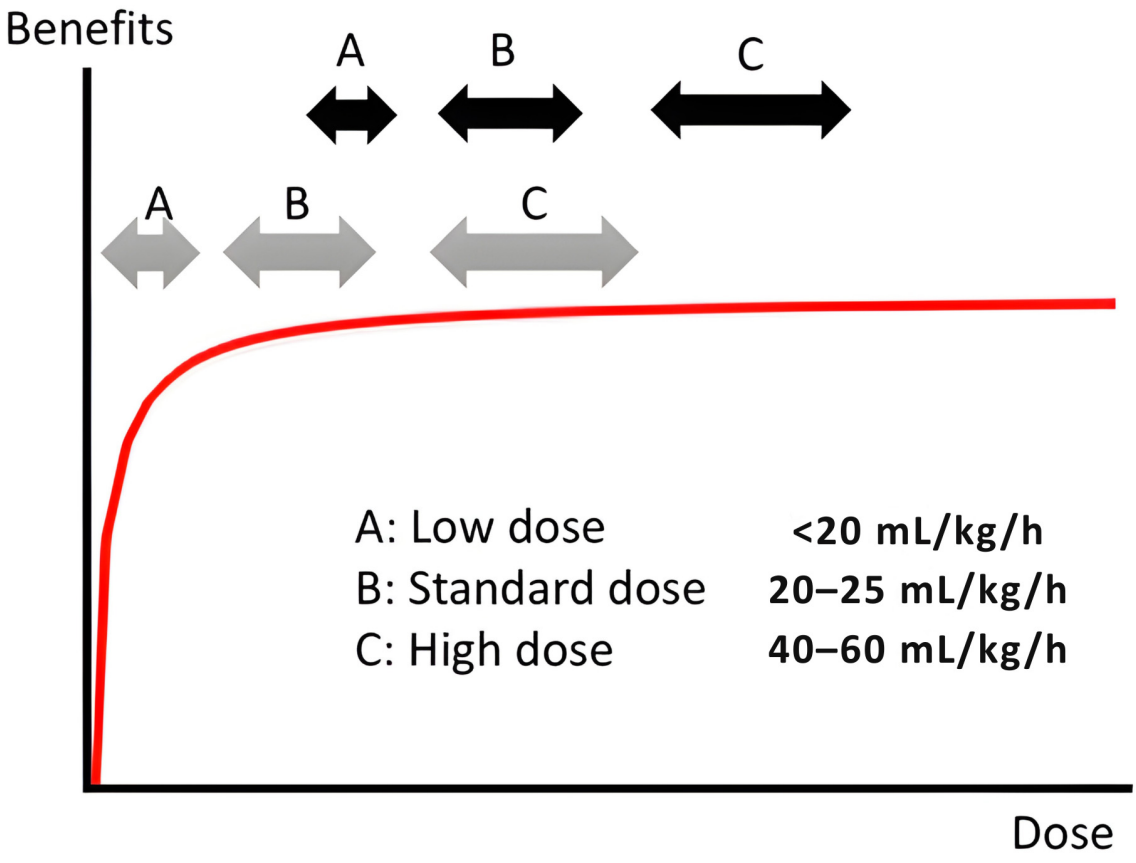

FIGURE 1. Hypothetical dose-response curve of CRRT dose and clinical benefit, assuming a population in which net clinical benefit approaches zero without CRRT. Large randomised clinical trials (RCTs) demonstrated no survival difference between the standard dose (B) and high dose (C), indicating that the inflection point at which dose begins to affect outcomes lies between zero and B. Based on past RCTs, the current clinical guidelines assume that the curve plateaus near the standard dose (grey arrows). However, whether this plateau occurs at a lower dose (A), as indicated by black arrows, remains unclear.

tubule mass through the observation of normalised N-acetyl-glucosaminidase content at 2 weeks [37]. These experimental findings supported the concept that acute uraemia confers early post-ischemic renal-cytoprotection and led to a concept of permissive azotaemia, which targets a blood urea nitrogen of 100–150 mg/L in prescribing RRT patients with AKI [28], but they have not established clinical benefits.

The Standard Versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial was a pivotal clinical trial addressing the timing of RRT initiation and provided insights into the potential benefits of permissive azotaemia [9]. The trial compared accelerated and standard initiation strategies. In the accelerated group, patients received RRT within 12 h at stage 2 or 3 AKI, whereas in the standard group, patients did not receive RRT unless any conventional indications developed or stage 3 AKI persisted for >72 h [9]. While the accelerated strategy did not reduce 90-day mortality compared with the standard strategy, RRT dependence at 90 days was significantly higher in the accelerated group than in the standard group (10.4% *vs.* 6.0%). This finding, although a secondary outcome of the trial, suggests that greater exposure to RRT and the resulting solute clearance may compromise kidney repair and the recovery of endogenous kidney function [9].

