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Continuous versus intermittent renal replacement therapy: a meta-analysis

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Abstract *Objective*: Patients with critical illness commonly develop acute renal failure requiring mechanical support in the form of either continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IRRT). As controversy exists regarding which modality should be used for most patients with critically illness, we sought to determine whether CRRT or IRRT is associated with better survival. *Design*: We performed a meta-analysis of all prior randomized and observational studies that compared CRRT with IRRT. Studies were identified through a MEDLINE search, the authors' files, bibliographies of review articles, abstracts and proceedings of scientific meetings. Studies were assessed for baseline characteristics, intervention, outcome and overall quality through blinded review. The primary endpoint was hospital mortality, assessed by cumulative relative risk (RR). *Measurements and results*: We identified 13 studies (n=1400), only three of which were randomized. Overall there was no difference in mortality (RR 0.93 (0.79–1.09), p=0.29). However, study quality was poor and only six studies compared groups of equal severity of illness at baseline (time of enrolment). Adjusting for study quality and severity of illness, mortality was lower in patients treated with CRRT (RR 0.72 (0.60–0.87), p<0.01). In the six studies with similar baseline severity, unadjusted mortality was also lower with CRRT (RR 0.48 (0.34 –0.69), p<0.0005). *Conclusions*: Current evidence is insufficient to draw strong conclusions regarding the mode of replacement therapy for acute renal failure in the critically ill. However, the life-saving potential with CRRT suggested in our secondary analyses warrants further investigation by a large, randomized trial.

Keywords Hemofiltration · Hemodialysis · Continuous renal replacement therapy · Acute renal failure · Intensive care unit · Meta-analysis

Introduction

Acute renal failure (ARF) develops in 10–23% of patients admitted to intensive care units (ICUs) [1, 2, 3], 70% of whom require renal replacement therapy to sustain life [4]. Even with therapy, ARF occurring in the setting of critical illness is associated with mortality rates of 50–90% [1, 2, 5]. In the ICU, renal replacement therapies are primarily limited to intermittent hemodialysis (IRRT) and continuous renal replacement therapy (CRRT). IRRT first came into widespread clinical use in the early 1960s and remained the only treatment option for many years. One problem with IRRT was that it could not be used in many patients with hemodynamic instability. This led to the development of CRRT, first described by Kramer et al. in 1977 [6]. CRRT was proposed as an alternative to IRRT in the critically ill because it was better tolerated by hypotensive patients and

the continuous regulation of fluid avoided cycles of volume overload and depletion.

However, despite these theoretical advantages, CRRT has not been widely adopted. Several studies have compared both modalities, but these studies have been described as providing conflicting results, being of poor quality and often of inadequate sample size [7]. Importantly, most studies have been observational in nature, often with significant differences in patient characteristics at enrolment (baseline) between treatment arms. Studies have also included patients who received both treatment modalities [8, 9], the particular mode of CRRT often varied and other aspects of the intervention, such as dialysis dose and choice of dialysis membrane, were often different across treatment arms. Co-interventions, such as nutritional support, also confounded some studies [10, 11, 12].

This lack of good evidence regarding benefit, coupled with concerns over increased costs associated with CRRT, has fueled an on-going controversy regarding the optimal way to manage ARF in the ICU, with significant variation in practice. In 1996, Mehta surveyed 2000 nephrologists in the US and found that less than 20% of patients with ARF were treated with CRRT [13]. Use of CRRT is much more common in Europe, although its use is highly variable between centers [14], while CRRT is the predominant choice in Australia [15].

There has been no large randomized trial to address formally the question of whether the choice of dialysis therapy affects outcome and, given the strong commitment by many clinicians to one modality or the other, such a study may prove difficult in the future. Accordingly, we wished to review the available evidence more critically. Specifically, we conducted a meta-analysis to determine what effect choice of renal replacement therapy (CRRT versus IRRT) had on hospital mortality in critically ill patients with ARF. Because of concerns over study quality, differences in baseline characteristics and distribution of co-interventions, we structured our analysis to adjust for these factors.

