

Continuous renal replacement therapy: recent advances and future research

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Abstract | Continuous renal replacement therapy (CRRT) is the preferred treatment for acute kidney injury (AKI) in intensive care units (ICUs) throughout much of the developed world. Despite its widespread use, however, no formal proof exists that patient outcomes are improved when CRRT is used in preference to intermittent hemodialysis (IHD). In addition, controversy and center-specific practice variation in the clinical application of CRRT continues, owing to a lack of randomized multicenter studies of both CRRT and IHD providing level 1 data to inform clinical practice. Now, however, the publication of results from 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 (RENAL) trial have provided an unparalleled quantity of information to guide clinicians. These pivotal trials investigated different intensities of CRRT in the ICU and provided level 1 evidence that effluent flow rates >25 ml/kg per hour do not improve outcomes in patients in the ICU. In this Review, we discuss the background and results of the ATN and RENAL trials and the emerging consensus that CRRT is the most appropriate treatment for AKI in vasopressor-dependent patients in the ICU. Finally, we describe the remaining controversies regarding the use of CRRT and the questions that remain to be answered.

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Introduction

Methods of extracorporeal renal replacement therapy (RRT) have been used for the supportive treatment of acute kidney injury (AKI) for over 60 years.¹ In the intervening period, much of the treatment of AKI has moved from the renal ward into intensive care units (ICUs)² and treatment methodologies have become increasingly sophisticated. The basic principles guiding the use of RRT, however, have changed very little. Supportive treatment of AKI has traditionally been aimed at averting the immediately life-threatening consequences of severe renal dysfunction—acidosis, electrolyte imbalances, uremia, and fluid overload—to preserve life and allow organ recovery to occur. This ‘bare minimum’ concept of RRT places little emphasis on the optimal quality, quantity and timing of treatment. Unsurprisingly, therefore, variations in techniques and the clinical application of acute RRT persist despite the progressive improvements in treatment options. Over time, these improvements enabled effective renal support for sicker patients and culminated in the introduction of continuous renal replacement therapy (CRRT) into ICUs in the early 1980s.³

CRRT technology

Although the first CRRT treatments were performed using circuits driven by arterial blood pressure, it is in the

form of roller-pumped, venovenous therapy that CRRT became a mature technology.³ CRRT originated—and remains widely practiced—in the form of continuous hemofiltration,⁴ in which solute clearance occurs by convection alone and ultrafiltration in excess of fluid balance requirements is replaced with a physiologically balanced replacement solution. This solution may be infused before or after the hemofilter (pre-dilution or post-dilution, respectively), with the former method enhancing circuit lifespan at the expense of some decrease in clearance.⁵ In addition, a slow countercurrent flow of dialysate can be incorporated into the hemofiltration circuit to increase the clearance of small molecules, resulting in hemodiafiltration.⁶ CRRT in the form of continuous venovenous hemodialysis is also used.⁷ Theoretically, most solute clearance with continuous hemodialysis occurs by diffusion. However, when modern high-flux membranes are used, considerable backfiltration of dialysate (effectively a form of hidden hemofiltration) occurs during treatment, so that in practice this therapy performs similarly to hemodiafiltration in terms of small and middle-sized solute removal.⁸ Although the different CRRT options enable clinical flexibility, they also contribute to variation in clinical practice and can compromise the generalization of research recommendations.

CRRT and alternatives in clinical practice

During CRRT, alterations in fluid balance, electrolyte levels, acid–base balance and solute concentrations happen gradually, with equilibrium occurring between plasma and body compartments.⁹ As a continuous

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Competing interests

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Key points

- Continuous renal replacement therapy (CRRT) is now the leading form of renal replacement therapy for acute kidney injury (AKI) in intensive care units (ICUs) worldwide
- Practice variation in the application of CRRT remains considerable owing to the absence of clear evidence-based guidelines
- Two large, multicenter, randomized controlled trials have now established that increasing the dose of CRRT above an effluent flow rate of 25 ml/kg per hour is not beneficial
- CRRT is now widely accepted as the most appropriate therapy for vasopressor-dependent patients who require renal replacement therapy for AKI in the ICU
- A number of aspects of CRRT require further research, particularly the optimal threshold and timing of CRRT
- Factors such as local experience and cost will probably continue to determine choice of therapy in different regions

Box 1 | Perceived advantages of CRRT over IHD in critical illness

- Allows adequate volume of nutrition without compromising fluid balance
- Decreased vasopressor requirements during fluid removal
- Increased hemodynamic stability
- Optimizes fluid balance in lung injury
- Continuous control of fluid balance

Abbreviations: CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis.

