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Renal Replacement Therapy in Patients With Acute Renal Failure

A Systematic Review

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ACUTE RENAL FAILURE (ARF) IS increasingly common and is associated with high costs and adverse clinical outcomes, including excess mortality, increased length of hospital stay, and the requirement for chronic dialysis in survivors.¹ Diverse options are currently available for prescribing acute renal replacement, including intermittent, continuous, and extended-duration hemodialysis and hemofiltration and combinations thereof. Despite advances in dialysis technology, many questions remain about how best to provide renal replacement to patients with ARF.

This review will critically evaluate current evidence for the optimal dialytic management of ARF, present an evidence-based approach to this clinically important problem, and identify key areas for future research.

METHODS

This study was conducted and reported in accordance with published guidelines.^{2,3}

Data Sources

An expert librarian conducted a comprehensive search to identify prospective cohort studies of renal replacement therapies (RRTs) in patients with ARF. Only articles published as full manuscripts in English were considered. MEDLINE (1966-October 2007),

Context Acute renal failure requiring dialytic support is associated with a high risk of mortality and substantial morbidity.

Objectives To summarize current evidence guiding provision of dialysis for patients with acute renal failure, to make recommendations for management, and to identify areas in which additional research is needed.

Data Sources Systematic searches of peer-reviewed publications in MEDLINE, EMBASE, and All EBM Reviews through October 2007.

Study Selection Randomized controlled trials (RCTs) and prospective cohort studies studying dialytic support in adults with acute renal failure that reported the incidence of clinical outcomes such as mortality, length of stay, need for chronic dialysis, or development of hypotension.

Data Extraction Quality was independently assessed by 2 reviewers using the Jadad score (RCTs) and the Downs and Black checklist (cohort studies). A single reviewer extracted data, which were independently verified by a second reviewer. Results of RCTs were pooled using a random-effects model.

Data Synthesis From 173 retrieved articles, 30 RCTs and 8 prospective cohort studies were eligible. No conclusions could be drawn about optimal indications for or timing of renal replacement. Available data comparing continuous renal replacement therapy (CRRT) with intermittent hemodialysis demonstrated no clinically relevant difference between modalities, including for all-cause mortality (relative risk [RR], 1.10; 95% confidence interval [CI], 0.99-1.23; $I^2=0\%$) or for the requirement for chronic dialysis treatment in survivors (RR, 0.91; 95% CI, 0.56-1.49; $I^2=0\%$). For patients treated with CRRT, limited data suggest that bicarbonate may be preferable to other forms of dialysate alkali and that citrate infusion may be an alternative to systemic anticoagulation in patients at high risk of bleeding. Among patients treated with continuous venovenous hemofiltration (CVVHF), the risk of death was lower at doses of 35 mL/kg per hour (RR of death compared with doses of 20 mL/kg per hour, 0.74; 95% CI, 0.63-0.88). The use of unsubstituted cellulosic membranes should be avoided in intermittent hemodialysis (RR of death compared with biocompatible membranes, 1.23; 95% CI, 1.01-1.50).

Conclusions Based on current data, intermittent hemodialysis and CRRT appear to lead to similar clinical outcomes for patients with ARF. If CVVHF is used, a dose of 35 mL/kg per hour should be provided. Given the paucity of good-quality evidence in this important area, additional large randomized trials are needed to evaluate clinically important outcomes.

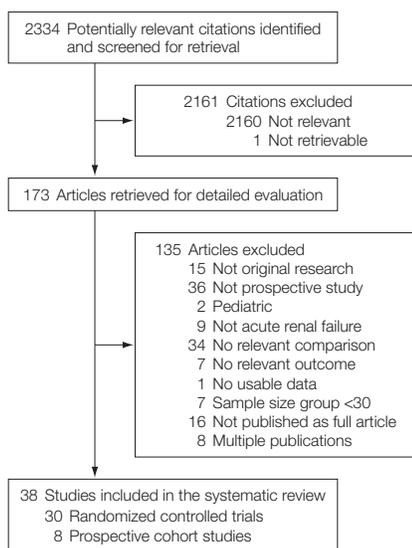
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EMBASE (1988-October 2007), All EBM Reviews (October 2007), and a variety of gray-literature sources (n=36) were searched (clinical trial registries, health technology assessment agencies, and manufacturer Web sites; for detailed search strategies, see the Alberta Kidney Disease Network Web site at <http://www.akdn.info>). Each citation or abstract was

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Figure 1. QUOROM Flow Diagram

QUOROM indicates Quality of Reporting of Meta-analyses.

screened by a subject specialist and a methodologist. Any study considered relevant by 1 or 2 reviewers was retrieved for further review. The reference lists of included trials and relevant reviews were also reviewed for pertinent trials. We also contacted manufacturers of renal replacement therapy products and the authors of included studies for information about further studies.