Materials and methods

Study identification and selection

Studies were identified through a MEDLINE search from 1977 to 1998, a review of abstracts and proceedings of national and international meetings, our files and bibliographies of review articles. Non-English language articles were included and translated prior to data abstraction. Studies were included if they compared some form of continuous therapy with IRRT and mortality rates for each group were available, either in the report or by contacting the authors.

Data abstraction and literature appraisal

Data were abstracted from each study regarding study methodology, population, interventions, co-interventions and outcome. Hospital mortality was the primary outcome measure. Data were also abstracted regarding ICU mortality, hospital and ICU length of stay, recovery of renal function and the costs of care.

A blinded review of methods and results was conducted by three investigators to assess study quality and baseline severity of illness (measured at study enrolment). The review instrument was developed using existing evidence-based review methodology [16, 17, 18, 19] and was expanded to include issues specific to ARF in the critically ill (e.g., potentially confounding variables such as dialysis dose and membrane). The instrument assessed quality across three domains (study enrolment, intervention and outcome), with each domain assessed by six to ten questions. The instrument was used to generate mean scores for each domain and to assess overall study quality (further details are provided in Appendix I).

In the review we included questions designed to address the extent to which information on baseline characteristics and study design suggested treatment arms were comparable. A score ranging from 1–5 was generated where "1" indicated that the groups were "definitely different", "3" indicated "uncertainty," and "5" indicated that the groups were "definitely equal". This assessment was made on the basis of baseline Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, organ failure, hypotension and need for mechanical ventilation. Missing data were sought by contacting the authors of individual studies. To score well on this index, a study had to provide detailed information on underlying severity of illness, and that information had to suggest groups were comparable. For the purposes of analysis, we defined studies with comparable treatment arms as those with mean scores of more than 3.0 (range: 1–5).

Dialysis dose, membrane classification and missing data

Previous reviews of the literature comparing CRRT and IRRT have pointed out that neither the amount of solute clearance (the "dialysis dose") nor the dialysis membranes has been standardized across treatment arms [8], and both have been suggested to affect outcome [8, 20]. Accordingly, data were abstracted on both dose and membranes. Dialysis dose was classified into two categories, standard dose (CRRT ≤1 l/h and IRRT ≤20 h/week) and high dose (CRRT >1l/h and IRRT >20 h/week), based on previous work [21, 22]. When only the modality was specified, IRRT and arteriovenous hemofiltration (CAVH) were classified as "standard dose", whereas CVVH was classified as "high dose". The membranes used in each arm were classified in terms of biocompatibility based on available information [20]. Cuprammonium rayon and cuprophan membranes were classified as non-biocompatible, while all other membranes used in the studies reviewed were classified as biocompatible or semi-biocompatible.

Statistical analysis

Primary analysis

All patients who received both forms of therapy during the acute phase of the renal failure were classified under the IRRT group. Since these were most often crossovers from IRRT to CRRT, this represented the closest approximation to an intention-to-treat analysis. Cases in which IRRT was used later in the hospital course after the acute episode for treatment of chronic renal failure were not considered to be crossovers. Individual and cumulative risk ratios (RRs) were calculated for mortality across individual studies using the Mantel-Haenszel test. All RR results are presented with the corresponding 95% confidence limits. Since only summary data was used in the analysis, a fixed effects model was used. A p value of less than 0.05 was considered significant. We evaluated inter-reviewer agreement using a 3-rater weighted Kappa statistic [23].

Sensitivity and subgroup analyses

We assessed the robustness of our findings from the primary analysis to the effects of baseline severity of illness, study quality, crossover assignment, year of publication and co-interventions through a series of sensitivity analyses [24]. First, we used thresholds for similarity in baseline severity of illness and for study quality. We combined the unadjusted data after excluding studies that failed to achieve these thresholds. A threshold of 3.0 (5-point scale) was used to identify studies with similar baseline characteristics between the two treatment arms (scores <3 indicate dissimilarity) and the mean score was used as the threshold to identify studies of acceptable quality. Next, we used the severity and quality scores to re-weight study sample size for (a) overall quality, (b) disparity in baseline severity of illness between treatment arms and (c) both a and b together. The following procedure was used for re-weighting. First, an average across rating domains (enrollment, intervention and outcome) was calculated for each study. We then calculated a mean across these values and each individual study average was subsequently divided by this overall value. Finally, we subtracted the maximum of these scaled values from each and added back 1. This scaled the new weights to a range from 0–1, although no values were observed to be close to 0.

