Intermittent versus continuous renal replacement therapy for acute renal failure in adults (Review)

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[Intervention Review]

Intermittent versus continuous renal replacement therapy for acute renal failure in adults

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ABSTRACT

Background

Renal replacement therapy (RRT) for acute renal failure (ARF) can be applied intermittently (IRRT) or continuously (CRRT). It has been suggested that CRRT has several advantages over IRRT including better haemodynamic stability, lower mortality and higher renal recovery rates.

Objectives

To compare CRRT with IRRT to establish if any of these techniques is superior to each other in patients with ARF.

Search strategy

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL). Authors of included studies were contacted, reference lists of identified studies and relevant narrative reviews were screened. *Search date*: October 2006.

Selection criteria

RCTs comparing CRRT with IRRT in adult patients with ARF and reporting prespecified outcomes of interest were included. Studies assessing CAPD were excluded.

Data collection and analysis

Two authors assessed trial quality and extracted data. Statistical analyses were performed using the random effects model and the results expressed as risk ratios (RR) for dichotomous outcomes or mean difference (MD) for continuous data with 95% confidence intervals (CI).

Main results

We identified 15 studies (1550 patients). CRRT did not differ from IRRT with respect to in-hospital mortality (RR 1.01, 95% CI 0.92 to 1.12), ICU mortality (RR 1.06, 95% CI 0.90 to 1.26), number of surviving patients not requiring RRT (RR 0.99, 95% CI 0.92 to 1.07), haemodynamic instability (RR 0.48, 95% CI 0.10 to 2.28) or hypotension (RR 0.92, 95% CI 0.72 to 1.16) and need for escalation of pressor therapy (RR 0.53, 95% CI 0.26 to 1.08). Patients on CRRT were likely to have significantly higher mean arterial pressure (MAP) (MD 5.35, 95% CI 1.41 to 9.29) and higher risk of clotting dialysis filters (RR, 95% CI 8.50 CI 1.14 to 63.33).

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Authors' conclusions

In patients who are haemodynamically stable, the RRT modality does not appear to influence important patient outcomes, and therefore the preference for CRRT over IRRT in such patients does not appear justified in the light of available evidence. CRRT was shown to achieve better haemodynamic parameters such as MAP. Future research should focus on factors such as the dose of dialysis and evaluation of newer promising hybrid technologies such as SLED. Triallists should follow the recommendations regarding clinical endpoints assessment in RCTs in ARF made by the Working Group of the Acute Dialysis Quality Initiative Working Group.

PLAIN LANGUAGE SUMMARY

Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Acute renal failure (ARF) is an abrupt reduction in kidney function with elevation of blood urea nitrogen (BUN) and plasma creatinine and a fall in urine output. In most cases correction of the underlying cause leads to recovery, however for many some form of renal replacement therapy (RRT - a treatment that removes waste products, salts and excess water form the body) may be required. RRT can either be intermittent (IRRT- performed for less than 24 hours in each 24 hour period, two to seven times per week) or continuous (CRRT- performed continuously without any interruption throughout each day). It has been suggested that CRRT has several advantages over IRRT including better haemodynamic stability (blood pressure control and blood circulation), improved survival and greater likelihood of renal recovery. Our systematic review identified 15 randomised studies with 1550 patients comparing CRRT with IRRT. We did not find any difference between CRRT and IRRT with respect to mortality, renal recovery, and risk of haemodynamic instability or hypotension episodes.

BACKGROUND

Acute renal failure (ARF) is defined as a sudden, sustained decline in glomerular filtration rate (GFR), usually associated with uraemia and a fall in urine output (Nissenson 1998). The incidence of ARF requiring renal replacement therapy (RRT) in the adult population in Scotland has been reported to be 207/million/year (Metcalfe 2002). In many cases of ARF, correction of underlying problems may allow recovery, but in a substantial fraction of patients, particularly those patients in intensive care units (ICUs) who frequently have additional clinical problems, recovery is less certain and there is a requirement for continuing support with RRT. The mortality for ARF patients who require RRT in an ICU setting is estimated to be 50% to 70%, a figure that has changed little over the past 30 years, despite advances in medical care (Barton 1993; Chertow 1995; Kennedy 1973). The failure to reduce ARF mortality may be due, at least in part, to increases in the age and complexity of current patients with ARF (Turney 1996).

A number of strategies for RRT may be used in ARF. RRT can be applied intermittently (IRRT), e.g. intermittent haemodialysis (IHD) or continuously (CRRT), as in continuous venovenous haemofiltration (CVVHF). In IHD removal of fluid, solutes and toxins is achieved typically through a dual venous access, over a period of three to five hours, three to seven times weekly. Solute removal is achieved by diffusion and is rapid and efficient (Murray 2000). Rapid fluid removal during IHD has been suggested to lead to hypotension, with the potential for further renal injury and prolongation of ARF (Manns 1997).

All continuous therapies use highly-permeable filters such that the bulk of solute removal occurs by convective transfer (Murray 2000). Convective solute removal is less efficient than diffusive, but the continuous nature of the therapy compensates for this and bulk solute removal has been reported to be higher than with IHD (Clark 1994). In some forms of CRRT dialysate is run countercurrent to the blood flow, so that the diffusive solute removal of haemodialysis is combined with the convective solute removal of haemofiltration. This form of RRT called haemodiafiltration (HDF) has been reported to offer superior solute removal. Access for CRRT may be via dual venous access (CVVH, CVVHF, CVVHDF) or via arterial and venous access (CAVH, CAVHF, CAVHDF). For all forms of CRRT, putative advantages include improved haemodynamic stability, more effective control of acid/base and electrolyte status, improved removal of uraemic

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toxins, and removal of inflammatory mediators, particularly in those patients with systemic inflammatory response syndrome (SIRS; septic shock) (De Vriese 1999; Jakob 1996). While these advantages are widely reported, they are not universally accepted (Jakob 1996). The principal disadvantages of CRRT modalities include the need for prolonged systemic anticoagulation, with attendant risk of major bleeding, and the requirement for additional nursing and other resources.

There is evidence for both IRRT (Schiffl 2002) and CRRT (Ronco 2000), that increasing the delivered dialysis dose improves outcome. What is less clear is which, if any, approach is preferable. Individual studies comparing the therapies have suggested that CRRT offers superior biochemical control and improved patient outcomes (Bellomo 1995; Kruczynski 1993). However, a number of authoritative reviews that have addressed the pros and cons of IHD versus CRRT for patients with ARF have been unable to provide objective evidence of the superiority of one approach over the other (Kellum 2002; Tonelli 2002a). The purpose of this systematic review is to evaluate whether IHD or CRRT provides superior outcomes for patients with ARF.

OBJECTIVES

To compare CRRT with IRRT to establish if any of these techniques is superior to each other in patients with ARF.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs - either parallel or crossover design) in which patients have been allocated to treatment with IRRT or CRRT for ARF and reporting outcomes of interest to this review were considered. Quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) studies were excluded. Authors' definition of ARF was accepted.

Types of participants

All adult patients (≥ 18 years) requiring RRT for ARF were considered eligible for inclusion. It was planned that if there are sufficient number of studies subgroup analysis according to varying degrees of comorbidity will also be undertaken.

Types of interventions

- IRRT was defined as any form of RRT (haemodialysis (HD), haemofiltration (HF), haemodiafiltration (HDF), isolated ultrafiltration (UF)) prescribed for a period of < 24 hours within any 24 hour period.
- CRRT was defined as any form of RRT (HD, HF, HDF, UF) that was intended to run on a continuous basis until recovery of renal function occurred.
- Studies of peritoneal dialysis (PD) were not considered in this review.

For the purpose of this review, CRRT is considered the treatment intervention and IRRT is considered the control intervention.

Types of outcome measures

Outcome measures that will be evaluated will include mortality, recovery of renal function, cardiovascular stability and complications of treatment.

Mortality

1. Death prior to ICU discharge.
2. Death prior to hospital discharge.
3. Time to hospital death or discharge.
4. Time to ICU death/discharge.

Recovery of renal function

1. Requirement for RRT beyond hospital discharge or GFR >15 mL/min
2. Serum creatinine/GFR at hospital discharge.
3. Requirement for RRT beyond 90 days (whether hospitalised or not).

Cardiovascular stability

1. Reported incidence of hypotension.
2. Reported blood pressure (systolic, diastolic or mean arterial pressure (MAP)).
3. Requirement for inotropic drugs (epinephrine, norepinephrine, dopamine, dobutamine, vasopressin).
4. Dose of inotropic drugs.

Complications of therapy

1. Reported incidence of bleeding.
2. Sepsis (related to vascular access).

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Search methods for identification of studies

Relevant RCTs were identified using the Cochrane Collaboration search strategy to identify RCTs. The search strategy was conducted by KSR and NM and included (see Appendix 1 - *Electronic search strategies)*

1. MEDLINE (1966 - October 2006)
2. EMBASE (1980 - October 2006)
3. Cochrane Central Register of Controlled Trials - CENTRAL (in *The Cochrane Library* - Issue 4 2006).
4. Authors of studies identified as potentially eligible for inclusion were contacted both to clarify missing data or methodological details and to ask for additional published or unpublished studies.
5. Studies presented in conference proceedings were included. No additional search strategy to identify these was used.
6. Reference lists of previous reviews (including systematic reviews) and previous studies were included
7. The Trials Search Co-ordinator of the Cochrane Renal Group were contacted for references of studies not yet identified by the search process.
8. Papers in languages other than English were included and translation facilities within the Cochrane Collaboration were used when needed.
9. Duplicate publications: The most recently published version were used. Where relevant outcomes were only published in earlier versions their data will be included. There, source was highlighted. Any discrepancy between published versions were highlighted.

Data collection and analysis

All titles and abstracts were independently assessed by KSR and NM. Full papers were be obtained for those studies that might fulfil the inclusion criteria and were independently assessed by KSR and NM. Disagreements were resolved by discussion or if necessary by the decision of a third author (AMM).

Study quality

The quality of included studies was assessed independently by at least two authors (KSR, NM, JA) without blinding to authorship or journal using the checklist developed by the Cochrane Renal Group. Discrepancies were resolved by discussion among the authors. The quality items to be assessed were allocation concealment, blinding of investigators, participants, outcome assessors and data analysers, intention-to-treat analysis and the completeness of follow-up.

Quality checklist

Allocation concealment

- Adequate (A): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
- Unclear (B): Randomisation stated but no information on method used is available
- Inadequate (C): Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group

Blinding

- Blinding of investigators: Yes/no/not stated
- Blinding of participants: Yes/no/not stated
- Blinding of outcome assessor: Yes/no/not stated
- Blinding of data analysis: Yes/no/not stated

Intention-to-treat analysis

- Yes: Specifically reported by authors that intention-to-treat analysis (ITT) was undertaken and this was confirmed on study assessment, or not stated but evident from study assessment that ITT was undertaken.
- Unclear: Reported but unable to confirm on study assessment, or not reported and unable to confirm by study assessment.
- No: Lack of intention-to-treat analysis confirmed on study assessment (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation) regardless of whether ITT reported or not.