Study Selection

Each potentially relevant study was independently assessed by 2 reviewers for inclusion in the review using predetermined eligibility criteria and a pre-printed form. Studies meeting the following criteria were eligible: (1) Study design: randomized controlled trials (RCTs) or prospective cohort studies with 10 or more allocated participants in at least 2 intervention groups. Data collected prospectively for the purposes of registries or quality assurance databases were categorized as retrospective⁴ and therefore excluded. (2) Population: adults with ARF. (3) Comparison: RRT modality, time of RRT initiation, dose, schedule, flux, membrane type, buffer, and anticoagulant. (4) Out-

comes: mortality, length of stay, chronic dialysis dependence, blood pressure, and hypotension (filter failure and bleeding complications for anticoagulant comparison). Disagreements regarding eligibility arose with 10% of the articles ($\kappa=0.79$); disagreements were resolved by a third party through consensus.

Quality Assessment

We assessed characteristics of study quality for all RCTs (eg, method of allocation concealment⁵ and Jadad score⁶). Prospective cohort studies were assessed using 4 items from the Downs and Black checklist⁷: by whom and when treatment groups were accrued, description of withdrawals/dropouts, and whether there was adjustment for potential confounders. Additionally, we extracted data on funding sources⁸ and intention-to-treat design, given their potential to introduce bias. Two reviewers assessed each included study independently. Disagreements (observed in 17% to 33% of cases) were resolved by consensus with the aid of a third party.

Data Extraction

We used a standard method to record the following properties of each study: study characteristics (country, design, sample size, setting, duration of follow-up); participants (age, sex, presence of liver failure or systemic inflammatory response syndrome), illness severity (levels of serum creatinine and urea, Acute Physiology and Chronic Health Evaluation score, need for mechanical ventilation, use of vasopressors or inotropes); renal replacement regimens (technique, device and manufacturer, membrane material and flux, dose, schedule, buffer, prescribed blood flow, prescribed dialysate flow, anticoagulation regimen); outcomes (timing of outcome, in all patients or in survivors only); and results. We considered the following outcomes: mortality (in-intensive care unit [ICU], in-hospital, at any other time point); length of stay (ICU, hospital); chronic dialysis dependence, blood pressure (mean arterial pressure [MAP], hypotension); filter life; and bleeding compli-

cations. One reviewer extracted the data and a second checked for accuracy.

Statistical Analysis

We analyzed data using Review Manager version 4.2.7 (The Cochrane Collaboration, Oxford, England) and Stata release 10.0 (StataCorp, College Station, Texas). Due to the differences expected between studies, we decided a priori to combine results using a random-effects model.⁹ Furthermore, we pooled results for RCTs but not for prospective cohort studies, given the susceptibility to bias in observational studies.¹⁰ For dichotomous outcomes, we used the relative risk (RR) to pool outcomes. Change in MAP was pooled using the weighted mean difference. A correlation of 0.5 was substituted when change-from-baseline correlations were not available in the published reports.¹¹ Length-of-stay data were generally associated with highly right-skewed distributions and therefore were not pooled. Measures of central tendency, spread, tests, and corresponding *P* values were extracted for each group.

Statistical heterogeneity was quantified for pooled results using the *I*² statistic,^{12,13} which approximates the percentage of total variation (within and between studies) due to between-study variation. We did not assess publication bias,¹⁴ because each pooled estimate included fewer than 10 trials.

RESULTS

Of 173 studies reviewed in detail, 30 RCTs¹⁵⁻⁴⁴ and 8 prospective cohort studies⁴⁵⁻⁵² comparing dialytic strategies in ARF were eligible for inclusion (FIGURE 1, TABLE 1, and TABLE 2). Pooled results for the effect of these strategies on clinically important outcomes are presented in FIGURE 2, FIGURE 3, and FIGURE 4. Additional forest plots that present the results in more detail are available at the Alberta Kidney Disease Network Web site (<http://www.akdn.info>) or by contacting the authors.