therapy, CRRT can be rapidly tailored to changes in a patient's clinical condition during critical illness. Thus, in comparison to intermittent hemodialysis (IHD), CRRT is advocated as being more likely to promote hemodynamic stability and less likely to cause abrupt changes in plasma biochemistry. Consequently, CRRT is believed to permit better control of fluid balance¹⁰ (Box 1). These perceived advantages have contributed to the widespread uptake of CRRT as the first-choice RRT in ICUs throughout Australia,¹¹ Japan and Europe.¹² In these regions, CRRT is usually initiated, prescribed and managed within the ICU, with RRT being integrated with other aspects of the management of critical illness. In North America, however, traditional structures of ICU management favor an 'open-ICU' approach.¹³ Within this model, RRT is usually prescribed by a nephrologist in the ICU and is initiated by a dialysis nurse.^{14–16} In this environment, IHD has the advantage of requiring only daily or alternate-day attendance by the renal team. Conversely, the relative labor costs of providing CRRT are increased, an effect that is compounded by the larger fixed costs and higher consumable requirements of CRRT. These logistic factors have led to a preference for IHD over CRRT being maintained in ICUs that use the North American model,^{15,16} a stance further justified by the lack of compelling evidence from controlled trials in favor of CRRT.

Practice variation in the application of CRRT and recurrent controversies concerning its optimal intensity may account for the failure of attempts to substantiate the putative superiority of continuous therapy. Two large multicenter, randomized controlled trials, the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network (ATN) study¹⁷ and the Randomized Evaluation

of Normal versus Augmented Level Replacement Therapy (RENAL) trial,¹⁸ have now, however, examined the use of RRT in the ICU and provided a more consistent set of clinical data with which to answer questions concerning the clinical application of CRRT. In this Review, we explain the background to these trials and discuss the quality of the previously available evidence. We then examine the new data, discuss clinical recommendations that can now be made and describe important unresolved issues that require further research.

Clinical studies of CRRT in the ICU

The diversity of clinical approaches to the treatment of AKI in the ICU is illustrated by the results of the BEST Kidney study,¹² the only multinational epidemiological study of RRT practice in the ICU. The BEST Kidney study documented the treatment of AKI in 1,738 patients in 54 ICUs on five continents. CRRT was the most common choice of initial RRT treatment, with 80% of patients on CRRT;¹² IHD use was mostly restricted to ICUs in North and South America, where it was used as initial therapy in 30–40% of patients, while, by contrast, CRRT is used first in 100% of ICUs in Australia.¹⁹ Among patients receiving CRRT, however, marked variation in the modality, intensity, timing and threshold of use was observed,^{20,21} making it difficult to compare outcomes between patients on CRRT and those on IHD.

CRRT versus IHD

Comparisons between CRRT and IHD in observational studies are liable to be confounded by differences in underlying illness severity, as CRRT is often employed in sicker patients and is thus associated with poorer outcomes.¹² An analysis of 1,218 patients from the BEST Kidney study²² showed that patients who were first treated with CRRT had a significantly greater degree of organ failure and a higher risk of hospital mortality than patients initially treated with IHD. However, after multivariate statistical adjustment for illness severity, RRT modality did not predict hospital survival. In addition, RRT modality did not predict survival in a study of 2,642 Swedish patients receiving RRT in the ICU,²³ where baseline characteristics were similar in intermittent and continuous therapy groups. In both the Swedish study and the BEST Kidney study, however, only a minority (approximately 20%) of patients were treated with IHD.

A number of randomized controlled trials have compared the use of CRRT with the use of IHD for the treatment of AKI in the ICU^{24–30} (Table 1). Collectively, these studies failed to demonstrate improved survival or renal recovery with the use of CRRT. These studies were, however, relatively small and considerable variation was present in treatment methodology and patient selection; only two of the studies included more than 300 patients and were prospective, randomized, and multicenter in design.^{29,30} In the first of these studies, the Hemodiafiltration study, which took place in 21 French ICUs,²⁹ investigators randomized 360 patients with multiorgan failure including AKI to alternate-day IHD or continuous venovenous hemodiafiltration (CVVHDF). No differences in

Table 1 | Randomized trials comparing CRRT with IHD in the ICU

Study	Type	n	Comparison	Mortality*	Renal recovery†	Comment
Lins <i>et al.</i> (2009) ³⁰	Multicenter RCT	316	CVVHF vs IHD	58% vs 63% (P=ns)	35% vs 29% (P=ns)	Some hemodynamically unstable patients excluded
Vinonneau <i>et al.</i> (2006) ²⁹	Multicenter RCT	359	CVVHDF vs IHD	32% vs 33% at day 60 (P=ns)	63% vs 60% (P=ns)	Change in relative survival during time-course of study
Uehlinger <i>et al.</i> (2005) ²⁸	Single-center RCT	125	CVVHDF vs IHD	47% vs 51% (P=ns)	50% vs 42% (P=ns)	Study terminated early
Augustine <i>et al.</i> (2004) ²⁷	Single-center RCT	80	CVVHD vs IHD	68% vs 70% (P=ns)	13% vs 10% (P=ns)	—
Kielstein <i>et al.</i> (2004) ²⁵	Single-center RCT	39	CVVHF vs extended daily dialysis	40% vs 40% (P=ns)	Not reported	Survival was not the primary outcome
Mehta <i>et al.</i> (2001) ²⁴	Multicenter RCT	166	CVVHDF vs IHD	66% vs 48% (P=0.02)	30% vs 48% (P=ns)	Unbalanced randomization favoring IHD
John <i>et al.</i> (2001) ²⁵	Single-center RCT	30	CVVHF vs IHD	70% vs 70% (P=ns)	Not reported	Survival was not the primary outcome