Completeness of follow-up

The percentage of participants for whom data was complete at defined study end-point. Where interim analyses are reported 'not stated' was recorded.
We did not use a summary scoring system to assess study quality.

Data extraction

Two of three authors (KSR, NM, JA) extracted data independently for each included study. Data extraction was done using the Cochrane Renal Group prescribed data extraction form. Discrepancies were resolved by discussion with AMM. Letters were sent to authors to clarify missing or unclear data.
Information was collected on participant characteristics (number, age and sex), co-morbid illnesses, comorbidity scores such as APACHE scores, length of ICU and hospital stay, duration on

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dialysis, duration of dialysis sessions, type of dialysis membrane used, and need for RRT after hospital discharge.

Statistical analysis

KSR and NM entered data separately. For dichotomous data (mortality, patients dependent on dialysis after hospital discharge, patients with complications secondary to RRT) risk ratios (RR) was used with 95% confidence intervals (CI). For continuous data (length of ICU and hospital stay, blood pressure and pressor doses), mean difference (MD) with 95% CI was used. Data were pooled using the random effects model but the fixed effects model was also be analysed to ensure robustness of the model chosen and susceptibility to outliers. Heterogeneity of treatment effects between studies was formally tested using the Q (heterogeneity χ^2) and the I^2 statistic (Higgins 2003).

Subgroup analysis was planned to be undertaken, if appropriate, according to comorbidity, severity of acute illness, and quality of study.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

The combined search identified 1080 articles, of which 1052 articles were excluded initially. Major reasons for exclusion were: (1) duplicate references, (2) non-RCTs, and (3) RCTs of other interventions not stated in the inclusion criteria and (4) animal and basic research studies. Full-text assessment of 28 potentially eligible reports identified 15 eligible RCTs (Augustine 2004; Davenport 1991; Gasparovic 2003; John 2001; Kielstein 2004; Kierdorf 1994; Mehta 2001; Misset 1996; Noble 2006; Ronco 1999a; Ronco 2001; SHARF 2005; Stefanidis 1995; Uehlinger 2005; Vinsonneau 2006) with 1550 patients (see Figure 1- *Flow chart of literature search*) published in 19 reports. Data for one study (Uehlinger 2005) that was initially published as conference abstracts was obtained from the unpublished manuscript provided by the authors. The data was later verified by checking with the published version (Uehlinger 2005). The raw data from Noble 2006 was very kindly provided by the authors.

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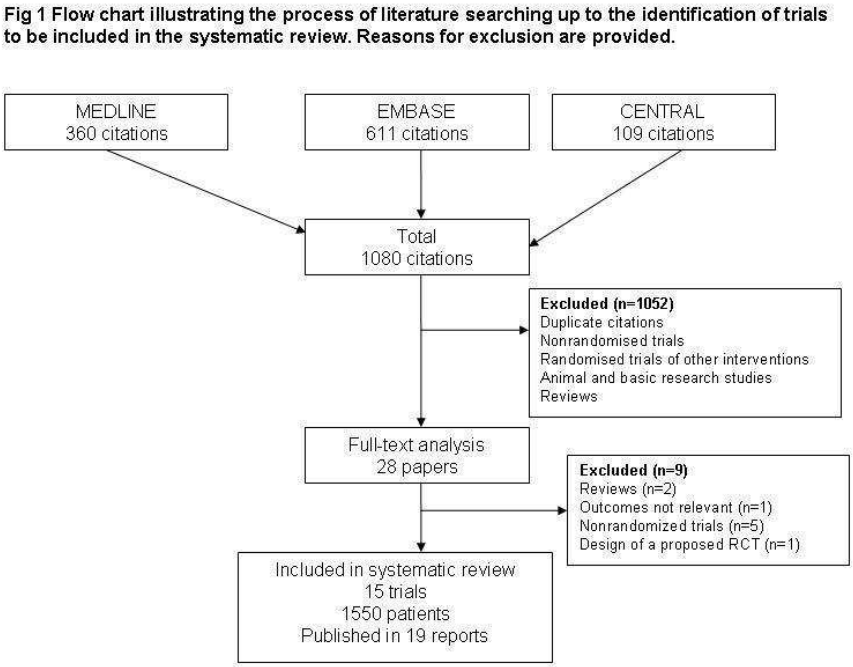
Figure 1. Flow chart of literature search



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Twelve of 15 studies (80%) used IHD as the IRRT modality. Kielstein 2004 used extended daily dialysis (EDD), Ronco 2001 used intermittent ultrafiltration and Davenport 1991 used intermittent haemofiltration as the IRRT modality. CVVHF was the most commonly user CRRT modality (7/15 studies). Mean age of the study populations ranged from 53.5 to 66.5 years. Apart from two studies (Ronco 1999a; Ronco 2001) all the other studies were conducted in an ICU setting. Five studies (Augustine 2004; John 2001; Kielstein 2004; Misset 1996; Vinsonneau 2006) explicitly stated that patients with pre-existing chronic renal failure were excluded. In one trial (Davenport 1991) the cause for ARF was exclusively due to fulminant liver failure due to paracetamol overdose and one trial included only patients with ARF due to sepsis (John 2001). Two studies (Mehta 2001; Noble 2006) used bioincompatible membranes (cuprophane) for IRRT. All the other studies used biocompatible synthetic membranes for both RRT modalities. Mehta 2001 excluded patients with MAP of less than 70 mm Hg and similarly Kielstein 2004 and SHARF 2005 excluded patients with hypotension. In five studies (John 2001; Kielstein 2004; Misset 1996; Ronco 1999a; Ronco 2001) the RRT modalities were assessed only over a 24 hour period.

In four studies 176/938 patients switched from one RRT modality to the other (Augustine 2004; Mehta 2001; SHARF 2005; Vinsonneau 2006). The number of patients crossing on account of medical reasons (complications due to the RRT such as clotting, haemodynamic instability) were 89/488 in the CRRT group compared to 56/450 in the IRRT group. SHARF 2005 contributed to 70% of patients switching from IRRT to CRRT and all the patients switched modality due to "coagulation problems". In the studies by Mehta 2001 and Vinsonneau 2006 31 patients crossed over from CRRT to IRRT as their clinical condition had improved and they were felt to be stable enough to be maintained on IRRT or according to a prespecified study design protocol.

Risk of bias in included studies

Data on study quality is given in Table 1 - *Study design, characteristics and quality assessment*.

Table 1. Study design, characteristics and quality assessment

Study ID	Comparisons	Design	ARF definitions	Allocation concealment	Blinding	ITT	% lost to follow-up
Augustine 2004	CCVHD vs IHD	Parallel	NS	Unclear	None	Yes	0
Davenport 1993	CAVHF/ CAVHD vs IHF	Parallel	NS	Adequate	None	Yes	0

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Table 1. Study design, characteristics and quality assessment *(Continued)*

Gasparovic 2003	CVVHF vs IHD	Parallel	At least 2 of the following: - 3 fold rise in creatinine - Hyperkalaemia with K > 5.5 mmol/L - Base deficit of -6	Adequate	None	Yes	0
John 2001	CVVHF vs IHD	Parallel	- Creatinine > 3 mg/dL AND/OR - Urine output < 10 mL/h	Adequate	None	No	0
Kielstein 2004	CVVHF vs EDD	Parallel	Urinary output < 500 mL/d	Adequate	None	No	0
Kierdorf 1994	CVVHF vs IHD	Parallel	NS	Adequate	None	No	5
Mehta 2001	CVVHDF/ CAVHDF vs IHD	Parallel	- Blood urea nitrogen > 40 mg/dL (140 mmol/L) OR - Serum creatinine > 2.0 mg/dL (177 umol/L) OR - Rise in serum creatinine > 1 mg/dL (88.4 umol/L) from baseline values	Adequate	None	Yes	0
Misset 1996	CAVHF vs IHD	Crossover	- Serum creatinine > 400 umol/L OR - Urea > 30 mmol/L	Unclear	None	No	0
Noble 2006	CVVHD vs IHD	Parallel	NS	Adequate	None	No	0
SHARF 2005	CVVHF vs IHD	Parallel	Creatinine > 2 mg	Adequate	None	Yes	0

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Table 1. Study design, characteristics and quality assessment *(Continued)*

Ronco 1999a	CVVHF vs IHD	Parallel	NS	Unclear	None	Yes	0
Ronco 2001	SCUF vs Intermittent UF	Crossover	NS	Unclear	None	Yes	0

NS = not stated

Allocation concealment

Eight authors were contacted for details regarding allocation concealment, five replied with the requested information. Twelve of 15 studies (80%) had an adequate allocation concealment method.

Blinding

None of the studies blinded or reported blinding participants, investigators, outcome assessors or data analysers.

Intention-to-treat

Ten of 15 (66.6%) studies either explicitly stated or actually did an intention-to-treat analysis.

Completeness of follow-up

Only five patients from were lost to follow-up, and all the patients belonged to Kierdorf 1994. However a total of 43 patients from six studies (John 2001; Kielstein 2004; Mehta 2001; Misset 1996; Noble 2006; Uehlinger 2005) did not receive RRT or were excluded from analysis excluded from analysis post-randomisation. All these six studies have explicitly stated the reasons for such post-randomisation exclusion, the main reason being protocol violation.

Effects of interventions

For the purpose of this review, CRRT is considered the treatment intervention and IRRT is considered the control intervention.

Mortality

In-hospital mortality

There was no difference in in-hospital mortality between the two treatment groups (Analysis 1.1.1 (7 studies, 1245 patients): RR 1.01, 95% CI 0.92 to 1.12). There was no evidence of significant heterogeneity across the studies (χ^2 = 8.19, P = 0.22, I^2 = 26.7%). The study by Mehta 2001 had significant disparities between both patient groups in terms of higher APACHE III score and number of patients with liver failure in the CRRT group and eventually showed a significantly higher mortality in this patient group. The removing Mehta 2001 from the analysis (Analysis 1.1.3 (6 studies, 1079 patients): RR 0.97, 95% CI 0.89 to 1.06) or restricting the analysis to studies in peer-reviewed publications only (Analysis 1.1.4 (6 studies, 929 patients): RR 1.03, 95% CI 0.92 to 1.16) showed no significant difference in in-hospital mortality between either patient group.