To explore the effects of potential predictor variables identified prospectively, the primary analysis was again repeated after stratifying studies on the basis of the presence of infection, dialysis dose, dialyzer membranes, nutritional support and date of publication. A multivariate logistic regression analysis was also performed where the unit of analysis was each study, the dependent variable was hospital mortality, and the independent variables were treatment assignment, underlying severity of illness, membrane, dialysis dose, nutritional support and presence of sepsis.

Results

Search results

Twenty studies were identified that compared CRRT to IRRT but seven were excluded for failing to meet inclusion criteria (see Appendix II). The remaining 13 studies [8, 9, 10, 11, 12, 25, 26, 27, 28, 29, 30, 31, 32] represented 1400 patients. Of note, only three studies [27, 30, 32] were randomized controlled trials and none of these were published other than in abstract form. APACHE II scores were reported in eight studies [8, 10, 11, 12, 25, 28, 31, 32]. Information on dialysis dose in eight studies [8, 10, 11, 12, 25, 28, 31, 32], membranes in all 13 studies and nutritional support in five studies [9, 10, 11, 12, 31] was available, either from the manuscripts or by contact with the authors. Cost data were available only in limited fashion from two studies and were not analyzed further.

Study quality and baseline severity of illness assessments

The results of the blinded review are presented in Table 1. Overall, inter-rater agreement was fair (82%, mean Kappa 0.41). The overall quality and severity scores are shown in Table 1. Studies were generally of poor quality, ranging from 1.92–3.24 out of a possible 5 points (mean 2.62). Similarly, most studies scored poorly in terms of similar baseline severity of illness (measured at study enrolment) in each group. Scores ranged from 1.0–5.0 with a mean of 2.67. We were able to assess baseline severity of illness in 12 studies. In only half of these studies, representing one-third of the total number of patients (6 studies, *n*=481) were the baseline characteristics deemed similar by blinded review. In four studies (622 patients) severity was greater in the CRRT arms while in two studies (202 patients) severity was greater in IRRT arms. Co-interventions were not controlled for in any of these studies. However, nutritional support was the only co-intervention that was identified by the blinded review to have been applied differently between treat-

Table 1 Summary of individual studies (*CRRT* continuous renal replacement therapy, *IRRT* intermittent renal replacement therapy)

Study	Reference	Year	*n*	Mortality CRRT	Mortality IRRT	Quality score	Severity score
Mauitz	29	1986	58	75.0%	90.9%	3.11	4
Bartlett	10	1986	56	71.9%	87.5%	2.63	4
Simpson	12	1987	32	50.0%	66.7%	2.47	3.67
McDonald	9	1991	42	77.3%	75.0%	2.40	1
Kierdorf	26,27	1991	146	78.1%	93.2%	2.73	5
Bosworth	8	1991	320	82.1%	66.2%	1.92	1.33
Bastien	25	1991	66	50.0%	75.0%	2.20	3.33
Bellomo	11	1993	167	59.0%	70.2%	2.98	2.33
Krucynski	28	1993	35	33.3%	82.6%	2.81	2
Simpson	30	1993	123	70.8%	82.8%	2.29	3.33
Kierdorf	[a]	1994	95	60.4%	66.0%	2.62	2.67
van Bommel	31	1995	94	56.7%	41.2%	2.85	1
Mehta	32	1996	166	65.5%	47.6%	3.24	1
Overall			1400	68.0%	73.5%	2.62	2.67

[a] This study has not been published except as a thesis. Therefore, despite being a randomized trial, it was assigned the mean quality and severity scores for the remaining studies. Both quality and severity scores used a 5-point scale where higher values denote better quality and more equal distribution of baseline (point of enrolment) severity of illness between treatment arms –see Appendix I for details

ment arms. In four studies [9, 10, 11, 12] nutritional support was judged to be absent or inferior in the IRRT group compared to the CRRT group.