Only prospective randomized controlled trials published in peer-reviewed journals in English are included. *In-hospital mortality unless stated otherwise. †Percentage alive and off renal replacement therapy at hospital discharge. Abbreviations: CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; CVVHF, continuous venovenous hemofiltration; IHD, intermittent hemodialysis; ns, nonsignificant ($P>0.05$); RCT, randomized controlled trial.

survival, duration of RRT or length of stay in the ICU or in hospital were observed between groups. However, the results of the study did cause some concern because survival rates improved significantly over time in the IHD group (relative risk of death 0.67 per year; $P<0.0001$). This finding suggested that outcomes were affected by modulations in clinician behavior concerning factors external to the study protocol. In the other study,³⁰ 316 patients with AKI admitted to nine Belgian ICUs were stratified according to their illness severity and patients in each stratum were randomly assigned to daily IHD or continuous venovenous hemofiltration (CVVHF). RRT modality did not affect survival rates, renal recovery or duration of ICU or hospital stay. However, 124 patients from the eligible population were excluded from the trial for medical reasons, including hemodynamic instability, which were deemed incompatible with the use of IHD. This study feature limits the generalization of the results to unselected patients with AKI in the ICU.

Meta-analyses of trial and observational data comparing CRRT and IHD in the ICU^{31–33} have also found insufficient evidence to favor one modality of therapy over the other. Given this lack of evidence, some researchers have suggested that CRRT is not cost effective in comparison to IHD;^{32,34} however, relative costs may be context specific.³⁵ Conversely, other researchers remain convinced of the clinical superiority of CRRT,⁶ despite the lack of formal evidence. They argue that CRRT is the most appropriate treatment for AKI in the ICU as such a strategy matches the uninterrupted management of other types of organ failure (for example, vasopressor therapy for circulatory failure or mechanical ventilation for respiratory failure). As sepsis is responsible for >50% of cases of AKI in the ICU, AKI will frequently occur in the context of multiorgan dysfunction. Approximately 70% of patients in the BEST Kidney study¹² received vasopressors and about 75% received mechanical ventilation; therefore, concerns about the selection of a form of RRT appropriate for unstable patients with multiorgan

failure would apply to the majority of patients with AKI in the ICU. In particular, CRRT can aid the management of fluid balance.³⁶ Use of IHD for the treatment of AKI in the ICU has been associated with progressively more positive fluid balances whereas use of CRRT enables net fluid removal.³⁷ Positive fluid balances have, in turn, been associated with adverse outcomes in critically ill patients with AKI^{37,38} and, more generally, with worse postoperative outcomes^{39,40} and with worse outcomes in patients with acute lung injury.⁴¹ However, removal of the volume of ultrafiltrate required to maintain a net neutral fluid balance in the ICU during short sessions of IHD can precipitate intradialytic hypotension.⁴² This intradialytic hypotension has, in turn, been associated with an increased risk of recurrent renal injury and nonrecovery of renal function.^{43,44} Conversely, initial treatment with CRRT has been associated with higher rates of renal recovery than initial treatment with IHD in critically ill individuals, independent of any associations with survival.^{22–24,45} Thus, like many ICU technologies, outcomes of RRT may be more dependant on the way in which therapy is administered rather than on the treatment itself. In addition, many beneficial effects of therapy, including clinically important and patient-centered outcomes such as renal recovery, might not be well demonstrated in studies that are primarily aimed at examining patient survival. Similarly, disadvantages of IHD in patients with hemodynamic instability can be offset by therapy modifications such as increased dialysis time and use of high-sodium and low-temperature dialysate, as adopted in the Hemodiafe study.²⁹ Unless trials are designed with these aspects in mind, they may be less likely to demonstrate any associated advantages or disadvantages of CRRT and IHD.