ICU mortality

There was no difference between CRRT and IRRT with respect to ICU mortality (Analysis 1.1.2 (5 studies, 515 patients): RR 1.06, 95% CI 0.90 to 1.26). There was no evidence of significant heterogeneity across the studies (χ^2 = 5.06, P = 0.28, I^2 = 21.0%).

Time to hospital death or discharge

Augustine 2004 assessed time to hospital discharge in those who survived, and survival time in patients who died. There was no difference between CRRT and IRRT for either number of days until hospital discharge (Analysis 1.2 (25 patients): MD -6.10, 95% CI -26.45 to 14.25) or survival time in patients who died (Analysis 1.3 (55 patients): MD 3.60, 95% CI -3.75 to 10.95).

Time to ICU discharge or death

This outcome was not assessed in any of the included studies.

Recovery of renal function

Surviving patients not requiring dialysis

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Patients on CRRT were no more likely than those on IRRT to be off dialysis on discharge (Analysis 1.4.1 (3 studies, 161 patients): RR 0.99, 95% CI 0.92 to 1.07). There was no evidence of heterogeneity across the studies (χ^2 = 0.97, P = 0.62, I^2 = 0%).

Serum creatinine or GFR at hospital discharge

SHARF 2005 reported data on surviving patients who had GFR > 15 mL/min. This outcome was not different between either patient group (Analysis 1.4.2 (129 patients): RR 1.13, 95% CI 0.94 to 1.36).

Requirement for RRT beyond 90 days (whether hospitalised or not)

This outcome was not assessed in any of the included studies.

Cardiovascular stability

Patients with haemodynamic instability

This outcome was assessed in two studies (Augustine 2004; Uehlinger 2005). Augustine 2004 did not explicitly stated the criteria used to define patients as being haemodynamically stable and Uehlinger 2005 stated that it was the average variability between the maximum and minimum daily MAP. There was no difference between patients on either group for having lesser risk of haemodynamic instability (Analysis 1.5 (2 studies, 205 patients): RR 0.48, 95% CI 0.10 to 2.28). There was no heterogeneity across the studies (χ^2 = 1.67, P = 0.20, I^2 = 40.2%).

Patients with hypotension

Three studies (John 2001; Uehlinger 2005; Vinsonneau 2006) reported this outcome. John 2001 defined hypotension as decrease in MAP > 20 mm Hg from baseline, Uehlinger 2005 defined hypotension as average MAP < 65 mm Hg throughout ICU stay and in Vinsonneau 2006 hypotension was defined as a systolic arterial pressure of 80 mm Hg or less or a fall greater than 50 mm Hg from the baseline value. There was no difference between patients in either group for having lesser risk of hypotension (Analysis 1.6 (3 studies, 514 patients): RR 0.92, 95% CI 0.72 to 1.16). There was no heterogeneity across the studies (χ^2 = 1.81, P = 0.40, I^2 = 0%).

Mean arterial pressure at end of study period

Patients on CRRT had a significantly higher MAP than those on IRRT (Analysis 1.7 (2 studies, 112 patients): MD 5.35, 95% CI 1.41 to 9.29). There was no evidence of significant heterogeneity across the studies (χ^2 = 0.19, P = 0.66, I^2 = 0%). Three studies (Davenport 1991; Ronco 1999a; Ronco 2001) in which results were not reported in a meta-analysable format also reported that patients on CRRT had significantly higher MAP.

Systolic blood pressure (absolute change from baseline)

No difference was found between either treatment interventions for this outcome (Analysis 1.8 (1 study, 30 patients): MD 6.00, 95% CI -10.85 to 22.85).

Patients requiring escalation of pressor therapy

Patients on CRRT had a significantly reduced risk of requiring escalation of pressor therapy when this outcome was analysed according to a fixed effects model (Analysis 1.9 (3 studies, 149 patients): RR 0.49, 95% CI 0.27 to 0.87). There was no evidence of heterogeneity across the studies (χ^2 = 2.92, P = 0.23, I^2 = 31.6%). However when analysed by a random effects model, there was no difference in this outcome between either RRT modality although the trend appeared to favour CRRT (RR 0.53, 95% CI 0.26 to 1.08).

Dose of inotropic drugs

There was no difference between norepinephrine dose required between patients on CRRT and IRRT (Analysis 1.10 (2 studies, 69 patients): MD -0.01, 95% CI -0.36 to 0.33). There was no evidence of heterogeneity across the studies (χ^2 = 0.11, P = 0.74, I^2 = 0%).

Complications of RRT

Number of patients with bleeding complications

There was no significant difference in the risk of bleeding between either patient group (Analysis 1.11 (5 studies, 638 patients): RR 1.03, 95% CI 0.59 to 1.80). There was no heterogeneity across the studies (χ^2 = 0.83, P = 0.93, I^2 = 0%).

Number of patients with clotting of dialysis filter

Patients on CRRT had significantly higher risk of recurrent dialysis filter clotting when compared to those on CRRT (Analysis 1.12 (3 studies, 149 patients): RR 8.50, 95% CI 1.14 to 63.33). There was no evidence of heterogeneity across the studies (χ^2 = 0.68, P = 0.41, I^2 = 0%).

Number of patients with arrhythmias during dialysis therapy

There was no difference in risk of arrhythmias between patients in either group (Analysis 1.13 (2 studies, 439 patients): RR 0.50, 95% CI 0.23 to 1.05).

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Sepsis (related to dialysis vascular access)

This outcome was not reported by any of the included studies.

RRT modality switching due to complications

The number of patients crossing to an alternate RRT modality due to medical reasons was not statistically significant (Analysis 1.14.1 (4 studies, 920 patients): RR 1.42, 95% CI 0.58 to 3.48). There was significant heterogeneity (χ^2 = 11.20, P = 0.01, I^2 = 73.2%). This was due to Mehta 2001. When this study was removed less patients switched from IRRT to CRRT with no significant heterogeneity (Analysis 1.14.2 (3 studies, 756 patients): RR 1.89, 95% CI 1.36 to 2.63; χ^2 = 1.23, P = 0.54, I^2 = 0%).

Publication bias and subgroup analyses

We planned to do analysis for publication bias and subgroup analysis according to comorbidity, severity of acute illness, and quality of study. However these analyses could not be undertaken due to the lack of sufficient number of studies to carry out these analyses.

DISCUSSION

We identified 15 RCTs with 1550 patients comparing CRRT with IRRT. The key findings from our systematic review are:

- CRRT offers no survival advantage over IRRT in patients with ARF
- Patients surviving ARF who are managed with CRRT have a similar expectation of recovery of renal function as those treated with IRRT
- CRRT is associated with a significantly higher MAP
- CRRT is associated with a significantly increased risk of recurrent filter clotting compared to IRRT

The results of this review are consistent with those reported in individual RCTs that have compared CRRT and IRRT directly. They are however, at odds with the generally positive benefits for CRRT compared to IRRT reported in some single centre or non-randomised studies (Ji 2001; Swartz 1999b; van Bommel 1995). These studies, in general, are weaker in design, often employing historic controls. The disease severity scores in these studies were generally higher for patients on CRRT. A recent observational study (Cho 2006) comparing 206 patients on CRRT with 192 patients on IRRT and adjusting for confounding factors such as age, organ failure, sepsis and propensity scores reported a significantly higher mortality in patients on CRRT (RR 1.92, 95% CI 1.28 to 2.89). A meta-analysis of non-randomised studies (Tonelli 2002b) had previously failed to show a difference in mortality between CRRT and IRRT (12 studies, 1252 patients: RR 1.00, 95% CI 0.92 to 1.08).

Our systematic review in keeping with previous meta-analyses (Kellum 2002; Tonelli 2002b) has not shown CRRT to be better than IRRT with respect to the most important clinical outcomes of mortality and renal function survival. It is interesting to note that even the latest reported trial (Vinsonneau 2006) shows a high mortality rate of 58%. Two recent observational studies from the US have shown that whilst mortality from ARF remains high, it has declined gradually over the past two decades (Waikar 2006; Xue 2006). However it is unclear if the wider usage of CRRT during the time period of these observational studies has had any role in the mortality decline (Lameire 2006).

Renal recovery has important implications for both the patient and the health care system. Not only can it result in considerable savings by way of avoiding the need for chronic dialysis it can also result in significantly improved quality of life for the patient (de Wit 1998; Merkus 1997). CRRT has been shown to have a beneficial effect in terms of better renal recovery (Manns 2003). Our review has however found no difference between either modality with respect to renal recovery amongst surviving patients. A recent narrative review by Palevsky 2005b on factors affecting renal recovery following ARF has also concluded that no overall benefit can be ascribed to either modality with regards to renal recovery when the competing mortality risk is taken into account.

This analysis also indicates that CRRT is associated with an increased likelihood of filter clotting compared to IRRT. In fact failure to maintain integrity of the CRRT dialysis circuit was the major reason for patients switching from CRRT to IRRT in the studies assessed. Individual non-randomised studies have reported this previously.

Advantages with CRRT found in our review are that patients on CRRT show a trend towards being less likely to need escalation of their pressor treatment and having significantly high mean arterial pressures. Our analysis however did not show any difference between both treatment groups with regards to the risk of episodes of haemodynamic instability or hypotension. It has been suggested by Kellum 2002 that a large RCT involving 660 patients per group would be necessary in order to resolve the mortality question definitively. Such a study would be very expensive and, it has been suggested, impractical to run as a multicentre trial involving many different intensive care units. We feel that our meta-analysis probably obviates the need for such a trial. Our in-hospital mortality analysis included seven studies with 1245 patients, almost closely approaching the total number of patients suggested by Kellum 2002 and importantly, the analysis also indicated that there was no significant heterogeneity between the studies.

The major strengths of this analysis are that it represents a comprehensive systematic review based on a detailed pre-study proto-

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col developed in conjunction with the Cochrane Collaboration, rigid inclusion criteria for RCTs only, and a very comprehensive search strategy of all major medical electronic databases and other sources. Data extraction, data analysis, and method quality assessment for each study were performed by two independent investigators. As far as we are aware this systematic review is the most up to date meta-analysis of all published and unpublished RCTs that have compared CRRT to IRRT for patients with ARF. We have also been quite comprehensive in the assessment of outcomes when compared to previous reviews. In addition to the major outcomes such as mortality and renal recovery, we have also assessed other clinically important outcomes such as haemodynamic stability, complications of treatment such as clotting of filters and bleeding.

Despite the inclusion of four further studies (Gasparovic 2003; Kielstein 2004; SHARF 2005; Vinsonneau 2006) with 820 patients that were published since the last systematic review by Tonelli 2002b, the principal conclusions remain unchanged.