Hospital mortality

Continuous renal replacement therapy was associated with a reduced risk of hospital death in the six studies in which baseline severity of illness was similar (RR 0.48, 0.34–0.69, $p<0.0005$), see Fig. 1. There was no significant reduction in mortality when all 13 studies were included in an unadjusted comparison (RR 0.93, 0.79–1.09, $p=0.29$). However, when adjusting for study quality (RR 0.78, 0.65–0.94, $p<0.01$), similarity of baseline severity of illness (RR 0.72, 0.59–0.88, $p<0.001$), or both (RR 0.72, 0.60–0.87, $p<0.001$), the overall effect in favor of CRRT was again apparent (Fig. 2).

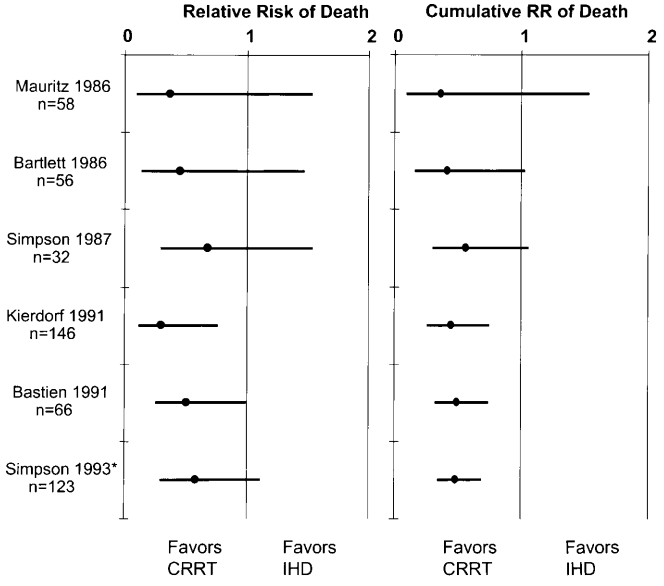

Fig. 1 Individual and cumulative relative risk (mortality) for the six studies that compared patients of equal severity of illness. *Indicates randomized controlled trials

Sensitivity and subgroup analyses

The results of the sensitivity analysis are presented in Fig. 3. Under no condition, either of inclusion criteria or adjustment method, did CRRT result in worse outcome when compared to IRRT. Furthermore, no significant differences in RRs were identified for changes in the adjustment methods used. After adjustment for study quality, illness severity, or both, CRRT was associated with an improved survival compared to IRRT. This difference persisted despite altering the method of quality adjustment or changing the way patients receiving both therapies (crossovers) were analyzed.

Results of the separate univariate analyses to determine the effects of co-interventions and other confounding variables, including date of publication, dialysis dose, membrane, nutritional support and presence of sepsis, are presented in Table 2. Although there were trends in these data regarding sepsis and membranes, no individual variable appeared to be significant. However, publication date did appear to affect outcome in that studies completed after 1992 reported a significantly lower mortality in both the IRRT (RR 0.70, 0.57–0.88, $p=0.002$) and CRRT (RR 0.68, 0.54–0.86, $p<0.001$) groups (Table 2). Interestingly, there did not appear to be