Nomenclature and Epidemiology

Changes in urine output and levels of serum creatinine traditionally have been used to identify and define ARF.

Table 1. Characteristics of Populations in Included Studies

Source; Country (Setting)	No.	Mean Age, y	Men, %	APACHE II Score, Mean	Serum Creatinine, mg/dL	Vasopressor Use, %	SIRS, %	Liver Failure/Dysfunction, %	Allocation ^a	Quality ^b	LFU, %		Funding
Randomized Controlled Trials													
Morgera, ¹⁵ 2006; Germany (ICU/general surgical unit)	28	64	57	26	2.25	NR	100	NR	Unclear	1	NR	NR	
Saudan, ¹⁶ 2006; Switzerland (ICU)	206	63	61	25	4.83	NR	60	NR	Adequate	3	0	NR	
Vinsonneau, ¹⁷ 2006; France (ICU)	360	65	73	64 ^c	4.82	NR	87	63	Adequate	3	0	Mixed	
Kutsogiannis, ¹⁸ 2005; Canada (ICU)	30	65	50	NR	3.58	NR	53	NR	Unclear	2	0	Mixed	
Uehlinger, ¹⁹ 2005; Switzerland (ICU)	125	67	69	55 ^c	3.83	77	46	32	Unclear	3	0	Public	
Augustine, ²⁰ 2004; United States (ICU)	80	61	68	NR	4.80	54	NR	NR	Unclear	1	NR	NR	
Hein, ²¹ 2004; Germany (ICU)	26	70	62	77 ^d	3.41	NR	12	NR	Unclear	2	4	Private	
Kielstein, ²² 2004; Germany (ICU)	40	51	69	33	3.71	100	82	NR	Unclear	2	3	Private	
Kumar, ²³ 2004; United States (ICU)	54 ^e	53	63	30	4.13	NR	NR	NR	Inadequate	1	NR	NR	
Sugahara, ²⁴ 2004; Japan (NR)	28	65	64	19	2.96	NR	NR	NR	Unclear	1	NR	NR	
Gasparovic, ²⁵ 2003; Croatia (ICU)	104	NR	NR	21	NR	NR	50	NR	Unclear	1	NR	NR	
Bouman, ²⁶ 2002; Netherlands (ICU)	106	68	59	23	6 ^f	NR	NR	NR	Unclear	2	0	Private	
Schiff et al., ²⁷ 2002; Germany (ICU)	160 ^e	60	55	87 ^d	4.74	NR	36	NR	Inadequate	0	18	NR	
Mehta, ²⁸ 2001; United States (ICU)	166	55	76	25	4.49	NR	NR	36	Unclear	3	0	Public	
John, ²⁹ 2001; Germany (ICU)	30	61	87	34	5.10	NR	100	NR	Unclear	2	0	NR	
Pettita, ³⁰ 2001; Finland (ICU)	39	48	82	20	5.07	NR	79	NR	Adequate	3	3	NR	
Ponikvar, ³¹ 2001; Slovenia (ICU)	72	62	76	24	6.51	67	42	NR	Unclear	1	NR	Public	
Albright, ³² 2000; United States (NR)	66 ^e	67	55	22	NR	NR	18	NR	Inadequate	0	NR	NR	
Barenbrock, ³³ 2000; Germany (ICU)	117	61	74	26	3.55	NR	45	NR	Unclear	2	NR	NR	
Gastaldello, ³⁴ 2000; Belgium (hospital)	159	60	69	24	NR	55	57	14	Unclear	1	2	Public	
Ronco, ³⁵ 2000; Italy (ICU)	425	61	56	23	3.59	NR	12	NR	Unclear	2	0	NR	
Jörres, ³⁶ 1999; Europe (NR)	171	59	64	24	5.75	NR	23	NR	Adequate	3	2	Private	
Bret, ³⁷ 1998; France (ICU)	29	61	66	NR	NR	NR	48	NR	Unclear	2	17	NR	
Himmelfarb, ³⁸ 1998; United States (hospital)	153 ^e	58	65	27	5.71	NR	19	NR	Inadequate	0	NR	Mixed	
Jones (study 2), ³⁹ 1998; United Kingdom (ICU)	197	53	67	28	NR	NR	NR	28	Unclear	1	NR	Public	
Kurtal, ⁴⁰ 1995; Germany (ICU)	57 ^e	64	54	22	7.33	NR	26	NR	Inadequate	0	NR	NR	
Hakim, ⁴¹ 1994; United States (NR)	74 ^e	51	71	29	5.20	NR	17	NR	Inadequate	0	NR	Public	
Schiff, ⁴² 1994; Germany (ICU)	52	65	77	24	7.72	100	0	NR	Unclear	1	NR	NR	
Davenport, ⁴³ 1993; United Kingdom (NR)	30	35	53	24	6.86	100	0	100	Unclear	1	NR	Public	
Gillum, ⁴⁴ 1986; United States (renal unit)	34 ^e	57	85	NR	>8.0	NR	29	NR	Inadequate	2	NR	NR	
Prospective Cohort Studies													
Uchino, ⁴⁵ 2007; international (ICU)	1218	65	65	48 ^c	3.29	74	11	NR	Unclear	Yes	NR	Public	
Liu, ⁴⁶ 2006; United States (ICU)	243	56	61	NR	358	NR	41	38	Clinical judgment	Yes	NR	Public	
Noble, ⁴⁷ 2006; United Kingdom (ICU) ⁹	128	53	71	NR	4.25	NR	45	1	First 32 patients unclear, later randomized	No	0	NR	
Swartz, ⁴⁸ 2005; United States (renal unit)	383	61	59	83 ^d	4.46	55	41	24	Clinical judgment	Yes	NR	Mixed	
Brause, ⁴⁹ 2003; Germany (ICU)	56	54	50	70 ^d	2.96	NR	50	NR	Different period	No	0	NR	
Guerin, ⁵⁰ 2002; France (ICU)	587	61	70	54 ^c	NR	78	NR	12	Unclear	Yes	NR	Mixed	
Morgera, ⁵¹ 1997; Germany (ICU)	84	61	70	21	3.06	NR	45	NR	Different period	No	NR	NR	
Neveu, ⁵² 1996; France (ICU)	169	NR	NR	NR	NR	NR	NR	NR	Unclear	No	NR	Public	