The major weakness of this analysis is that none of the RCTs are individually large enough to provide an accurate evaluation of the differences in outcome between the treatments, given the effect size suggested by the retrospective analyses. The studies by Mehta 2001 and Uehlinger 2005 included patients with pre-existing chronic kidney disease while all of the other RCTs excluded such patients. In Mehta 2001 there are differences between groups in APACHE III score at enrolment. Crossovers from one modality to the other could have influenced the results. The number of patients crossing to an alternate RRT modality was 89/488 in the CRRT group, more than those on IRRT (56/450). This was due to medical reasons (complications due to the RRT such as clotting, haemodynamic instability), this difference was not statistically significant (RR 1.42, 95% CI 0.58 to 3.48) when Mehta 2001 was included however when Mehta 2001 was omitted, statistically less patients switched from IRRT (RR 1.89, 95% CI 1.36 to 2.63). Considerable variations were noted in the definitions for ARF and key outcomes such as haemodynamic stability and hypotension. The lack of consistency in the reporting of key outcomes such as mortality is one of the major weaknesses in this whole area. The included studies have been conducted over varying time periods and showed considerable clinical heterogeneity in terms of the dialysis treatment (dose, dialysis membrane) and patient characteristics.

Several outcomes (number of days until hospital discharge, survival time in patients who died, mean arterial pressure, systolic blood pressure, number of patients requiring escalation of pressor therapy, dose of inotropes and patients with clotting of dialysis filter) should be interpreted with caution owing to the fact that very few studies reported these outcomes and patient numbers in these analyses are quite small. It must also be noted that several RCTs excluded patients considered to be haemodynamically unstable from the randomisation process itself. It is therefore possible that these studies may have not been able to demonstrate the superiority of CRRT over IRRT with respect to haemodynamic stability.

The cost of RRT for patients with ARF is high. For IRRT major costs include the need for supervision by a trained dialysis nurse, which can become an economic issue if IRRT is performed on a frequent or daily basis. For CRRT major costs include disposables and replacement fluids. A recent economic analysis of the costs of RRT for patients with ARF estimated that mean adjusted total costs were Can$1342/week for IRRT compared to Can$3486/week for CRRT (Manns 2003). Another study (Rauf 2005) showed that the total hospitals cost (from start of RRT to hospital discharge) for patients on CRRT was US$57,000 more than that for those on IRRT. Although currently CRRT is the mode of choice for acutely ill patients with haemodynamic compromise, the case for CRRT in haemodynamically stable patients with ARF is not quite convincing based on clinically important outcomes such as mortality and renal recovery. Therefore in this subgroup of patients the additional expenses associated with CRRT may not be justified.

AUTHORS' CONCLUSIONS

Implications for practice

In patients with ARF who are haemodynamically stable, the RRT modality does not appear to influence important patient outcomes and therefore the preference for CRRT over IRRT in such patients does not appear to be justified in the light of available evidence. In haemodynamically unstable patients, CRRT may however be preferable as patients on CRRT appear to achieve higher MAP and show a trend towards lesser need for escalation of vasopressor therapy and arrhythmias.

Implications for research

Future research should focus on factors such as the dose of dialysis and evaluation of newer promising hybrid technologies such as SLED. Triallists should also endeavour to follow the recommendations regarding clinical endpoints assessment in RCTs in ARF made by the Working Group of the Acute Dialysis Quality Initiative Working Group (Palevsky 2002). All studies should endeavour to use common definitions for ARF and outcomes such as hypotension. The Acute Renal Failure Trial Network study (Palevsky 2005a) aims to recruit 1164 patients with ARF the design of the study is intended to deliver data on comparison between low and high dose of dialysis using both IRRT and CRRT techniques. The Augmented Versus Normal Renal Replacement Therapy in Severe Acute Renal Failure study by The Australia and New Zealand Intensive Care Group (ANZICS 2005) will compare CVVHDF at a dose of 25 or 40 mL/kg/h in 1500 patients. These two large RCTs that are under way look very promising in providing clinicians with robust data that will help deliver the most appropriate RRT strategies for patients with ARF.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Augustine 2004

Methods	Country: USA Setting: University teaching hospital Time frame: November 1995 to January 1999 Design: Parallel Randomisation method: Adequate, using sealed envelopes Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analyses: NS Intention-to-treat analysis: Yes Follow-up period: Patients were followed up until death or hospital discharge Lost to follow-up: 0/80
Participants	CRRT GROUP Number: 40 Mean age: 61.4 years Sex (M/F): 28/12 Mean Cleveland Clinic Foundation Organ severity score: 11.6 Surgery: 65% IRRT GROUP Number: 40 Mean age: 61.4 years Sex (M/F): 26/14 Mean Cleveland Clinic Foundation Organ severity score: 12.0 Surgery: 67.5%
Interventions	TREATMENT GROUP CVVHD Low-flux polysulfone membrane Blood flow rate: 200 mL/min Dialysate flow varied according to dry weight Bicarbonate dialysate: 35 mEq/L Anticoagulation: Heparin Dose adjusted to achieve weekly Kt/V of 3.6 CONTROL GROUP IHD 3 times/week Low-flux polysulfone Blood flow rate: 300 mL/min Dialysate flow: 500 mL/min Duration of HD varied to achieve weekly Kt/V of 3.6

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Augustine 2004 (*Continued*)

Outcomes	Mortality Patients off dialysis on discharge Patients requiring increase in pressor therapy Haemodynamic instability Arrhythmias Recurrent clotting of dialysis filter MAP Number of days until hospital discharge Mean survival time in those who died
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Method of randomisation, blinding COMPLETENESS OF FOLLOW-UP - Enrolled/randomised: 80 - Analysed: 80 - Per cent followed: 100%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Davenport 1991

Methods	Country: UK Setting: NS Timeframe: NS Design: Parallel Randomisation method: Adequate, random numbers Blinding - Participants: NS - Investigators: NS - Outcome assessors: NS - Data analyses: NS Intention-to-treat analysis: Yes Follow-up period: 24 hours Lost to follow-up: 0/22
Participants	INCLUSION CRITERIA Acute oliguric renal failure (urine output < 10 mL/h) Grade IV hepatic coma Creatinine > 400 μmol/L Intubated (electively hyperventilated) PATIENT CHARACTERISTICS Sex (M/F): 14/8 Median age: 30 years (range 21-62)

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Davenport 1991 (*Continued*)

	Exact patient characteristics for each of the groups were not stated separately EXCLUSION CRITERIA: NS
Interventions	CRRT GROUP CAVHF/CAVHD Hospal 2400 membrane Ultrafiltration rate: 900 mL/h Dialysate flow rate: 1400 mL/h IRRT GROUP IHF Polyamide hollow fibre hemofilter Blood pump speed: 200 mL/min Transmembrane pressure: 200 mmHg
Outcomes	MAP
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS COMPLETENESS OF FOLLOW-UP - Enrolled/randomised: 22 - Analysed: 22 - Per cent followed: 100%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gasparovic 2003

Methods	Country: Croatia Setting: University hospital Timeframe: NS Design: Parallel Randomisation method: Adequate, coin toss Blinding - Participants: NS - Investigators: NS - Outcome assessors: NS - Data analyses: NS Intention-to-treat analysis: Yes Follow-up period: 21 days Lost to follow-up: 0/104
Participants	INCLUSION CRITERIA ARF definition: At least two of the three following criteria - threefold increase in creatinine, hyperkalaemia > 5.5 μmol/L, base excess > -6

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	Multiple organ failure CRRT GROUP Number: 52 Sepsis: 83% Mean APACHE II score: 21.9 Mean SOFA score: 11.0 Mean MARSHAL score: 10.1 IRRT GROUP Number: 52 Sepsis: 71% Mean APACHE II score: 20.3 Mean SOFA score: 9.8 Mean MARSHAL score: 8.8 EXCLUSION CRITERIA: NS
Interventions	TREATMENT GROUP CVVHF First 33 patients had low volume HF (18 mL/kg/h) and the next had high volume HF (35 mL/kg/h) using polysulfone membrane CONTROL GROUP IHD 3-4 hour treatments Blood flow: 200-250 mL/min Dialysate flow: 500 mL/min Membrane: polysulfone, most frequently without heparin
Outcomes	Mortality
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 0/104 STOP OR END POINT/S: NS COMPLETENESS OF FOLLOW-UP - Enrolled/randomised: 104 - Analysed: 104 - Per cent followed: 100%

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

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John 2001

Methods	Country: Germany Setting: University teaching hospital Time frame: NS Design: Parallel Randomisation method: Adequate Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analyses: NS Intention-to-treat analysis: No Follow-up period: 24 hours Lost to follow-up: 0/30
Participants	INCLUSION CRITERIA All patients admitted to the ICU aged between 18-80 years Body weight between 50-100 kg ARF (creatinine >3 g/L and or urine output <10 mL/h) Presence of severe septic shock according to ACCP/CSSM conference criteria Need for mechanical ventilation: > 48 hours APACHE II score: between 20-45 Pulmonary Capillary Wedge Pressure: >12 mm Hg and <18 mm Hg All patients had septic shock CRRT GROUP Number: 20 Mean age: 59 years Sex (M/F): 17/3 APACHE II score: 34 IRRT GROUP Number: 10 Mean age: 64 years Sex (M/F): 9/1 APACHE II score: 33 EXCLUSION CRITERIA No previous history of CRF Life threatening electrolyte disorders that made IHD mandatory Surgical procedure performed within 48 hours of admission Concomitant participation in any other trial Clearly irreversible condition with expectedly rapid fatal course during the next 48 hours or the decision to limit treatment Any form of RRT 12 hours prior to inclusion
Interventions	TREATMENT GROUP CVVHF High-flux polysulfone membranes Fluid removal was between 1.2-1.8 L/24 h Vasopressor support increased during RRT to maintain MAP not lower than 20% of baseline Blood flow: 250 mL/min Ultrafiltration rate: 2 L/h

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	Fluids rewarmed to 37C and infused post-dilutionally CONTROL GROUP IHD Low-flux polysulfone membranes for 4 hours Fluid removal was between 1.2-1.8 L/24 h Vasopressor support increased during RRT to maintain MAP not lower than 20% of baseline Blood flow: 250 mL/min Bicarbonate-based dialysate
Outcomes	Hypotensive episodes (decrease in MAP > 20% from baseline) Patients requiring increase in vasopressor support due to poor response to fluid challenge Noradrenaline dose at 24 hours (mg/h) Arrhythmias (causing treatment conversion) Recurrent clotting (causing treatment conversion) Systolic BP (absolute change from baseline)
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 3 (1 each from the IHD and CVVHF groups were excluded as a rapidly fatal course was expected. 1 patient on CVVHF was excluded because of hyperkalaemia) STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Method of randomisation COMPLETENESS OF FOLLOW-UP - Enrolled/randomised: 33 - Analysed: 30 - Per cent followed: 90%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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Kielstein 2004