Timing of CRRT

In the BEST Kidney study, median time from ICU admission to commencement of RRT was 5 days and the interquartile range (IQR) was large (1–12 days).²⁰ Similarly,

the spread of urea concentrations at commencement of RRT was wide (IQR 15.4–34.9 mmol/l).²⁰ The timing of RRT can be defined with respect to time from ICU admission or with respect to the severity of biochemical renal dysfunction at commencement of RRT (including fulfillment of biochemical consensus criteria for AKI⁴⁶). Observational studies have found that both increased serum urea level^{47,48} and higher RIFLE classification of AKI⁴⁹ at commencement of RRT are associated with increased ICU mortality. Other investigators have reported, however, that increased serum creatinine level before RRT is associated with improved survival,²⁰ possibly as higher serum creatinine concentrations are associated with greater muscle mass and are thus indicative of a better premorbid condition. Biochemical indices of AKI are very imprecise and are significantly confounded by illness severity;⁵⁰ complex interactions between acute and chronic illness and clinical decision-making may also explain these conflicting results.

Observational data show that late initiation of RRT with respect to ICU admission is consistently associated with an increased risk of mortality, longer duration of RRT, longer hospital stay and greater dialysis dependence.^{20,51,52} To what extent these findings are related to the timing of the intervention, or to the timing of AKI with respect to ICU admission, remains undetermined. Only one small, single-center, randomized study has prospectively evaluated the issue of CRRT timing.⁵³ In this study, early therapy was commenced on the basis of oliguria and a low creatinine clearance, whereas late therapy was triggered by traditional indications for RRT. No benefits from early therapy were found.

Observational studies investigating the effects of delay in CRRT initiation from ICU admission are open to bias. Early treatment can lead to the inclusion of patients whose renal function subsequently improves, thus avoiding eligibility for late CRRT. Such patients would be expected to have a better outcome irrespective of treatment or baseline characteristics. Conversely, some patients might die before meeting 'late criteria' for CRRT, but could be included in an early treatment group. These patients may negatively affect outcomes. Other patients may present to the ICU without AKI and, despite active treatment, develop AKI later in the course of their ICU stay, thus seeming to require late intervention but being at increased risk of mortality. This scenario would misleadingly convey the perception that late RRT was responsible for an increased risk of death. To avoid these confounders, future studies on the timing of CRRT could allocate treatment groups on the basis of predefined enrollment criteria and could analyze subsequent outcomes on an intention-to-treat basis. Although timing seems to be important, the issue of adequacy of RRT dose or intensity of treatment has received the greatest attention in clinical studies.

Dose or intensity of CRRT

The intensity or dose of RRT is conventionally compared using measures of urea clearance. Use of this marker has considerable limitations, however, particularly in patients with critical illness, as urea concentrations can be affected

by many external and internal factors including nutritional input, tissue catabolism, premorbid nutritional status, liver function and extracellular volume expansion.⁵⁴ Urea is itself relatively nontoxic and is conventionally regarded to be a surrogate for unspecified low-molecular-weight uremic toxins. Furthermore, the clearance of metabolites with higher molecular weights can show little or no correlation with urea clearance. Nevertheless, in the absence of another convenient standard measure, urea clearance remains the established comparator of RRT dose. During CRRT, urea clearance is approximately equal to the CRRT effluent flow rate (combined dialysate and ultrafiltrate flow rates—after allowing for the effect of pre-dilution, if used). Thus, the dose of CRRT is reported as effluent flow in ml per hour or ml/kg body weight per hour (ml/kg per hour). Prescribed intensities of CRRT vary widely and in many cases are not adjusted to patient size. The IQRs for CRRT dose were large in both the BEST Kidney study (15.3–27.7 ml/kg per hour),²¹ and in a study by the DO-RE-MI study group (22.1–33.9 ml/kg per hour).⁵⁵ Such variations seemed worrisome given previous findings which suggested that CRRT intensities >35 ml/kg per hour are associated with better survival rates than a CRRT intensity of 20 ml/kg per hour.⁵⁶ Three subsequent small randomized controlled trials subsequently examined RRT dose–response relationships in the ICU. Results from one of these studies supported a beneficial effect of increased dialysis dose on patient survival;⁵⁷ the other two studies failed to demonstrate any beneficial effects of increased dialysis intensity on patient survival or renal recovery^{53,58} (Table 2). These trials were, however, relatively small and varied in geographical location, patient case-mix and mode of CRRT. The need for larger, multicenter, randomized controlled trials to determine the optimal intensity of CRRT in the ICU led to the initiation of the ATN and RENAL studies.

The ATN and RENAL trials

The ATN and RENAL studies were large, multicenter, randomized controlled trials that investigated the effects of RRT dose on patient outcomes. The ATN study was conducted in ICUs throughout the US and the RENAL study was conducted in ICUs in Australia and New Zealand (Table 3). Comparison of these studies is of particular interest given the almost universal use of CRRT in Australia and the continued popularity of IHD in ICUs in the US. It is important to recognize that these studies differed in methodology and patient characteristics and that any comments made from their comparison can only be regarded as inferential. However, we feel that as the trials enrolled comparable patient populations (all patients were critically ill, all had been admitted to an ICU, and mean APACHE scores were equivalent at randomization), the marked discrepancies in outcomes in the two trials demand examination, even if any conclusions might be seen as controversial.