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; LFU, lost to follow-up; NR, not reported; SIRS, systemic inflammatory response syndrome.

SI conversion factor: To convert serum creatinine values to $\mu\text{mol/L}$, multiply by 88.4.

^aAllocation concealment (randomized controlled trials only) or group allocation (prospective cohort studies only).

^bJadad score (range, 0-5) (randomized controlled trials only) or confounder adjustment (prospective cohort studies only).

^cStudy used Simplified Acute Physiology Score II instead of APACHE II.

^dStudy used APACHE III instead of APACHE II.

^eQuasi-randomized controlled trial.

^fStudy measured creatinine clearance (expressed as mL/min) instead of serum creatinine level.

⁹Randomized controlled trial combined with prospective cohort study.

Oliguria is an insensitive indicator of ARF, and nonoliguric ARF may be overlooked if urine output remains adequate. Serum creatinine level is also insensitive to acute changes in renal function⁵³ and may be affected by factors such as age, sex, race, muscle mass, and medications.^{54,55} Therefore, cystatin C may better reflect true glomerular filtration rate in this setting.⁵⁶ Despite these caveats, changes in levels of serum creatinine remain the gold standard for detection of ARF.

To date, there have been more than 35 published definitions of ARF,⁵⁷ which has hampered comparisons between studies. A group that attempted to produce a consensus definition (the Risk, Injury, Failure, Loss, and End-stage Kidney [RIFLE] criteria⁵⁷) stratified patients into 3 categories of severity (risk, injury, and failure) and 2 outcomes (receipt of RRT for >4 weeks and permanent kidney failure), and proposed that the term “acute renal failure” be replaced by “acute kidney injury.” More recently, these criteria have been simplified to focus only on change in levels of serum creatinine (>0.3 mg/dL [25 μmol/L] or a 50% increase) and urine output (<0.5 mL/kg per hour for longer than 6 hours).⁵⁸ While such changes in levels of serum creatinine have been repeatedly linked to adverse outcomes,⁵⁹ the urine output criteria have not been similarly evaluated. The applicability of the RIFLE and Acute Kidney Injury Network criteria to non-critically ill patients is unknown. At present, there is no universally accepted nomenclature for this condition, and we have used the term “acute renal failure” in this review.