Methods	Country: Germany Setting: University teaching hospital Time frame: NS Design: Parallel Randomisation method: Adequate, random numbers Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analyses: NS Intention-to-treat analysis: No Follow-up period: 24 hours Lost to follow-up: 0/40
Participants	INCLUSION CRITERIA Need for respirator support Presence of oliguric/anuric ARF (urine output < 500 mL/d) CRRT GROUP Number: 19 Mean age: 50.1 years Sex (M/F): 12/7 APACHE II score: 32.3 Sepsis: 75% IRRT GROUP Number: 20 Mean age: 50.8 years Sex (M/F): 15/5 APACHE II score: 32.6 Sepsis: 85% EXCLUSION CRITERIA Pre-existing CKF/ESKD Severe clotting or bleeding problems
Interventions	CRRT GROUP CVVH Polysulfone high-flux dialysers Blood flow: 200 mL/min The treatment dose for CVVH, i.e. substitute fluid infused was at least 30 mL/kg/h CVVH given for 24 hours IRRT GROUP Extended dialysis using polysulfone high-flux membrane given for 12 hours Blood flow: 200 mL/min
Outcomes	Number of patients with clotting of dialysis filter Number of patients requiring escalation of pressor therapy Norepinephrine dose
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 1 patient in the CRRT group was excluded after randomisation due to displacement of the dialysis catheter STOP OR END POINT/S: NS

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Kielstein 2004 (*Continued*)

	ADDITIONAL DATA REQUESTED FROM AUTHORS: None COMPLETENESS OF FOLLOW-UP - Enrolled/randomised:40 - Analysed: 39 - Per cent followed: 97.5%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Kierdorf 1994

Methods	Country: Germany Setting: University teaching hospital Time frame: NS Design: Parallel Randomisation method: Adequate, coin toss Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analyses: NS Intention-to-treat analysis: No Follow-up period: NS. However it appears that patients were followed up only up to their death in ICU or discharge from ICU Lost to follow-up: 5/100
Participants	INCLUSION CRITERIA Patients admitted to the ICU in the authors' hospital requiring RRT for ARF CRRT GROUP Number: 52 Mean APACHE II score: 26 IRRT GROUP Number: 48 Mean APACHE II score: 24.8 EXCLUSION CRITERIA: NS
Interventions	TREATMENT GROUP CVVHF Polyacrylonitrile membrane CONTROL GROUP IHD Polymethylmethacrylate (PMMA) membrane 6 to 7 times/wk
Outcomes	Mortality

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Kierdorf 1994 (*Continued*)

Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 5 patients were excluded post-randomisation. Authors have not stated why they were excluded STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Method of randomisation COMPLETENESS OF FOLLOW-UP - Enrolled/randomised: 100 - Analysed: 95 - Per cent followed: 95%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Mehta 2001

Methods	Country: USA Setting: Multicentre trial Time frame: January 1991 to September 1995 Design: Parallel Randomisation method: Adequate. Computerised random number generator Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analyses: NS Intention-to-treat analysis: Yes Follow-up period: Patients were followed up until death or hospital discharge Lost to follow-up: 0/166
Participants	INCLUSION CRITERIA All adult ICU patients with ARF in whom a nephrology consultation was obtained ARF definition: BUN > 40 mg/dL (140 mmol/L) or a serum creatinine > 2.0 mg/dL (177 μmol/L) or ARF defined as rise in creatinine > 1 mg/dL compared with baseline in patients with known CRF Patients should require dialysis MAP > 70 mm Hg with or without pressor support CRRT GROUP Number: 84 Mean age: 54.5 years Male: 83.3% APACHE II score: 25.5 APACHE III score: 96.4 Surgery: 23.8% Liver failure: 42.9% IRRT GROUP Number: 82 Mean age: 56.3 years

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	Male: 68.3% APACHE II score: 23.7 APACHE III score: 87.7 Surgery: 31.7% Liver failure: 29.3% EXCLUSION CRITERIA Previous dialysis for acute or CKF Kidney transplantation ARF from urinary tract obstruction or volume responsive prerenal state
Interventions	TREATMENT GROUP CAVHDF in the first two years followed by CVVHDF in the following years. Polysulfone or polyacrylonitrile membranes Blood flow: 100 mL/min Dialysate flow rate: 16.7 mL/min Ultrafiltration rate: 400-800 mL/h Anticoagulation: Heparin, citrate or saline flushes At least 25 hours treatment was considered necessary as satisfactory intervention period CONTROL GROUP IHD using bicarbonate dialysate Dialysate flow rate: 500 mL/min Blood flow rate: 200-300 mL/min Both cellulose and synthetic membranes were used At least 2 sessions of at least 3 hours each was necessary for considering as successful intervention
Outcomes	Mortality (ICU and in-hospital) Patients with complete renal recovery at discharge Number of surviving patients on dialysis at hospital discharge Patients with bleeding complications Length of stay in ICU Length of stay in hospital
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 14 (3 from the IRRT and 11 from the CRRT group. 7 patients died and 7 had improvement in renal function) STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None COMPLETENESS OF FOLLOW-UP - Enrolled/randomised: 166 - Analysed: 166 - Per cent followed: 100%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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Misset 1996

Methods	Country: France Setting: Single-centre study in ICU Timeframe: NS Design: Crossover Randomisation method: Unclear Blinding - Participants: NS - Investigators: NS - Outcome assessors: NS - Data analyses: NS Intention-to-treat analysis: Yes Follow-up period: 24 hours Lost to follow-up: 0/39
Participants	INCLUSION CRITERIA ARF definition: Creatinine > 400 μmol/L or urea > 30 mmol/L Mechanical ventilation for more than 48 hours PATIENT CHARACTERISTICS Mean age: 62 years Sex (M/F): 19/8 Mean SAPS score: 15 Sepsis: 59.2% Cardiac surgery: 25.9% EXCLUSION CRITERIA Hyperkalaemia: > 7 mEq/L Absence of femoral arterial access Dialysis in previous week or for CRF Decision to limit the intensity of care
Interventions	TREATMENT GROUP CAVHD Polyamide membrane Ringers lactate Ultrafiltration rate: 15 mL/min Anticoagulation: Heparin 24 hour washout period between treatments CONTROL GROUP IHD Single pump extra-corporeal circuit Cuprophane membrane Bicarbonate Blood flow: 100-200 mL/min 24 hour washout between treatments
Outcomes	MAP
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 12 patients were excluded post-randomisation out of which 11 died and 1 had clotting of the CAVH system, STOP OR END POINT/S: NS COMPETENESS OF FOLLOW-UP

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	- Enrolled/randomised: 39 - Analysed: 27 - Per cent followed: 69%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Noble 2006

Methods	Country: UK Setting: University teaching hospital Time frame: January 1984 to November 1991 Design: Parallel Randomisation method: Adequate, random numbers Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analyses: NS Intention-to-treat analysis: No Follow-up period: Until patient death or hospital discharge Lost to follow-up: 0/94
Participants	INCLUSION CRITERIA Need for mechanical ventilation via an endotracheal tube for acute respiratory failure Need for RRT for ARF CRRT GROUP Number: 54 Mean age: 53.9 years Sex: 74% male Surgical: 42.59% Sepsis: 61.11% IRRT GROUP Number: 40 Mean age: 53.35 years Sex: 75% male Surgical: 55.0% Sepsis: 55.0% EXCLUSION CRITERIA Pre-existing ESKD Kidney transplantation Refusal of consent
Interventions	TREATMENT GROUP CHD via a Scribner shunt or venous dialysis catheter Bicarbonate dialysate

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	Blood flow: 150 mL/min Dialysate flow:300-500 mL/min Dialysis membranes: Fresenius polysulfone CONTROL GROUP IHD Cuprophane membranes for 4 h/d every day
Outcomes	ICU and In-hospital mortality Bleeding complications
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 9 patients (4 from the IRRT and 5 from the CRRT group). Reason for exclusions: 5 patients died, 3 were not ventilated and 1 did not receive RRT in ICU STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Authors provided their trial's raw data COMPLETENESS OF FOLLOW-UP - Enrolled/randomised: 94 - Analysed: 94 - Per cent followed: 100%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Ronco 1999a

Methods	Country: Italy/Australia Setting: ICU/nephrology ward Timeframe: NS Design: Crossover trial Randomisation method: Unclear Blinding - Participants: NS - Investigators: NS - Outcome assessors: NS - Data analyses: NS Intention-to-treat analysis: Yes Follow-up period: 2 days Lost to follow-up: 0/10
Participants	PATIENT CHARACTERISTICS Number: 10 Surgery: 60% EXCLUSION CRITERIA Major fluid loss Bleeding disorder

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Ronco 1999a (*Continued*)

Interventions	TREATMENT GROUP CVVHD Blood flow: 200 mL/min Membrane: AN69 Sodium: 140 mEq/L Bicarbonate buffer Overnight washout CONTROL GROUP IHD, 4 hour treatment blood flow: 250 mL/min Membrane: AN69 Dialysate flow: 500 mL/min Sodium: 140 mEq/L Bicarbonate buffer Overnight washout
Outcomes	MAP
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 0/10 STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Method of randomisation COMPLETENESS OF FOLLOW-UP - Enrolled/randomised: 10 - Analysed: 10 - Per cent followed: 100%

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

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Ronco 2001

Methods	Country: Italy/Australia Setting: ICU/nephrology ward Timeframe: NS Design: Crossover trial Randomisation method: Unclear Blinding - Participants: NS - Investigators: NS - Outcome assessors: NS - Data analyses: NS Intention-to-treat analysis: Yes Follow-up period: 48 hours Lost to follow-up: 0/22
Participants	PATIENT CHARACTERISTICS Number: 22 No other patient characteristic stated EXCLUSION CRITERIA: NS
Interventions	TREATMENT GROUP Slow continuous ultrafiltration CONTROL GROUP Intermittent ultrafiltration
Outcomes	MAP
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 0/22 STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Method of randomisation COMPLETENESS OF FOLLOW-UP - Enrolled/randomised: 22 - Analysed: 22 - Per cent followed: 100%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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SHARF 2005