Study characteristics and primary outcomes

The ATN study¹⁷ randomly assigned critically ill adults with AKI requiring RRT to high-intensity or low-intensity

Table 2 | Randomized controlled trials comparing CRRT dose in the ICU

Study	Type	n	Comparison	Mortality	Mortality end point	Comment
RENAL (2009) ¹⁸	Multicenter RCT	1,508	40 ml/kg per h vs 25 ml/kg per h post-dilution CVVHDF	45% vs 45% (<i>P</i> =ns)	Day 90	—
ATN (2008) ¹⁷	Multicenter RCT	1,124	Pre-dilution CVVHDF 35 ml/kg per h or SLEDD 6 times weekly or IHD 6 times weekly vs pre-dilution CVVHDF 20 ml/kg per h or SLEDD 3 times weekly or IHD 3 times weekly	54% vs 52% (<i>P</i> =ns)	Day 60	Choice of CRRT/SLEDD vs IHD based on daily cardiovascular SOFA score
Tolwani <i>et al.</i> (2008) ⁵⁸	Single-center RCT	200	Pre-dilution CVVHDF 20 ml/kg per h vs 35 ml/kg per h	56% vs 49% (<i>P</i> =ns)	ICU discharge or day 30	—
Saudan <i>et al.</i> (2006) ⁵⁷	Single-center RCT	204	CVVHF (1–2.5 l/h) vs CVVHDF (1–2.5 l/h HF + 1–1.5 l/h HD)	59% vs 39% (<i>P</i> =0.0005)	Day 28	Addition of HD to HF (as HDF) vs HF alone
Bouman <i>et al.</i> (2002) ⁵³	Two-center RCT	106	CVVHF 72–96 l per day early vs 24–36 l per day early vs 24–36 l per day late	26% vs 31% (<i>P</i> =ns) vs 25% (<i>P</i> =ns)	Day 30	Combined trial of dose and timing (early vs late)
Ronco <i>et al.</i> (2000) ⁵⁶	Single-center RCT	425	Post-dilution CVVHF 20 ml/kg per h vs 35 ml/kg per h vs 45 ml/kg per h	41% vs 57% vs 58% (<i>P</i> <0.002 for 20 ml/kg per h vs 35 ml/kg per h and 45 ml/kg per h and <i>P</i> =ns for 35 ml/kg per h vs 45 ml/kg per h)	Day 15	Unorthodox mortality outcome (day 15 post-CRRT)

Only prospective randomized controlled trials published in peer-reviewed journals in English are included. Abbreviations: CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenous hemodiafiltration; CVVHF, continuous venovenous hemofiltration; HD, hemodialysis; HDF, hemodiafiltration; HF, hemofiltration; IHD, intermittent hemodialysis; ns, nonsignificant (*P*>0.05); RCT, randomized controlled trial; SLEDD, slow extended-duration dialysis; SOFA, sequential organ failure assessment.

RRT. Within these groups, patients were then allocated to CRRT or IHD on the basis of cardiovascular stability: patients received CRRT when the cardiovascular component of their Sequential Organ Failure Assessment (SOFA) score was 3 or 4 and received IHD if their cardiovascular SOFA score was ≤ 2 . However, patients receiving CRRT only switched to IHD if their cardiovascular SOFA score was 0–1 for >24 h. A cardiovascular SOFA score of 3 or 4 indicates that a patient's blood pressure is supported by (increasingly greater) doses of vasopressor drugs.⁵⁹ As 54.7% of patients had a baseline cardiovascular SOFA score of 3 or 4, it would be expected that the same percentage of patients would receive CRRT as their first study RRT modality; however, CRRT was in fact provided to 69.7% of patients as their initial therapy.⁶⁰ Switching between modalities occurred at similar rates in high-intensity and low-intensity groups.⁶⁰ Among patients who survived to day 60, 84.2% received IHD at some stage during their ICU stay.⁶⁰

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.¹⁷ 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 times or three times weekly (in the high-intensity and low-intensity groups, respectively), in centers where CRRT was not available.¹⁷ Comparing the dialysis doses provided by intermittent RRT and CRRT is complex.⁶¹ In the ATN study, the higher intensity IHD produced mean pre-dialysis plasma urea levels similar to those in patients receiving low-intensity CRRT (16.1 mmol/l versus 16.8 mmol/l, respectively). Thus, if RRT dose is assessed by the monitoring of peak urea concentration,⁶¹ RRT doses received by patients assigned

to low-intensity CRRT and high-intensity IHD would be considered equivalent, despite assignment to different treatment groups. However, if dose is assessed by time-averaged urea concentration, doses of CRRT and IHD seem closely matched within high-intensity and low-intensity treatment groups.⁶⁰ Given the controversies in dose comparison between treatment modalities, the ATN trial might best be described as a test of maximization of intensity of RRT within current US practice, rather than a test of a quantifiable dose–response relationship.