Several recent studies suggest that the incidence of in-hospital ARF has increased by more than 10% per year over the last decade,⁶⁰⁻⁶⁵ probably due to the increasing average age and comorbidity of hospitalized patients. Using a large national database, Waikar et al⁶⁴ found that the incidence of ARF in the United States was 21 per 1000 hospital discharges in 2002. The epidemiology of ARF has been best characterized in critically ill populations,⁶⁰⁻⁶² in whom the incidence varies between 15% and 80% by RIFLE cri-

teria.⁵⁹ The incidence of acute dialysis-dependent renal failure is considerably lower (3.4% to 4.9%), and associated in-hospital mortality generally is between 60% and 70%.⁶⁶⁻⁷⁰ While the requirement for renal replacement clearly portends a poor prognosis in patients with ARF, long-term outcomes have not been well studied. The majority of survivors are able to discontinue acute dialysis,^{70,71} although recent data suggest that up to 30% of such patients will require chronic dialysis within 3 years.^{72,73}

In summary, acute dialysis-dependent renal failure is associated with a substantial increase in short-term mortality and may cause or accelerate chronic kidney disease, including kidney failure. A critical review of the evidence on which current dialytic support for patients with ARF is based may identify opportunities to improve these long-term outcomes.

Indications and Timing of RRT for Treatment of ARF

Although it is generally accepted that patients with ARF require renal replacement when reduced glomerular filtration rate leads to established or incipient complications of solute imbalance or extracellular fluid volume overload, the specific indications for initiation of RRT are controversial. The traditional indications for chronic dialysis (such as encephalopathy, pericarditis, and coagulopathy) are late complications of ARF and are rarely seen in contemporary patients with ARF. Critically ill patients should be thoroughly evaluated for non-renal causes of these conditions when present. Similarly, metabolic acidosis, hyperkalemia, and hypervolemia can often be medically managed. Arguably, the only absolute indications for RRT in critically ill patients are metabolic acidosis, hypervolemia, and hyperkalemia that do not respond to other forms of therapy. Although the early initiation of renal replacement might be beneficial in theory, data guiding the optimal timing of dialysis in patients with ARF are scarce.^{46,74,75}

To date only 2 randomized trials^{24,26} have addressed this question, both in

critically ill patients. In one trial²⁶ (n=106), “early” dialysis was started after 6 hours of urine output of less than 30 mL/h but did not affect mortality or dialysis dependence in survivors. The other trial²⁴ (n=28) found a large reduction in mortality among patients with an earlier initiation (RR, 0.17; 95% confidence interval [CI], 0.05-0.61) but had several markers of poor quality and used unusual definitions of “early” and “late” initiation of dialysis, which would be difficult to implement in clinical practice. The single eligible prospective cohort study reported that the risk of death in critically ill patients was significantly lower among patients starting RRT with blood urea nitrogen levels of 76 mg/dL (27 mmol/L) or less (adjusted hazard ratio, 0.54; 95% CI, 0.34-0.86).⁴⁶ Thus the available literature is inconclusive as to the optimal indications for and timing of renal replacement in ARF.

Dialysis Modalities for ARF

Renal replacement for ARF may include peritoneal dialysis, intermittent hemodialysis, or continuous renal replacement therapies (CRRTs). Although acute peritoneal dialysis is an important method for treatment of adults with severe ARF in developing countries, it is infrequently used in high-income countries and is not further considered in this review. Intermittent hemodialysis is performed using venovenous access for a few hours at variable intervals (typically 4 hours, 3 to 4 times per week).⁷⁶ Sustained, low-efficiency dialysis (SLED) or extended daily dialysis are submodalities of intermittent hemodialysis in which the duration of dialysis is extended (6-12 hours), allowing for more gradual removal of solutes and fluid.⁷⁷

CRRT is performed continuously (ie, approximately 24 hours per day) through arteriovenous or venovenous vascular access, using much slower blood flow rates as compared with intermittent hemodialysis, and is typically only delivered in an intensive care setting. The most commonly applied submodalities of CRRT are continuous venovenous