Methods	Country: Belgium Setting: Multicentre Timeframe: April 2002 to March 2004 Design: Parallel Randomisation method: Adequate, done electronically Blinding - Participants: NS - Investigators: NS - Outcome assessors: NS - Data analyses: NS Intention-to-treat analysis: Yes Follow-up period: Until end of RRT Lost to follow-up: 0/316
Participants	INCLUSION CRITERIA Age: >18 years Creatinine: >2 mg/dL CRRT GROUP Number: 172 Mean age: 65 years Sex (M/F): 103/69 Surgical: 27.1% Mean APACHE II score: 26.3 Mean SOFA score: 10.7 IRRT GROUP Number: 144 Mean age: 67 years (range 20-96) Sex (M/F): 84/60 Surgical: 29% Mean APACHE II score: 27.1 Mean SOFA score: 10.8 EXCLUSION CRITERIA CKD (creatinine > 1.5 mg or small kidneys on renal tract ultrasound)
Interventions	CRRT GROUP CVVHF, 24 h/d Blood flow rate: 100-200 mL/min Substitution rate: 1-2 L/h Lactate or bicarbonate solutions were used Membrane: Polysulfone or AN69 CONTROL GROUP IHD Membrane: Polysulfone or AN69 Bicarbonate dialysate Blood flow: 100-300 mL/min Dialysate flow: 100-500 mL/min 4-6 hour sessions daily

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SHARF 2005 (*Continued*)

Outcomes	Mortality (in-hospital) Renal recovery expressed as GFR (mL/min) Hospital length of stay ICU length of stay
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S : NS COMPETENESS OF FOLLOW-UP - Enrolled/randomised: 316 - Analysed: 316 - Per cent followed: 100%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Stefanidis 1995

Methods	Country: Germany Setting: Single centre, University hospital ICU Timeframe: NS Design: Parallel Randomisation method: Adequate, coin toss Blinding - Participants: NS - Investigators: NS - Outcome assessors: NS - Data analyses: NS Intention-to-treat analysis: Yes Follow-up period: Unclear Lost to follow-up: 0/35
Participants	INCLUSION CRITERIA Patients with ARF Definition ARF: NS PATIENT CHARACTERISTICS Number: 35 Mean age: 61 years Sex (M/F): 25/10 EXCLUSION CRITERIA Patient with venous thrombosis Pulmonary embolism Arterial thrombosis or embolism Artificial mechanical valves

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Stefanidis 1995 (*Continued*)

Interventions	CRRT GROUP CVVHF High-flux polysulfone membranes IRRT GROUP IHD PMMA membrane
Outcomes	Mortality Bleeding complications
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 0/35 STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: Method of randomisation COMPETENESS OF FOLLOW-UP - Enrolled/randomised: 35 - Analysed: 35 - Per cent followed: 100%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Uehlinger 2005

Methods	Country: Switzerland Setting: Single centre, ICU in the University Hospital of Berne Timeframe: June 1998 to December 2000 Design: Parallel Randomisation method: Adequate, computer generated random numbers Blinding - Participants: NS - Investigators: NS - Outcome assessors: NS - Data analyses: NS Intention-to-treat analysis: NS Follow-up period: Patients were followed up until hospital discharge Lost to follow-up: 0/129
Participants	INCLUSION CRITERIA All adult ICU patients for whom RRT was scheduled for ARF ARF definition: serum creatinine > 350 μmol/L (4 mg/dL) and/or urine output < 20 mL/h CRRT GROUP Number: 70 Median age: 67 years Sex (M/F): 46/24 Sepsis: 43%

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	Median SAPS score: 55 IRRT GROUP Number: 55 Median age: 66 years Sex (M/F): 40/15 Sepsis: 51% Median SAPS score: 55 EXCLUSION CRITERIA Pre-existing CKF treated by RRT Specific forms of RRT required for intoxication
Interventions	CRRT GROUP CVVHDF Membrane: AN69 high-flux hemofilter Blood flow: 100-180 mL/min Standard lactate-buffered fluid was used as dialysate and a substitute at a combined rate of 2000 mL/h Fluids given in a predilution fashion IRRT GROUP IHD Membrane: Polysulfone Blood flow: 150-300 mL/min Bicarbonate buffered dialysate was used Ultrafiltration rate: 250-1000 mL/h Usual HD session lasted for 3-4 hours
Outcomes	Mortality (ICU and in-hospital) Number of patients with hypotension episodes Renal recovery (number of surviving patients not requiring dialysis) Number of patients with haemodynamic instability
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 4 excluded after randomisation due to violation of randomisation procedures STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None COMPETENESS OF FOLLOW-UP - Enrolled/randomised: 129 - Analysed: 125 - Per cent followed: 100%

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

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Vinsonneau 2006

Methods	Country: France Setting: Multicentre Timeframe: October 1999 to March 2003 Design: Parallel Randomisation method: Adequate, computer generated Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analyses: NS Intention-to-treat analysis: Yes Follow-up period: 90 days Lost to follow-up: 0/360
Participants	INCLUSION CRITERIA ARF definition: serum urea concentration >/= 36 mmol/L or serum creatinine concentration >/= 310 μmol/L Need for RRT Multiple-organ dysfunction syndrome: Defined by a logistic organ dysfunction score 15 of 6 or more. Authors selected a logistic organ dysfunction score of 6 or more because their definition of ARF already assumed a score of at least 5 A new criterion was introduced due to low recruitment rates after 8 months of trial inception Oliguria: Urine output < 320 mL for 16 h, despite appropriate fluid loading CRRT GROUP Number: 176 Mean age: 65 years Sex (M/F): 129/46 Mean SAPS II Score: 65 Sepsis: 56% IRRT GROUP Number: 184 Mean age: 65 years Sex (M/F): 132/52 Mean SAPS II Score: 64 Sepsis: 69% EXCLUSION CRITERIA Pregnancy Age: < 18 years CKF: Creatinine > 180 ARF due to vascular/obstruction ACE inhibitor therapy Coagulation disorder (PT< 20%, platelets < 30,000) Uncontrolled haemorrhage SAPS II score < 37 Moribund Severe disease with life expectancy less than 8 days
Interventions	CRRT GROUP CVVHDF Blood flow: >/= 120 mL/min

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	Dialysate flow: >/= 500 mL/h Ultrafiltration flow> >/= 1000 mL/h The recommendations also suggested that treatment should be given continuously with a change of membrane every 48 h Membrane: Polyacrylonitrile IHD GROUP Blood flow: >/= 250 mL/min Dialysate flow: 500 mL/min To achieve optimum haemodynamic stability a high sodium concentration (150 mmol/L) dialysate at a low temperature (35°C) was used Therapy was started simultaneously connecting to the catheter both lines of the circuit filled with 09% saline (isovolemic connection), be applied for at least 4 h, and be given every 48 h if anuria or oliguria were present In other cases, the frequency was defined to maintain a urea concentration of less than 40 mmol/L Membrane: Polyacrylonitrile
Outcomes	Mortality Hypotension Bleeding episodes Arrhythmias Catheter infections Length of ICU stay Length of hospital stay
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 1 patient in the CRRT group withdrew consent after randomisation STOP OR END POINT/S: 60 days, primary end-point COMPETENESS OF FOLLOW-UP - Enrolled/randomised: 360 - Analysed: 360 - Per cent followed: 100%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

ARF - acute renal failure; CAVHD - continuous arteriovenous haemodialysis; CAVHDF - continuous arteriovenous haemodiafiltration; CAVHF - continuous arteriovenous haemofiltration; CHD - continuous haemodialysis; CKF - chronic kidney failure; CRRT - continuous renal replacement therapy; CVVHD - continuous venovenous haemodialysis; CVVHDF - continuous venovenous haemodiafiltration; CVVHF - continuous venovenous haemofiltration; ESKD - end-stage kidney disease; GFR - glomerular filtration rate; IHD - intermittent haemodialysis; IHF - intermittent haemofiltration; IRRT - intermittent renal replacement therapy; MAP - mean arterial pressure; NS - not stated; RRT - renal replacement therapy

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Characteristics of excluded studies *[ordered by study ID]*

Cho 2006	Non randomised study
Davenport 1993	Included non randomised patients as well along with the randomised cohort
Kellum 2002	Review article, meta-analysis of RCTs and on RCTS
Kumar 2004	Non randomised study
Ronco 1999b	Outcomes not relevant to the review
Swartz 1999a	Non randomised study
Tonelli 2002a	Review article, meta-analysis of RCTs

Characteristics of ongoing studies *[ordered by study ID]*

ANZICS 2005

Trial name or title	Multicentre, unblinded, randomised, controlled trial to assess the effect of augmented vs. normal continuous renal replacement therapy (CRRT) on 90-day all-cause mortality of intensive care unit patients with severe acute renal failure (ARF)
Methods	
Participants	The patient fulfils at least ONE of the following clinical criteria for initiating CRRT: 1. The treating clinician believes that the patient requires CRRT for acute renal failure. 2. The clinician is uncertain about the balance of benefits and risks likely to be conferred by treatment with higher intensity or lower intensity CRRT. 3. The treating clinicians anticipate treating the patient with CRRT for at least 72 hours. 4. Informed consent has been obtained
Interventions	"Augmented" CRRT regimen to deliver an effluent rate of 40 ml/kg/hr compared to "normal" CRRT at an effluent rate of 25ml/kg/hr in ICU patients with severe ARF
Outcomes	Primary Outcome Measures: 1. Death from all causes at 90 days after randomisation. Secondary Outcome Measures: 1. Death within the in the intensive care unit. 2. Death within 28 days of randomisation. 3. Death prior to hospital discharge. 4. Length of ICU stay. 5. Length of hospital stay. 6. The need for and duration of other organ support (inotropic/vasopressor support and positive pressure

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	ventilation). 7. CRRT-free days. 8. Dialysis-independent survival.
Starting date	November 2005
Contact information	David Ali, PhD +61 2 99934567 Ext. 567 dali@thegeorgeinstitute.org Martin Gallagher, MD +61 2 9993 4552 Ext. 552 mgallagher@thegeorgeinstitute.org
Notes	

Palevsky 2005a

Trial name or title	CSP #530 - Intensive vs. Conventional Renal Support in Acute Renal Failure
Methods	
Participants	1. Males and females 18 Years and above 2. Acute renal failure clinically consistent with a diagnosis of acute tubular necrosis 3. Plan for renal replacement therapy by clinical team 4. Receiving care in a critical care unit 5. One non-renal organ failure or sepsis 6. Patient or surrogate provides informed consent
Interventions	In both arms, RRT will be initiated using the same criteria. Hemodynamically stable patients (SOFA cardiovascular score: 0-2) will receive intermittent hemodialysis (IHD) while hemodynamically unstable patients (SOFA cardiovascular score: 3-4) will be treated with continuous venovenous hemodiafiltration (CVVHDF) or sustained low-efficiency hemodialysis (SLED). Patients will convert between modalities of therapy as hemodynamic status changes over time. The intensity of therapy in IHD and SLED will vary between groups based on treatment frequency; with treatments provided 6-times per week in the intensive management strategy arm and 3-times per week in the conventional management strategy arm. In CVVHDF, intensity of therapy will vary based on effluent flow rate with a prescribed flow rate of 35 mL/kg/hour in the intensive management strategy arm and 20 mL/kg/hour in the conventional management strategy arm.
Outcomes	60-day all-cause mortality.
Starting date	July 2003
Contact information	Department of Veterans Affairs:
Notes	