In comparison, 1,508 critically ill adults meeting pre-determined criteria for the initiation of RRT in the RENAL study were randomly assigned to post-dilution CVVHDF with an effluent flow of either 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 (~7%) received IHD later in their ICU stay, a number similar to the proportion of patients who remained dependant on dialysis at day 90. The RENAL study thus constituted a more direct test of escalating intensity of CRRT.

Both the ATN and RENAL studies failed to detect any survival benefit from 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 patients requiring vasopressors. These results provide definitive evidence to recommend that escalation of CRRT intensity to beyond conventional doses of 25 ml/kg per hour is not beneficial for unselected ICU patients with AKI. Important differences between the ATN and RENAL studies should be highlighted (Table 3). Although these differences do not detract from the primary results, they do shed light on other aspects of RRT in the ICU.

Table 3 | Comparison of patient populations in VA/NIH ATN¹⁷ and RENAL¹⁸ studies

Characteristic	VA/NIH ATN study	RENAL study
<i>n</i>	1,124	1,508
Age (years)	59.7	64.5
Male (%)	70.6	64.6
Weight (kg)	84.1	80.7
CKD classification (%)*		
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	0 [¶]
Commenced on CRRT (%)	69.7	100
CRRT mode	Pre-dilution CVVHDF	Post-dilution CVVHDF
CRRT high-dose effluent target (ml/kg per h)	35	40
CRRT low-dose effluent target (ml/kg per h)	20	25
Time from ICU admission to first study RRT (days)	6.7	2.1
Urea concentration prior to first RRT (mmol/l)	23.8	24.2
Achieved dose with high-dose CRRT (ml/kg per h)	27.1 [§]	33.4
Achieved dose with low-dose CRRT (ml/kg per h)	17.5 [§]	22
Duration of study RRT in ICU (days)	13.1	6.1
Daily urea level on high-dose CRRT (mmol/l)	11.7	12.7
Daily urea level on low-dose CRRT (mmol/l)	16.8	15.9
Daily fluid balance on therapy (ml)	+130	–20
Mortality at day 60 (%)	52.5	NR
Mortality at day 90 (%)	NR	44.7
Survivors dependant on RRT at day 28 (%)	45.2	13.3
Survivors dependant on RRT at day 60 (%)	24.6	NR
Survivors dependant on RRT at day 90 (%)	NR	5.6

Values are mean values unless otherwise stated. *Where baseline renal function was not available, patients are assumed to have normal baseline renal function. [‡]Over a large population of patients, mean APACHE III score is approximately equivalent to four times the APACHE II score;⁷¹ thus, mean illness severity in the RENAL study (APACHE III: 102.4) is similar to that in the ATN study (APACHE II: 26.4). [§]Dose corrected for pre-dilution at median blood flow and replacement rates. ^{||}Only patients who had undergone <2 sessions of IHD or SLEDD or <24 h CRRT were included. [¶]Patients with prior RRT excluded. Abbreviations: CKD, chronic kidney disease; CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis; NR, not reported; RENAL, Randomized Evaluation of Normal versus Augmented Level Renal Replacement Therapy; RRT, renal replacement therapy; SLEDD, slow extended-duration dialysis; SOFA, sequential organ failure assessment; VA/NIH ATN, Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network.

Comparison of patient outcomes

Patients in the RENAL study were at lower risk of death than patients in the ATN trial (45% had died at 90 days in the RENAL study versus 53% at 60 days in the ATN study). In addition, patients in the RENAL study were over twice as likely to be alive and off dialysis at 28 days (54% versus 26%). These differences may well be accounted for by differences in case-mix and the lower

threshold for the initiation of RRT in the RENAL study,⁶² but are sufficient to suggest that a detailed examination of the findings is needed. Compared with patients in the ATN study, patients in the RENAL study had a somewhat lower incidence of sepsis and lower rates of mechanical ventilation, but were older and required more vasopressors. As mentioned previously, illness severity scores (APACHE II and APACHE III) in both studies were comparable. However, the ATN study excluded patients with a baseline serum creatinine level >174 μmol/l, whereas only the presence of end-stage renal disease excluded enrollment in the RENAL study. Thus, only the RENAL study included patients with stage 4 chronic kidney disease (CKD). Patients with pre-existing advanced CKD are more likely to develop AKI requiring RRT for less severe disease and are therefore at lower risk of mortality than patients who experience AKI with no prior history of CKD.⁶³ On the other hand, patients with pre-existing advanced CKD are at increased risk of dialysis dependence after AKI.^{22,63,64}

The RENAL study specified indications for commencement of RRT whereas the ATN study left the decision as to when to commence RRT—and thus study eligibility—to the physician. In the ATN study, therapy was also commenced much later in relation to ICU admission (median 6.7 days in the ATN study versus 2.1 days in the RENAL study). However, urea levels before first RRT treatment were similar in the ATN and RENAL studies, and >60% of patients in the ATN study had received some form of non-trial RRT in the 24 h prior to randomization and initiation of study treatment, whereas no patients in the RENAL study received pre-randomization RRT. Outcomes in the RENAL study may also have been artificially improved by the inclusion of a few patients whose renal function recovered rapidly and might have survived without RRT. On the other hand, the results might reflect a genuine advantage of a prompter initiation of RRT and increased use of continuous treatment. Further examination of these two studies offers some support for the wider use of CRRT.