5. Evidence from observational studies

Large epidemiological studies have highlighted substantial practice variation in CRRT dosing across regions and institutions. The CRRTnet multicentre registry from North America collected data from more than 1100 ICU patients treated with CRRT between 2013 and 2021 [38]. While the primary focus of the study was epidemiological description, it documented heterogeneity in CRRT settings across sites. They reported a median CRRT dose of 31 mL/kg/h (interquartile range, 25.6–40; range across sites, 25.3–36.8) in the study ICUs. By contrast, the typical CRRT prescription in Japan is considerably lower. Several observational studies have indicated an average dose of 13–16 mL/kg/h in Japanese ICUs [15, 16], partly driven by traditional custom and a regional reimbursement cap that covers approximately 700–800 mL/h of effluent. Despite this, reported hospital mortality in Japanese cohorts ranges from 50% [39] to 58.6% [15, 16], which is comparable to that in North American cohorts (58.9%) [38]. Another observational data suggested that lower-intensity CRRT may be associated with a slower rate of biochemical correction of metabolic acidosis when effluent doses fell below 20 mL/kg/h [36]. However, the study did not demonstrate a corresponding deterioration in mortality, indicating that differences in the speed of acid-base correction do not necessarily translate into differences in patient-centred outcomes [36].

However, the other edge of the low-dose CRRT should be noted. A single-centre observational study of nearly 500 patients receiving CRRT reported that a dose below 13 mL/kg/h was associated with an increased risk of death compared with that exceeding 13 mL/kg/h [40], which might imply the lowest end of the optimal dose.

These observations raise two possibilities: either lower-intensity CRRT is sufficient for most patients and higher doses are unnecessarily wasteful, or patients in Japan had other favourable characteristics, such as, greater nephrologist involvement [41], that confounded the dose–outcome relationship. Regardless, the absence of a clear signal of harm in large cohorts receiving 13–16 mL/kg/h is thought-provoking and warrants further clinical investigation.

It should also be noted that the adequacy of the CRRT dose should be accompanied by careful consideration of the balance between metabolic acid generation and achievable clearance. In clinical scenarios characterised by extreme or rapidly escalating solute production, such as severe rhabdomyolysis or tumour lysis syndrome, higher-dose solute control may be required to maintain physiological stability even temporarily. Conceptually, lower doses may be most appropriate when the clinical priority is gradual metabolic support and/or fluid management and when biochemical control can be maintained with close monitoring as in the ICU. Provided that patients are closely monitored, slower biochemical correction with lower-intensity CRRT does not appear to adversely affect clinical outcomes.

Beyond dose alone, observational data have indicated that patient characteristics and indications for CRRT vary widely. In the North American CRRTnet study, sepsis was the leading precipitant of AKI (42.6%), and fluid overload or oliguria was the most common reason for initiating CRRT (56.2%) [38]. These contexts may influence the required dose; for instance, a patient initiated on CRRT primarily for fluid removal may not require very high solute clearance if metabolic waste levels are not critically high. In such scenarios, a lower effluent rate focusing on ultrafiltration may be sufficient. In contrast, hypercatabolic patients with severe rhabdomyolysis or tumour lysis syndrome may require higher clearance to control potassium and urea, thereby justifying a higher dose [42]. Real-world practice appears to reflect this tailoring to some extent: a secondary analysis of the multinational STARRT-AKI trial showed that average doses delivered in Australia and New Zealand, where CRRT was often used to achieve lower cumulative fluid balance, were lower than those delivered in Europe, albeit within a relatively narrow range (−5.22 mL/kg/h) [14].

From another perspective, a recent study using material flow analysis of the environmental footprint in the ICU reported that CRRT fluids were the largest contributor [43]. If clinically beneficial, low-dose CRRT could, therefore, substantially reduce the environmental footprint in the ICU while also lowering overall resource consumption.

6. Completed and ongoing clinical trials

As reviewed in Section 3, two large RCTs, the RENAL trial [7] and the ATN trial [8], conclusively demonstrated no survival benefit of high-intensity CRRT (35–40 mL/kg/h) compared with a standard 20–25 mL/kg/h dose. In patients with septic shock, the IVOIRE trial similarly found no benefits of HVHF (approximately 70–85 mL/kg/h) compared with 35 mL/kg/h [34]. These trials shifted clinical guidelines to endorse the lower approach as valid, and the question was considered settled: more is not better and may even be worse.