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DATA AND ANALYSES

Comparison 1. CRRT versus IRRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 In-hospital mortality	7	1245	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.92, 1.12]
1.2 ICU mortality	5	515	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.90, 1.26]
1.3 In-hospital mortality (excluding Mehta 2001)	6	1079	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.06]
1.4 In-hospital mortality (peer-reviewed publications only)	6	929	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.92, 1.16]
2 Days until hospital discharge	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Survival time for patients who died	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Recovery of renal function	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Surviving patients not requiring RRT	3	161	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.07]
4.2 Surviving patients with GFR > 15 mL/min	1	126	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.94, 1.36]
5 Patients with haemodynamic instability	2	205	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.10, 2.28]
6 Patients with hypotension	3	514	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.72, 1.16]
7 Mean arterial pressure at end of study period	2	112	Mean Difference (IV, Random, 95% CI)	5.35 [1.41, 9.29]
8 Systolic blood pressure (absolute change from baseline)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 Patients requiring escalation of pressor therapy	3	149	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.26, 1.08]
10 Dose of norepinephrine	2	69	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.36, 0.33]
11 Patients with bleeding complications	5	638	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.59, 1.80]
12 Patients with recurrent clotting of dialysis filters	3	149	Risk Ratio (M-H, Random, 95% CI)	8.50 [1.14, 63.33]
13 Patients with arrhythmias during RRT	2	439	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.23, 1.05]
14 RRT modality switch due to complications	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Medical reasons	4	922	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.58, 3.48]
14.2 Medical reasons (Mehta 2001 excluded)	3	756	Risk Ratio (M-H, Random, 95% CI)	1.89 [1.36, 2.63]

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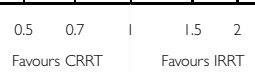
Analysis 1.1. Comparison 1 CRRT versus IRRT, Outcome 1 Mortality.

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Comparison: 1 CRRT versus IRRT

Outcome: 1 Mortality

Study or subgroup	CRRT n/N	IRRT n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 In-hospital mortality					
Augustine 2004	27/40	28/40		7.9 %	0.96 [0.72, 1.30]
Gasparovic 2003	37/52	31/52		8.6 %	1.19 [0.90, 1.58]
Mehta 2001	55/84	39/82		9.1 %	1.38 [1.05, 1.81]
Noble 2006	43/54	34/40		18.6 %	0.94 [0.78, 1.13]
SHARF 2005	100/172	90/144		20.2 %	0.93 [0.78, 1.11]
Uehlinger 2005	33/70	28/55		5.4 %	0.93 [0.65, 1.33]
Vinsonneau 2006	118/176	126/184		30.2 %	0.98 [0.85, 1.13]
Subtotal (95% CI)	**648**	**597**		**100.0 %**	**1.01 [0.92, 1.12]**
Total events: 413 (CRRT), 376 (IRRT)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 8.19, df = 6 (P = 0.22); I^2 =27%					
Test for overall effect: Z = 0.22 (P = 0.83)					
2 ICU mortality					
John 2001	14/20	7/10		8.5 %	1.00 [0.61, 1.64]
Kierdorf 1994	29/48	34/52		22.4 %	0.92 [0.68, 1.25]
Mehta 2001	50/84	34/82		21.2 %	1.44 [1.05, 1.96]
Noble 2006	42/54	30/40		38.2 %	1.04 [0.82, 1.30]
Uehlinger 2005	24/70	21/55		9.6 %	0.90 [0.56, 1.43]
Subtotal (95% CI)	**276**	**239**		**100.0 %**	**1.06 [0.90, 1.26]**
Total events: 159 (CRRT), 126 (IRRT)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 5.06, df = 4 (P = 0.28); I^2 =21%					
Test for overall effect: Z = 0.72 (P = 0.47)					
3 In-hospital mortality (excluding Mehta 2001)					
Augustine 2004	27/40	28/40		8.7 %	0.96 [0.72, 1.30]
Gasparovic 2003	37/52	31/52		9.5 %	1.19 [0.90, 1.58]
Noble 2006	43/54	34/40		20.5 %	0.94 [0.78, 1.13]
SHARF 2005	100/172	90/144		22.2 %	0.93 [0.78, 1.11]
Uehlinger 2005	33/70	28/55		6.0 %	0.93 [0.65, 1.33]
Vinsonneau 2006	118/176	126/184		33.2 %	0.98 [0.85, 1.13]



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Study or subgroup	CRRT n/N	IRRT n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**564**	**515**		**100.0 %**	**0.97 [0.89, 1.06]**
Total events: 358 (CRRT), 337 (IRRT)					
Heterogeneity: Tau² = 0.0; Chi² = 2.49, df = 5 (P = 0.78); I² =0.0%					
Test for overall effect: Z = 0.65 (P = 0.51)					
4 In-hospital mortality (peer-reviewed publications only)					
Augustine 2004	27/40	28/40		9.9 %	0.96 [0.72, 1.30]
Gasparovic 2003	37/52	31/52		10.8 %	1.19 [0.90, 1.58]
Mehta 2001	55/84	39/82		11.4 %	1.38 [1.05, 1.81]
Noble 2006	43/54	34/40		23.3 %	0.94 [0.78, 1.13]
Uehlinger 2005	33/70	28/55		6.8 %	0.93 [0.65, 1.33]
Vinsonneau 2006	118/176	126/184		37.9 %	0.98 [0.85, 1.13]
Subtotal (95% CI)	**476**	**453**		**100.0 %**	**1.03 [0.92, 1.16]**
Total events: 313 (CRRT), 286 (IRRT)					
Heterogeneity: Tau² = 0.01; Chi² = 7.48, df = 5 (P = 0.19); I² =33%					
Test for overall effect: Z = 0.57 (P = 0.57)					

0.5 0.7 1 1.5 2
Favours CRRT Favours IRRT

Analysis 1.2. Comparison 1 CRRT versus IRRT, Outcome 2 Days until hospital discharge.

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Comparison: 1 CRRT versus IRRT

Outcome: 2 Days until hospital discharge

Study or subgroup	CRRT N	Mean(SD)	IRRT N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Augustine 2004	13	35.8 (20.5)	12	41.9 (30.1)		-6.10 [-26.45, 14.25]

-20 -10 0 10 20
Favours CRRT Favours IRRT

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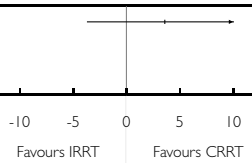
Analysis 1.3. Comparison 1 CRRT versus IRRT, Outcome 3 Survival time for patients who died.

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Comparison: 1 CRRT versus IRRT

Outcome: 3 Survival time for patients who died

Study or subgroup	CRRT N	Mean(SD)	IRRT N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Augustine 2004	27	14.3 (16.1)	28	10.7 (11.2)		3.60 [-3.75, 10.95]



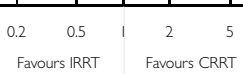
Analysis 1.4. Comparison 1 CRRT versus IRRT, Outcome 4 Recovery of renal function.

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Comparison: 1 CRRT versus IRRT

Outcome: 4 Recovery of renal function

Study or subgroup	CRRT n/N	IRRT n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Surviving patients not requiring RRT					
Augustine 2004	5/13	4/12		0.6 %	1.15 [0.40, 3.31]
Mehta 2001	25/29	40/43		24.6 %	0.93 [0.78, 1.10]
Uehlinger 2005	36/37	26/27		74.8 %	1.01 [0.92, 1.11]
Subtotal (95% CI)	**79**	**82**		**100.0 %**	**0.99 [0.92, 1.07]**
Total events: 66 (CRRT), 70 (IRRT)					
Heterogeneity: Tau² = 0.0; Chi² = 0.97, df = 2 (P = 0.62); I² =0.0%					
Test for overall effect: Z = 0.21 (P = 0.83)					
2 Surviving patients with GFR > 15 mL/min					
SHARF 2005	45/54	53/72		100.0 %	1.13 [0.94, 1.36]
Subtotal (95% CI)	**54**	**72**		**100.0 %**	**1.13 [0.94, 1.36]**
Total events: 45 (CRRT), 53 (IRRT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.33 (P = 0.18)					



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Analysis 1.5. Comparison 1 CRRT versus IRRT, Outcome 5 Patients with haemodynamic instability.

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Comparison: 1 CRRT versus IRRT

Outcome: 5 Patients with haemodynamic instability

Study or subgroup	CRRT n/N	IRRT n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Augustine 2004	0/40	4/40		21.8 %	0.11 [0.01, 2.00]
Uehlinger 2005	20/70	22/55		78.2 %	0.71 [0.44, 1.17]
Total (95% CI)	**110**	**95**		**100.0 %**	**0.48 [0.10, 2.28]**

Total events: 20 (CRRT), 26 (IRRT)

Heterogeneity: $Tau^2 = 0.75$; $Chi^2 = 1.67$, df = 1 (P = 0.20); $I^2 = 40\%$

Test for overall effect: Z = 0.93 (P = 0.35)

Analysis 1.6. Comparison 1 CRRT versus IRRT, Outcome 6 Patients with hypotension.

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Comparison: 1 CRRT versus IRRT

Outcome: 6 Patients with hypotension

Study or subgroup	CRRT n/N	IRRT n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
John 2001	9/20	6/10		11.8 %	0.75 [0.37, 1.51]
Uehlinger 2005	15/70	8/55		9.5 %	1.47 [0.67, 3.22]
Vinsonneau 2006	61/175	72/184		78.7 %	0.89 [0.68, 1.17]
Total (95% CI)	**265**	**249**		**100.0 %**	**0.92 [0.72, 1.16]**

Total events: 85 (CRRT), 86 (IRRT)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.81$, df = 2 (P = 0.40); $I^2 = 0.0\%$

Test for overall effect: Z = 0.72 (P = 0.47)

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Analysis 1.7. Comparison 1 CRRT versus IRRT, Outcome 7 Mean arterial pressure at end of study period.

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

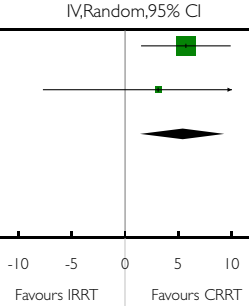
Comparison: 1 CRRT versus IRRT

Outcome: 7 Mean arterial pressure at end of study period

Study or subgroup	CRRT N	Mean(SD)	IRRT N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Augustine 2004	40	79.9 (9.3)	40	74.2 (10)		86.6 %	5.70 [1.47, 9.93]
Misset 1996	16	84 (16.4)	16	80.9 (14.6)		13.4 %	3.10 [-7.66, 13.86]
Total (95% CI)	**56**		**56**			**100.0 %**	**5.35 [1.41, 9.29]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.19, df = 1 (P = 0.66); I^2 =0.0%

Test for overall effect: Z = 2.66 (P = 0.0077)



Analysis 1.8. Comparison 1 CRRT versus IRRT, Outcome 8 Systolic blood pressure (absolute change from baseline).