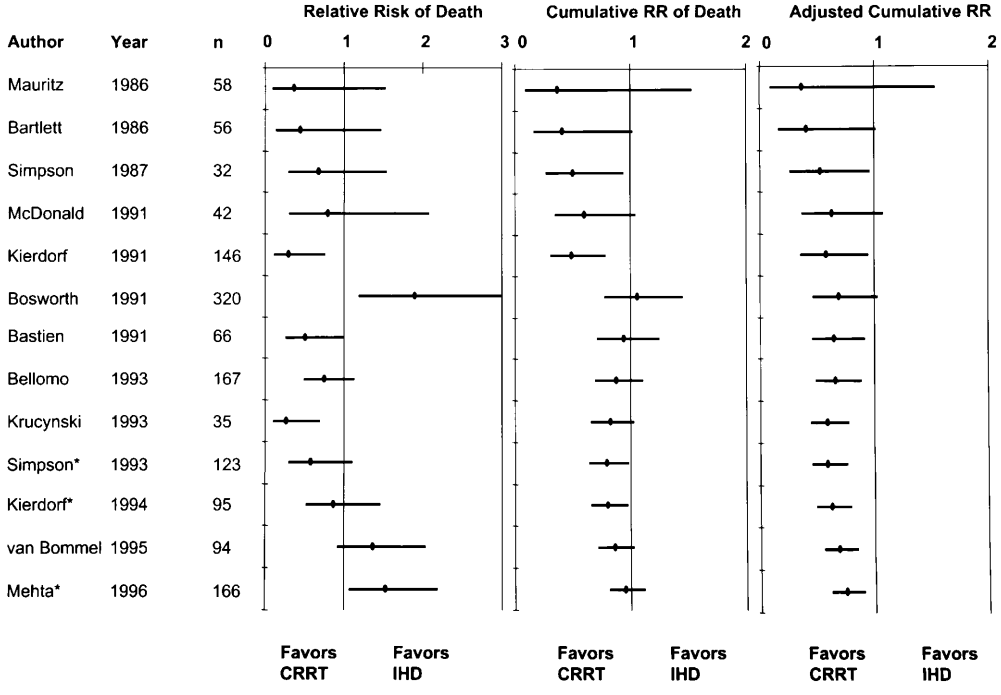

Fig. 2 Individual and cumulative relative risk for the entire cohort. **Panel A**: individual values; **Panel B**: cumulative, unadjusted values; **Panel C**: cumulative, adjusted values. Values shown in panel C are for the combined quality and severity adjustment. *Indicates randomized controlled trials. Similar results occurred with either severity or quality adjustments alone (Fig. 3)

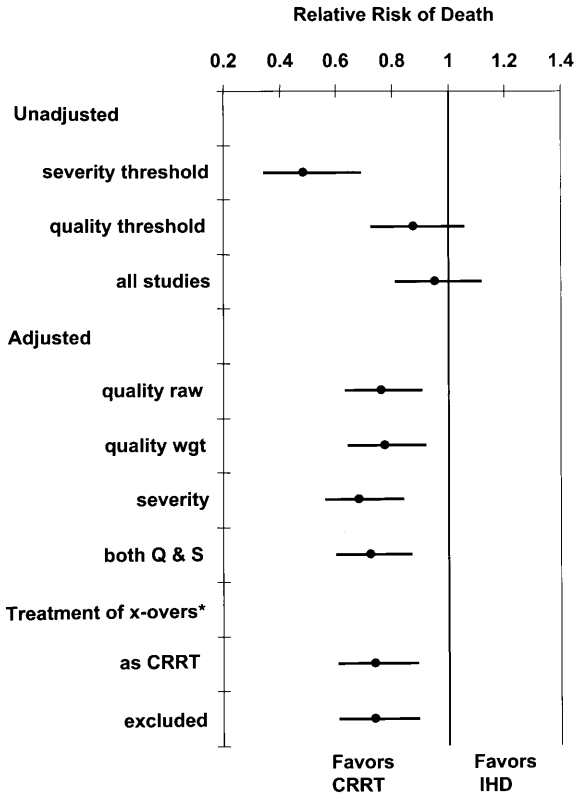

Fig. 3 Sensitivity analysis. (*Wgt* weighted, *Raw* unweighted, *q & s* quality and severity together) For the unadjusted comparisons, a severity score threshold of 3.0 and a quality score threshold of 2.62 were used. * Crossovers (*x-overs*) were included in the IRRT group for the primary analysis. Effects are shown for quality/severity adjusted RR with crossovers considered as CRRT or excluded

an effect of dialysis dose. In multivariate modeling, no covariates were significant. However, model stability was severely impaired by the small number of studies.

Our observations regarding the effects of publication date and dialysis dose on outcome prompted us to conduct a post-hoc analysis on the unadjusted data for the entire cohort, regardless of the therapeutic modality used. The results of this analysis suggest a significant improvement in all-cause mortality for patients enrolled in the studies after 1992 compared to those enrolled prior to 1992, regardless of treatment modality. However, there does not appear to be a similar effect for dialysis dose (see Table 3).