What remains unanswered is: how low should we go? None of the prior RCTs examined CRRT doses below 20 mL/kg/h, resulting in a lack of high quality evidence on outcomes associated with lower-dose CRRT. The observational studies evaluating low-dose CRRT are subject to biases from residual confounding, and also relatively modest in sample size, limiting power to detect small, but clinically meaningful, differences in outcomes. In addition, decisions regarding CRRT dose might be closely linked to clinical judgement and local practice patterns, both of which might have influenced outcomes. Furthermore, much of the evidence on low dose CRRT originated from Japan, where contextual factors may differ from those in other regions. The external validity, thus, warrants careful consideration (Table 1, Ref. [15, 16, 36, 40]).

Currently there are 3 ongoing RCTs [44–47] to fill this gap (Table 2, Ref. [44–47]). The KETZEREI trial is enrolling 150 patients requiring CRRT for AKI in ICUs in Europe and Brazil comparing a total effluent dose of 10–15 mL/kg/h intending to control azotaemia with a total effluent dose of 25–30 mL/kg/h [44, 45].

The LIMIT trial is a multicentre RCT conducted in Japan that compares low-intensity solute control using 12 mL/kg/h of dialysate and/or replacement fluid with a standard dose of 25 mL/kg/h [46]. The WISDOM trial is a multicentre pilot feasibility trial conducted in Canada [47], designed to evaluate the feasibility of delivering low-dose CRRT compared with standard-dose therapy [47]. The results of these trials are expected in the next several years. If low-dose CRRT is proven feasible and beneficial, or even if there is no apparent difference in the clinical outcomes and is proven to be feasible, the findings will likely prompt larger confirmatory trials assessing clinical benefits alongside economic and environmental impacts. Conversely, if these trials find that low-dose CRRT leads to worse outcomes, there results will validate current guidelines and suggest that we should avoid excessive dose reduction [44–47]. In either case, the findings are expected to refine the definition of "optimal" CRRT dose for the next generation of ICU protocols.

7. Considerations on regional citrate anticoagulation in dose reduction

Regional citrate anticoagulation (RCA) is recommended as first-line anticoagulation for CRRT because it reduces bleeding and prolongs filter life [11, 48]. However, as the effluent flow rate decreases, citrate clearance is reduced. Subsequently, metabolic disturbances and calcium imbalances may occur, particularly in patients with impaired citrate metabolism, such as those with liver failure or circulatory shock [49].

In RCA, the target is to keep ionised calcium (iCa) in the extracorporeal circuit between 0.25 and 0.35 mmol/L [50, 51]. To achieve this, the citrate infusion rate must be adjusted in proportion to the blood flow rate [50, 51]. Because citrate binds calcium and inhibits the coagulation cascade, the ratio between the blood flow rate and the citrate infusion rate directly determines the anticoagulant effect [50].

When the citrate infusion and blood flow rate are held constant, the effluent rate becomes a major determinant of citrate clearance and directly influences acid-base balance [51]. A reduction in the effluent rate decreases citrate removal, and hepatic metabolism of the retained citrate produces excess bicarbonate, potentially leading to metabolic alkalosis [51]. Residual citrate–calcium complexes may also increase the total calcium to ionised calcium ratio (total Ca/iCa >2.5) [52]. Conversely, in severely impaired citrate metabolism, such as severe liver failure or profound shock, unmetabolised citrate can accumulate and contribute to metabolic acidosis by increasing lactate and total Ca/iCa [52]. Increasing the effluent rate enhances citrate clearance and decreases net bicarbonate generation, shifting the acid-base balance towards mild metabolic acidosis. In most cases, these changes are modest and clinically manageable with adequate buffering capacity and close monitoring. Therefore, effluent rate adjustments should account not only for solute clearance, but also for metabolic safety when RCA is used. If the effluent rate must be lowered, the citrate infusion rate should be proportionally reduced or maintained to avoid citrate retention and excessive bicarbonate delivery.

The RICH trial demonstrated that RCA is safe and prolongs filter life compared with systemic heparin when CRRT is delivered at conventional effluent doses (typically 25–35 mL/kg/h) [48]. Although the study did not directly evaluate a dose–response relationship, it supports the metabolic safety of RCA within standard dosing practices. RCA should be considered not only as an anticoagulation strategy, but also as an integrated intervention encompassing anticoagulation, metabolic regulation, and solute removal. For safe implementation, it is important to maintain an appropriate balance among blood flow, effluent, and citrate infusion rates with continuous monitoring and adjustment.