Recovery of renal function

The most striking difference in outcomes between the RENAL and ATN studies is the rate of renal recovery. At 28 days, 45% of survivors in the ATN study were still dependant on RRT compared with only 13% of survivors in the RENAL study. Similarly, 25% of survivors in ATN remained on RRT at 60 days compared with only 6% in RENAL at 90 days, representing an almost fivefold difference in renal recovery. Disparities of this magnitude suggest that significant differences in factors causally related to recovery of renal function are likely to exist between the studies. Such differences may be in the patient populations, the treatments administered, or both. Again, the inclusion in the RENAL study of some patients with less severe underlying renal dysfunction, who might have escaped treatment if more conservative indications for RRT had been in place, might account for some of the observed differences in renal recovery between the studies. Against this idea, the recruitment of patients with more severe CKD in the RENAL study (Table 3) should have

impeded renal recovery in this study.^{62–64} Observational data have suggested that initial use of IHD is associated with poorer rates of renal recovery than initial use of CRRT for patients with AKI.^{21,23,45,65} This finding raises the possibility that factors associated with the use of IHD in the ATN study could account, in part, for the large differences in renal recovery observed between the studies.

Fluid balance and hypotension

Increasing evidence suggests that fluid overload might worsen patient and renal outcome in AKI.⁶⁶ In the RENAL trial, a median net fluid balance of -20 ml per day was achieved over the period of study treatment. In comparison, the median net fluid balance during the ATN trial was $+130$ ml per day over the first 14 days.⁶² To achieve this fluid balance using IHD, around 2 l of ultrafiltration was required per session, indicating that many patients experienced a considerable degree of pre-dialysis fluid accumulation. Additional treatments with isolated ultrafiltration were also required for fluid overload in a number of patients receiving less-intensive therapy in the ATN study (219 sessions in 561 patients) and 37% of intermittent hemodialysis sessions were complicated by hypotension.⁶² It is therefore possible that fluid accumulation and intradialytic hypotension associated with increased use of IHD might have contributed to the fact that renal outcomes were poorer in the ATN study than in the RENAL study. A meta-analysis of individual patient data⁶⁷ from ATN, RENAL and other trials comparing RRT doses in the ICU is now planned and may better explain the differences in outcomes observed. The meta-analysis will also address whether the different outcomes are related to earlier and broader use of CRRT in the RENAL study, IHD-associated hypotension in the ATN trial or the result of fluid balance differences between the two studies. Until the results from such an analysis or other prospective multicenter trials are undertaken, these ideas remain provocative, but hypothetical.

Future issues

Given the information that is now available regarding CRRT and IHD, what treatment recommendations can be made and what should future research priorities be?

CRRT versus IHD

The results of the RENAL study suggest that initial use of CRRT might be associated with greater recovery of independent renal function compared with use of IHD, but confirmation of this hypothesis in a prospective, multicenter, randomized controlled trial would be required for a strong recommendation for CRRT on this basis alone. Disadvantages of CRRT include its higher cost and the need for greater use of anticoagulation therapy with CRRT than with intermittent therapy. Despite a lack of formal evidence, however, in our opinion the clinical argument for use of CRRT in patients with hemodynamic instability does seem to be largely won. Although our preference for the use of CRRT in critical illness may be influenced by the fact that we practice in Australian and UK environments, even the ATN investigators in the US

did not feel that they had sufficient equipoise to assign hemodynamically unstable patients to IHD in their trial. This decision is an important point because it implies that, in a large group of Veterans Affairs and other academic hospitals in the US, clinicians felt that patients receiving vasopressor therapy should receive CRRT in preference to IHD. In the ATN trial, such patients formed the majority of individuals with AKI in the ICU. If facilities and training are required to provide CRRT for the majority of patients requiring RRT, the economic arguments against extending use of CRRT to other patients become less important. Although a large multicenter trial that directly compares use of IHD and CRRT is desirable, it is difficult to imagine a clinical environment where a suitably powered study could now occur, given the design of the ATN trial and the widespread use of CRRT in Europe and Australia. We feel, however, that a study comparing the combined use of CRRT in unstable patients and IHD in more stable patients (the ATN protocol) with universal use of CRRT (the RENAL protocol) is ethical, conceivable, and justifiable on the basis of available evidence.