Discussion

The major finding of this study is that, despite its widespread use, there is insufficient evidence to establish whether CRRT is associated with improved survival in critically ill patients with ARF when compared with IRRT. However, compared to IRRT, CRRT is associated with a large decrease in mortality when patients of similar baseline severity of illness are compared. This large effect would seem to demand that a large, carefully controlled, randomized clinical trial be undertaken. Our analysis further suggests that over the past decade the mortality associated with ARF for patients treated with IRRT has decreased and that sicker patients were more likely to receive CRRT, as evidenced from the growing disparity in underlying severity of illness. These considerations should be taken into account in the design of trials comparing CRRT with IRRT.

Our study highlights the importance of using quality assessments of the individual reports when conducting meta-analyses. The pooling of study results without re-

Table 2 Study subgroup analysis: mortality rates and relative risks for death by subgroup (*RR* relative risk of death for continuous renal replacement therapy (*CRRT*) versus intermittent renal replacement therapy (*IRRT*))

Variable	Number of studies	CRRT mortality	IRRT mortality	Unadjusted[a] RR (95% CI)	Adjusted[b] RR (95% CI)
Septic	4	59.8%	66.3%	0.84 (0.64–1.11)	0.84 (0.64–1.11)
Not septic	9	70.5%	71.6%	0.94 (0.78–1.14)	1.02 (0.84–1.23)
Dose					
> with CRRT	5	62.1%	66.4%	0.89 (0.71–1.11)	0.89 (0.71–1.11)
Not > with CRRT	8	71.2%	72.0%	0.97 (0.78–1.20)	1.01 (0.81–1.26)
Membranes[c]					
Biocompatible versus non-biocompatible	4	70.0%	69.6%	1.01 (0.80–1.29)	1.08 (0.84–1.40)
Biocompatible versus semi/biocompatible	8	64.9%	70.0%	0.85 (0.69–1.06)	0.85 (0.69–1.06)
Nutrition					
>with CRRT	5	61.6%	67.2%	0.85 (0.65–1.12)	0.87 (0.67–1.15)
Same	8	70.0%	70.8%	1.03 (0.85–1.26)	1.00 (0.83–1.11)
Publication date					
Before 1992	7	73.9%	74.6%	0.97 (0.76–1.25)	0.99 (0.76–1.29)
After 1992[d]	6	61.6%	64.0%	0.94 (0.77–1.14)	0.94 (0.77–1.14)

[a] Unadjusted for quality or severity but incorporating the Mantel-Haenszel weights
[b] Adjusted for combined quality and severity
[c] One study used non-biocompatible membranes in both groups
[d] The mortality rates associated with CRRT and IRRT were significantly different before and after 1992, p=0.002 and <0.0001, respectively

Table 3 Post-hoc analysis: effects of date and dose irrespective of modality

Variable	No. of studies[a]	No. of patients	Overall mortality	RR (95% CI)	*p* value
Publication date					
Before 1992	7	720	74.3%		
After 1992	6	680	62.8%	0.69 (0.59–0.81)	<0.0001
Dose					
Standard	12	1041	69.5%		
High	7	359	66.3%	0.90 (0.76–1.07)	NS

[a] All but one study included some patients treated with "standard" dialysis dose and six of these also included patients treated with "high dose" dialysis as defined in the text

gard to quality or baseline severity of illness yielded greater statistical heterogeneity and the overall estimate of effect was different from the adjusted estimate. Our results agree with the findings of Moher and colleagues [19] who examined the effects of quality in 11 meta-analyses involving 127 trials. These authors found that including a quality assessment, while more complex, significantly affected the estimate of treatment effect and reduced statistical heterogeneity. However, previous meta-analyses using randomized trials have found that including quality assessments reduces the effect size since lower quality trials tend to result in exaggerated effects [19, 33]. By contrast, including quality assessments in our analysis resulted in an increased effect size by reducing the influence of trials with selection bias. These trials most often allocated sicker patients to CRRT arms.