8. Conclusions

Two decades of clinical research have substantially advanced our understanding of CRRT dosing for AKI. Two large RCTs, the RENAL and ATN trials, established that more intensive CRRT (>30 mL/kg/h) offers no survival benefit over standard dosing. This evidence has shaped the current paradigm: an effluent rate of 20–25 mL/kg/h is generally sufficient for patients with AKI in the ICU and routine escalation beyond this is unwarranted. International guidelines have adopted this ground as the standard of care, with an emphasis on monitoring the delivered dose to ensure adequacy.

More recently, there is an emerging question whether the standard dose may exceed what is necessary. Accumulating observational data have shown no obvious adverse effects at lower doses of approximately 15 mL/kg/h. The concept of "permissive azotaemia" has evolved from a hypothetical concept to a testable clinical strategy, driven by the idea that injured kidneys may benefit from a period of reduced solute removal to activate intrinsic repair pathways. Therefore, the results of ongoing RCTs are highly anticipated.

For the moment, we suggest the following bedside approach outside the clinical research context: ensuring that the patient receives sufficient therapy to control life-threatening complications of AKI, while not exceeding the standard dose of 25 mL/kg/h, as there is no demonstrated benefit in removing additional electrolytes and nutrients.

TABLE 1. Key studies informing low-dose CRRT in critically ill acute kidney injury.

Study (Year)	Region	Design	Sample size (N)	Dose definition and comparison	Primary outcomes (as reported)	Confounding control	Key conclusions
Fujii *et al.* [16] (2012)	Japan	2 centres, observational	131	Prescribed median dose 16 mL/kg/h (IQR 14–20) comparators defined as below *vs.* above median	Hospital mortality	Multivariable logistic regression	The first study reporting clinical outcomes of low-dose CRRT, supporting no obvious harm.
Uchino *et al.* [15] (2013)	Japan, multinational	Multicentre, observational	Japan, 343; multinational 1006	Prescribed median dose 14.3 mL/kg/h (Japan), 20.4 mL/kg/h (multinational); low dose defined as <20 mL/kg/h	ICU mortality	Multivariable logistic regression	Multicentre study supporting the above study.
Yagi *et al.* [36] (2024)	Japan	Single-centre, observational	194	Prescribed dose <20 mL/kg/h *vs.* ≥20 mL/kg/h	Acid–base control	Inverse probability of treatment weighting	Lower intensity may slow acid-base correction, but without worsening clinical outcomes.
Okamoto *et al.* [40] (2024)	Japan	Single-centre, observational	494	Prescribed median dose 13.2 mL/kg/h; comparators defined as below *vs.* above median	90-day mortality	Multivariable Cox regression	13–16 mL/kg/h appeared acceptable, going below 13 mL/kg/h may be harmful in at least some settings.

ICU, intensive care unit; CRRT, Continuous renal replacement therapy; IQR, interquartile range.

TABLE 2. Trials investigating the effect of low dose versus standard dose CRRT.

Trial	KETZEREI trial [44, 45] NCT06021288	LIMIT trial [46] NCT06014801	WISDOM trial (pilot) [47] NCT06446739
Inclusion criteria	Critically ill patients with AKI requiring CRRT	Critically ill patients with AKI requiring CRRT	Critically ill patients with AKI requiring CRRT (≥48 h)
Key exclusion criteria	ESRD CKD G4 pH <7.2 at screening K >6.0 mmol/L	ESRD Received RRT within 48 hours Need for citrate RRT	ESRD Receipt of RRT for AKI during the current hospitalisation
Intervention 1	Total effluent of 10–15 mL/kg/h	Dialysate + replacement fluid = 12 mL/kg/h	Total effluent of 10–15 mL/kg/h
Intervention 2	Total effluent of 25–30 mL/kg/h	Dialysate + replacement fluid = 25 mL/kg/h	Total effluent of 25–30 mL/kg/h
Primary Outcome	Number of days alive and free from CRRT up to 28 days	Composite of death and duration of RRT at 28 days	Difference in delivered CRRT dose-intensity
Target sample size	165	400	100

AKI, Acute kidney injury; CKD, Chronic kidney disease; CRRT, Continuous renal replacement therapy; ESRD, End-stage renal disease; K, Potassium; RRT, Renal replacement therapy.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

NL and TF—conceived the structure and contents of the manuscript. SN—drafted the manuscript. NL—provided critical inputs to the draft. TF—supervised writing and revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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