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Comparison: 1 CRRT versus IRRT

Outcome: 8 Systolic blood pressure (absolute change from baseline)

Study or subgroup	CRRT N	Mean(SD)	IRRT N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
John 2001	20	5 (30)	10	-1 (17)		6.00 [-10.85, 22.85]

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Analysis 1.9. Comparison 1 CRRT versus IRRT, Outcome 9 Patients requiring escalation of pressor therapy.

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Comparison: 1 CRRT versus IRRT

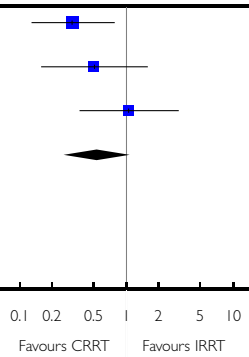
Outcome: 9 Patients requiring escalation of pressor therapy

Study or subgroup	CRRT n/N	IRRT n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Augustine 2004	5/40	16/40		39.8 %	0.31 [0.13, 0.77]
John 2001	4/20	4/10		28.4 %	0.50 [0.16, 1.59]
Kielstein 2004	5/19	5/20		31.9 %	1.05 [0.36, 3.07]
Total (95% CI)	**79**	**70**		**100.0 %**	**0.53 [0.26, 1.08]**

Total events: 14 (CRRT), 25 (IRRT)

Heterogeneity: Tau^2 = 0.13; Chi^2 = 2.92, df = 2 (P = 0.23); I^2 =32%

Test for overall effect: Z = 1.74 (P = 0.081)



Analysis 1.10. Comparison 1 CRRT versus IRRT, Outcome 10 Dose of norepinephrine.

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Comparison: 1 CRRT versus IRRT

Outcome: 10 Dose of norepinephrine

Study or subgroup	CRRT N	Mean(SD)	IRRT N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
John 2001	20	2.18 (1.79)	10	1.98 (1.68)		7.1 %	0.20 [-1.10, 1.50]
Kielstein 2004	19	0.39 (0.57)	20	0.42 (0.58)		92.9 %	-0.03 [-0.39, 0.33]
Total (95% CI)	**39**		**30**			**100.0 %**	**-0.01 [-0.36, 0.33]**

Heterogeneity: Chi^2 = 0.11, df = 1 (P = 0.74); I^2 =0.0%

Test for overall effect: Z = 0.08 (P = 0.94)

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Analysis 1.11. Comparison 1 CRRT versus IRRT, Outcome 11 Patients with bleeding complications.

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Comparison: 1 CRRT versus IRRT

Outcome: 11 Patients with bleeding complications

Study or subgroup	CRRT n/N	IRRT n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
John 2001	3/20	0/10		3.7 %	3.67 [0.21, 64.80]
Mehta 2001	1/56	1/64		4.1 %	1.14 [0.07, 17.85]
Noble 2006	3/54	2/40		10.2 %	1.11 [0.19, 6.34]
Stefanidis 1995	5/18	5/17		28.1 %	0.94 [0.33, 2.69]
Vinsonneau 2006	12/175	13/184		53.9 %	0.97 [0.46, 2.07]
Total (95% CI)	**323**	**315**		**100.0 %**	**1.03 [0.59, 1.80]**

Total events: 24 (CRRT), 21 (IRRT)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.83$, df = 4 (P = 0.93); $I^2 = 0.0\%$

Test for overall effect: Z = 0.12 (P = 0.91)

Analysis 1.12. Comparison 1 CRRT versus IRRT, Outcome 12 Patients with recurrent clotting of dialysis filters.

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Comparison: 1 CRRT versus IRRT

Outcome: 12 Patients with recurrent clotting of dialysis filters

Study or subgroup	CRRT n/N	IRRT n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Augustine 2004	9/40	0/40		19.00 [1.14, 315.80]
John 2001	3/20	0/10		3.67 [0.21, 64.80]
Kielstein 2004	0/19	0/20		0.0 [0.0, 0.0]
Total (95% CI)	**79**	**70**		**8.50 [1.14, 63.33]**

Total events: 12 (CRRT), 0 (IRRT)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.68$, df = 1 (P = 0.41); $I^2 = 0.0\%$

Test for overall effect: Z = 2.09 (P = 0.037)

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Analysis 1.13. Comparison 1 CRRT versus IRRT, Outcome 13 Patients with arrhythmias during RRT.

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Comparison: 1 CRRT versus IRRT

Outcome: 13 Patients with arrhythmias during RRT

Study or subgroup	CRRT n/N	IRRT n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Augustine 2004	0/40	2/40		6.2 %	0.20 [0.01, 4.04]
Vinsonneau 2006	9/175	18/184		93.8 %	0.53 [0.24, 1.14]
Total (95% CI)	**215**	**224**		**100.0 %**	**0.50 [0.23, 1.05]**

Total events: 9 (CRRT), 20 (IRRT)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.38$, df = 1 (P = 0.54); $I^2 = 0.0\%$

Test for overall effect: Z = 1.84 (P = 0.066)

Analysis 1.14. Comparison 1 CRRT versus IRRT, Outcome 14 RRT modality switch due to complications.

Review: Intermittent versus continuous renal replacement therapy for acute renal failure in adults

Comparison: 1 CRRT versus IRRT

Outcome: 14 RRT modality switch due to complications

Study or subgroup	CRRT n/N	IRRT n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Medical reasons					
Augustine 2004	9/40	6/40		22.3 %	1.50 [0.59, 3.82]
Mehta 2001	0/84	15/82		3.5 %	0.03 [0.00, 0.52]
SHARF 2005	63/172	29/144		51.1 %	1.82 [1.24, 2.66]
Vinsonneau 2006	17/176	6/184		23.2 %	2.96 [1.20, 7.34]
Subtotal (95% CI)	**472**	**450**		**100.0 %**	**1.42 [0.58, 3.48]**
Total events: 89 (CRRT), 56 (IRRT)					
Heterogeneity: $Tau^2 = 0.53$; $Chi^2 = 11.20$, df = 3 (P = 0.01); $I^2 = 73\%$					
Test for overall effect: Z = 0.77 (P = 0.44)					
2 Medical reasons (Mehta 2001 excluded)					
Augustine 2004	9/40	6/40		23.1 %	1.50 [0.59, 3.82]

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Study or subgroup	CRRT n/N	IRRT n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
SHARF 2005	63/172	29/144		52.9 %	1.82 [1.24, 2.66]
Vinsonneau 2006	17/176	6/184		24.0 %	2.96 [1.20, 7.34]
Subtotal (95% CI)	**388**	**368**		**100.0 %**	**1.89 [1.36, 2.63]**
Total events: 89 (CRRT), 41 (IRRT)					
Heterogeneity: Tau² = 0.0; Chi² = 1.23, df = 2 (P = 0.54); I² =0.0%					
Test for overall effect: Z = 3.81 (P = 0.00014)					

APPENDICES

Appendix 1. Electronic search strategies

Electronic database	Search strategy
MEDLINE	1. exp Kidney Failure, Acute/ 2. (acute renal failure or acute kidney failure or ARF).tw. 3. (acute renal insufficiency or acute kidney insufficiency).tw. 4. acute tubular necrosis.tw. 5. acute kidney tubular necrosis.tw. 6. ATN.tw. 7. or/1-6 8. *renal replacement therapy/ or *renal dialysis/ or *hemodiafiltration/ or *hemofiltration/ 9. (contin$ adj4 (dialy$ or hemodia$ or haemodia$ or hemofiltr$ or haemofiltr$ or hemodiafilt$ or haemodiafilt$ or filtrat$ or renal replacement therap$ or ultrafiltr$ or arteriovenous$ or venovenous$)).tw. 10. (CVVHD or CAVHD or CVVHDF or CAVHDF or CVVHF or CAVHF or CRRT or SCUF or CVVH or CAVH).tw. 11. or/8-10 12. and/7,11
EMBASE	1. acute kidney failure/ or acute kidney tubule necrosis/ 2. (acute renal failure or acute kidney failure or arf).tw. 3. (acute renal insufficiency or acute kidney insufficiency).tw. 4. (acute tubular necrosis or acute kidney tubular necrosis or ATN).tw. 5. or/1-4 6. (CVVHD or CAVHD or CAVHF or CVVHF or CVVHDF or CAVHDF or CRRT or scuf or CAVH or CVVH).tw. 7. (contin$ adj4 (dialy$ or hemodia$ or haemodia$ or hemofiltr$ or haemofiltr$ or hemodiafilt$ or haemodiafilt$ or filtrat$ or renal replacement therap$.tw or ultrafiltr$)).tw. 8. *dialysis/

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	9. *hemodialysis/ 10. *ultrafiltration/ 11. or/6-10 12. and/5,11
CENTRAL	1. (CVVHD or CAVHD or CVVHF or CAVHF or CAVHDF or CVVHDF or CRRT or CVVH or CAVH).tw. 2. (contin$ adj4 (dial$ or haemodial$ or hemodial$ or haemofilt$ or hemofilt$ or haemodiafilt$ or hemodiafilt$ or renal replacement therap$ or ultrafiltrat$ or filtrat$)).tw. 3. 1 or 2 4. kidney failure, acute.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 5. acute renal failure.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 6. acute kidney failure.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 7. ARF.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 8. ATN.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 9. acute renal insufficiency.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 10. acute tubular necrosis.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 11. exp kidney failure, acute/ or exp kidney tubular necrosis, acute/ 12. or/4-11 13. 3 and 12

WHAT'S NEW

Last assessed as up-to-date: 14 May 2007.

13 May 2008	Amended	Converted to new review format.

HISTORY

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Review first published: Issue 3, 2007

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CONTRIBUTIONS OF AUTHORS

NM conceived this review, screened titkes and abstracts, extracted dat and wrote the review

KSR conceived this review, screened titlles and abstracts, extracted data, performed data analysis, and wrote the review

JA extracted data and was involved in writing the eview and approving the final version

AMM conceived the review, arbitrated study selection, and was involved in correction and approval of the manuscript

DECLARATIONS OF INTEREST

We have no potential conflict of interest to declare.

INDEX TERMS

Medical Subject Headings (MeSH)

Hemodiafiltration [methods]; Kidney Failure, Acute [*therapy]; Randomized Controlled Trials as Topic; Renal Dialysis [*methods]; Renal Replacement Therapy [methods]

MeSH check words

Adult; Humans

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