Of the potential confounders analyzed by subgroup analysis, no single variable appears to explain the finding that, after adjustment for study quality or baseline severity, CRRT was associated with an increased survival compared to IRRT. Various potential benefits of CRRT have been suggested, including the greater use of biocompatible membranes and a higher dialysis dose [7, 20, 21]. Although there were trends toward a greater effect when the IRRT arm used bio-incompatible membranes or lower dialysis dose compared to the CRRT, neither of these variables appeared to account for the overall relative risk. Similarly, although recent evidence suggests a potential benefit of certain types of CRRT in patients with sepsis, we could not demonstrate that CRRT was superior in the subgroup of four studies [10, 11, 12, 31] where the majority of patients had sepsis or severe infection. However, our power to understand the effect of these variables was limited by small sample size.

There are limitations to our analysis. First, most of the studies we examined were non-randomized, and even when randomization occurred, it did not always ensure that patients were equally allocated to treatment arms in terms of baseline severity of illness. Our methods to account for differences in study quality and baseline severity of illness only down-graded the influence (i.e., reduced sample size) of poor quality studies and studies in which severity of illness was not similar between study arms. Also, our ability to determine differences in baseline severity of illness was dependent on limited summary information. More detailed information, such as the risk of hospital mortality predicted by APACHE II, would have facilitated a more thorough assessment. Given that more patients were enrolled in studies that appeared to allocate sicker patients to CRRT, any bias introduced by failure to adjust fully for differences in severity of illness would likely be against CRRT. The fact that CRRT appears to be beneficial despite this bias is notable.

Second, our methods were limited in their ability to determine the interactions between variables. It is possible that membrane biocompatibility, dialysis dose, hemodynamic and immunologic effects, and improved critical care services over time all contributed to the observed survival benefit of CRRT. Our multivariate analysis was not successful in dissecting out these interactions, and thus we are unable to determine which variables were decisive. Finally, the limited clinical information available in published reports precluded pooled estimates of the effects of CRRT and IRRT on outcomes other than all-cause mortality. In particular, information on the differential effects of these therapies on hemodynamics and organ function would have been useful.

It is disappointing that CRRT has been a therapeutic option in critical care practice for over 20 years without definitive evaluation of its benefits. While recent clinical trials have shown reduced all-cause mortality with changes in other forms of supportive care, such as mechanical ventilation [34], it is possible that changing dialysis modality will also reduce mortality. Our analysis suggests that a definitive trial comparing CRRT to IHD would require roughly 660 patients in each arm based on our confidence intervals for effect size. Such a trial should control for factors such as membrane and co-interventions and, based on recent evidence [35], should consider treatment dose, perhaps in factorial design with treatment modality. Efforts should be made to limit crossovers between treatment arms. Finally, it would seem to be important to stratify randomization on the presence or absence of hemodynamic instability because this is the major determining variable for who receives CRRT in practice. However, with entrenched practice patterns, as evidenced by physician surveys [13, 15], and with an increasing tendency to avoid allocating sicker patients to IRRT in recent studies, it is questionable whether a sufficiently large randomized trial will be conducted any time soon. Nevertheless, we suggest that such

a trial is necessary and, in the meantime, CRRT should be made available to at least some patients with ARF.

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Appendix I

Quality assessment instrument

Overall quality scores were generated using two approaches that varied with regard to the relative weighting of different questions. In the unweighted method, each question was given a score of 1–5 where 5 corresponds to "strongly agree" and 1 corresponds to "strongly disagree". Mean score across the three raters for each question were totaled and divided by the number of relevant questions within each domain (enrollment, intervention, outcome) to produce a domain score of 1–5. The mean of each domain score was then used as the overall quality assessment. The weighted method differed in that each question was weighted separately in its contribution to the overall score depending on its relative importance to overall quality based on prior recommendations [16, 17, 18]. These weights are shown in parentheses in tables below. For the weighted method, each domain score was divided by 10, yielding a number from 1–5