Dose of CRRT

The ATN and RENAL studies have now established an upper limit of intensity for CRRT. In addition, they found no evidence to suggest that any specific subgroups would benefit from higher doses of RRT, refuting previous smaller studies.⁵⁶ This finding does not imply that the estimation of dose is unimportant. A dose–response relationship is likely at lower treatment intensities (that is, <20 ml/kg per hour). Notably, international surveys^{21,55} have reported that a considerable minority of patients receive treatment intensities <20 ml/kg per hour.^{21,55} Given the likelihood of a dose–response relationship at treatment intensities <20 ml/kg per hour, delivery of doses lower than this seems to be undesirable.⁶⁸ To ensure outcomes similar to those seen in the ATN and RENAL trials, clinicians should prescribe CRRT on the basis of patient body weight to the established effluent flow rate target of 20–25 ml/kg per hour. Equally importantly, both the ATN study and the RENAL study demonstrated that the prescribed dose is 10–15% less than the delivered dose in these patients, presumably owing to treatment downtime. Thus, if clinicians wish to avoid delivering a dose <20 ml/kg per hour, they need to make appropriate adjustments to their prescription.

Timing of CRRT

Studies investigating the timing of CRRT have been predominantly observational and have provided some evidence that earlier therapy has beneficial effects on outcomes. CRRT was commenced earlier after ICU admission in the RENAL study than in the ATN trial, even when accounting for the use of up to 24 h of pre-study RRT in the ATN study. Given the differences in overall outcome between these studies, further research in this area should be prioritized. The design of future studies needs to ensure that early and late treatment arms are well matched in terms of underlying AKI severity, an aim that could be accomplished through the use of the RIFLE consensus definition of AKI.⁴⁶ When appropriately validated,

Box 2 | Status of issues concerning RRT use in the ICU

CRRT dose

A resolved issue in favor of conventional dosing (target effluent flow rate 20–25 ml/kg per h)

CRRT versus IHD

Consensus in favor of CRRT in hemodynamically unstable critically ill patients, but without formal evidence

Timing of CRRT

Unresolved issue that requires further research

CRRT outcomes

Unresolved issue; studies to date may have been too focused on mortality over renal recovery and other patient-centered outcomes

CRRT modality

Unresolved issue—CRRT modalities might be equivalent

Abbreviations: CRRT, continuous renal replacement therapy; ICU, intensive care unit; IHD, intermittent hemodialysis.

biomarkers of renal tubular injury (such as elevation of urinary neutrophil gelatinase-associated lipocalin⁶⁹) might also be useful for identifying eligible patients with AKI, enabling early randomization between treatment protocols varying in indications for—or timing of—CRRT.

Modality of CRRT

Few prospective clinical data exist to support the use of convection-based CRRT (that is, hemofiltration) over hybrid or predominantly diffusive therapies (that is, CVVHDF or continuous hemodialysis). Although in theory convection leads to improved clearance of middle-sized molecules, in practice continuous high-flux hemodialysis can provide equivalent clearances.⁸ Notably, the RENAL study used post-dilution hemodiafiltration whereas the ATN study used pre-dilution hemofiltration, but the results of these trials provide no evidence to favor one modality over the other. The local experience of physicians and the availability of CRRT devices and replacement fluid currently drive practice variation around the world. At present, we believe that there is no

clinical evidence to advocate changes to local modality choice for standard indications for CRRT in the ICU.

Outcomes

Historically, AKI complicating critical illness has been associated with mortality in excess of 50%.⁷⁰ Although mortality risk has apparently altered little over time, contemporary patients are often far sicker and have a greater burden of pre-morbidity chronic illness than patients from historical reports.⁷⁰ Thus, over time, a decreasing proportion of the rate of death may be attributable to AKI, and demonstration of a survival benefit from an intervention that targets a single organ system could become more difficult. In the future, efforts to refine the provision of CRRT in the ICU may need to focus on renal end points, such as recovery of kidney function, to allow new techniques to be successfully evaluated in reasonably sized clinical trials.

Conclusions

Much practice variation continues to exist in the provision of CRRT in the ICU. Two large prospective, multicenter, randomized controlled trials have now addressed the appropriate intensity of CRRT, but many questions remain regarding the timing of therapy, the role of intermittent dialysis in the ICU and the effect of therapy choice on renal recovery (Box 2). Further examination of the results from these two studies may shed light on some of these issues and might guide the conception of future clinical trials. Devising prescriptive guidelines for the management of all aspects of this complex and costly therapy that are widely applicable to differing clinical environments worldwide is likely to remain difficult.

Review criteria

Studies were identified from the PubMed electronic reference database using combinations of the following search terms: “renal replacement therapy”, “hemofiltration”, “renal dialysis”, “critical care”, and “acute kidney failure.” The bibliographies of published articles and the personal records of the authors were also searched.

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Author contributions

J. R. Prowle wrote the article and both authors contributed equally to researching data for the article, discussing the content, and reviewing and/or editing the manuscript before submission.