Enrollment

Question	Response range/score (weighted score)
Patient selection	
1. Was the selection process specified?	Strongly disagree – 1 (1), strongly agree – 5 (5)
2. Were patients uniformly identified at presentation (i.e., at the same stage in the disease process)?	Strongly disagree – 1 (1), strongly agree – 5 (5)
3. Were inclusion/exclusion criteria specified?	Strongly disagree – 1 (1), strongly agree – 5 (5)
4. Was information obtained on patients not enrolled?	Strongly disagree – 1 (1), strongly agree – 5 (5)
Patient assignment/confounder control	
1. Were patients randomized to treatment arm? If YES, answer questions 2–5. If NO, answer questions 6–8	Strongly disagree – 1 (2), strongly agree – 5 (10)
Randomized	
2. Was an appropriate randomization method used?	Strongly disagree – 1 (1), strongly agree – 5 (5)
3. Did randomization appear to work? (i.e. were reported variables evenly distributed?)	Strongly disagree – 1 (1), strongly agree – 5 (5)
4. Was underlying severity of illness similar for the two groups?	Strongly disagree – 1 (1), strongly agree – 5 (5)
5. Were known confounding variables reported in sufficient detail to permit adjustment?	Strongly disagree – 1 (1), strongly agree – 5 (5)
Non-randomized	
6. Were patients similar at the start of the trial? (with or without matching)	Strongly disagree – 1 (1), strongly agree – 5 (5)
7. Was the reason for treatment choice specified?	Strongly disagree – 1 (1), strongly agree – 5 (5)
8. Were known confounding variables reported in sufficient detail to permit adjustment?	Strongly disagree – 1 (1), strongly agree – 5 (5)

Intervention

Question	Response range/score (weighted score)
Primary intervention	
1. Which modalities were used?	Other or unknown – 1 (1), CAVH(D) versus IHD – 3 (3) CVVH(D) versus IHD – 5 (5)
2. Was dialysis dose equalized between treatment arms?	Other or unknown – 1 (1), dose quantified but unequal – 3 (3) dose equalized – 5 (5)
3. What dialyzer membranes were used?	Different or not specified – 1 (1), same class in both – 4 (4) same – 5 (5)
4. How were crossovers dealt with?	Crossovers unspecified or unknown– 1 (1), crossovers specified as to criteria and direction – 3 (3), No crossovers – 5 (5)
Co-interventions *(3 points each)*	
5. What was the impact of the investigators on the care of the patients?	Other or not specified – 1 (3), co-interventions controlled by protocol (same for both) – 3 (9), blinded – 5 (15)
6. Were there any uncontrolled co-interventions that could have significantly impacted survival?	Strongly disagree – 1 (3), strongly agree – 5 (15)

Outcome

Question	Response range/score (weighted score)
Follow-up	
1. Was follow-up complete?	Strongly disagree – 1 (1), strongly agree – 5 (5)
2. Were all patients accounted for?	Strongly disagree – 1 (1), strongly agree – 5 (5)
Outcomes	
3. Were all relevant outcomes reported?	
Survival?	Strongly disagree – 1 (1), strongly agree – 5 (5)
Renal recovery?	Strongly disagree – 1 (0.33), strongly agree – 5 (1.67)
ICU length of stay?	Strongly disagree – 1 (0.33), strongly agree – 5 (1.67)
Hospital length of stay?	Strongly disagree – 1 (0.33), strongly agree – 5 (1.67)
Analysis	
4. Were the data analyzed correctly?	
Intention to treat analysis?	Strongly disagree – 1 (3), strongly agree – 5 (15)
Crossovers analyzed separately?	Strongly disagree – 1 (0.5), strongly agree – 5 (2.5)
..by direction of crossover?	Strongly disagree – 1 (0.5), strongly agree – 5 (2.5)
5. Did the authors take appropriate action to control for confounding variables?	Strongly disagree – 1 (2), strongly agree – 5 (10)

Appendix II

Studies excluded from the meta-analysis

1. Alarabi AA, Danielson BG, Wikstrom B, Wahlberg J (1989) Outcome of continuous arteriovenous haemofiltration (CAVH) in one centre. Ups J Med Sci 94:299–303

Reason for exclusion: Uncontrolled study, all patients received CAVH.

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Reason for exclusion: Mortality rates were not reported in the paper, nor were they obtainable through contacting the authors.

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