Table 2. Characteristics of Dialytic Support in Included Studies

Source	Comparison	Intervention					Control				
		Technique (Device)	Membrane Material (Flux)	Buffer	Anti-coagulant	Dosage (Schedule)	Technique (Device)	Membrane Material (Flux)	Buffer	Anti-coagulant	Dosage (Schedule)
Randomized Controlled Trials											
Morgera, ¹⁵ 2006	CRRT membrane	CVWHF (NA)	P2SH (high)	B	H	2.5 L/h or 31 mL/kg per h	CVWHF (NA)	PA (high)	B	H	2.5 L/h or 31 mL/kg per h
Saudan, ¹⁶ 2006	CRRT technique	CVHDF (Prisma)	PAN (high)	B/L	NA	42 mL/kg per h or URR 50%	CVWHF (Prisma)	PAN (high)	B/L	NA	25 mL/kg per h or URR 40%
Vinsonneau, ¹⁷ 2006	CRRT vs IHD	CVHDF (Prisma)	PAN (high)	B	H	29 mL/kg per h	IHD (variable)	PAN (high)	B	H	500 mL/min (4 h/alternate d)
Kutsogiannis, ¹⁸ 2005	CRRT anti-coagulant	CVHDF (Prisma)	PAN (high)	B	TC	2 L/h	CVHDF (Prisma)	PAN (high)	B	H	2 L/h
Uehlinger, ¹⁹ 2005	CRRT vs IHD	CVHDF (Prisma)	PAN (high)	L	H/none	2 L/h or UCI ≈ 30 mL/min	IHD (MiroClav)	PS (high)	B	H/none	UCI ≈ 200 mL/min (3-4 h/session)
Augustine, ²⁰ 2004	CRRT vs IHD	CVVHD (NA)	PS (low)	B	H/none	Kt/V 3.6/wk	IHD (NA)	PS (low)	B	H/none	Kt/V 3.6/wk (3 sessions/wk)
Hein, ²¹ 2004	CRRT anti-coagulant	CVWHF (BM11/BM14)	PA (high)	NA	Hi	1-1.5 L/h	CVWHF (BM11/BM14)	PA (high)	NA	H	1-1.5 L/h
Kielstein, ²² 2004	CRRT vs IHD	CVWHF (BM11/BM14)	PS (high)	B	H	3.2 L/h (1 × 24-h session only)	IHD-extended (Genius)	PS (high)	B	H	URR 53% (12 h/session)
Kumar, ²³ 2004	CRRT vs IHD	CVVHD (2008H)	PS/PMMA (high)	NA	H	Mean serum urea 5 mmol/L	IHD-extended (2008H)	PS/PMMA (high)	B	H	Mean serum urea 13 mmol/L (6-8 h/session, 6 sessions/wk)
Sugahara, ²⁴ 2004	CRRT time of dialysis initiation	CVVHD (KM8600)	PAN/PMMA (high/NA)	L	NA	1 L/h	CVVHD (KM8600)	PAN/PMMA (high/NA)	L	NA	1 L/h
Gasparovic, ²⁵ 2003	CRRT vs IHD	CVWHF (NA)	PS (NA)	NA	H	18 & 35 mL/kg per h	IHD (NA)	PS (NA)	NA	H/none	NA (3-4 h/session)
Bouman, ²⁶ 2002 ^a	CRRT time of dialysis initiation and dose	CVWHF (Diapact/hemoprocessor)	CTA (high)	B	H/N/none	48 mL/kg per h	CVWHF (Diapact/hemoprocessor)	CTA (high)	B	H/N/none	20 mL/kg per h
Schiffi, ²⁷ 2002	IHD schedule	IHD (MTS2008C)	PS/PAN (high)	B	H/none	NA (alternate days)	IHD (MTS2008C)	PS/PAN (high)	B	H/none	NA (daily)
Mehta, ²⁸ 2001	CRRT vs IHD	CXVHDF (BSM 22/BM-11)	PS/PAN (high)	NA	H	UCI 22 mL/min	IHD (NA)	C/CA/PS/PMMA/PAN (low/high)	B	H	NA (3-4 h/session)
John, ²⁹ 2001	CRRT vs IHD	CVWHF (BSM 22)	PS (high)	B/L	H	2 L/h	IHD (AK 100)	PS (low)	B	H	NA (4 h/session)
Pettila, ³⁰ 2001	IHD technique	IHD (AK 100 Ultra)	PA (high)	B	E	164 L dialysate and 4 L ultrafiltration/session or URR 39.8% (3 h/first session, 4 h/other sessions)	IHD (AK 100 Ultra)	PA (high)	B	E	128 L dialysate and 40 L ultrafiltration/session or URR 39.9% (3 h/first session, 4 h/other sessions)
Ponikvar, ³¹ 2001	IHD membrane	IHD (NA)	PAN (high)	NA	H/TC	NA (4-6 h/session)	IHD (NA)	PS (low)	NA	H/TC	NA (4-6 h/session)
Albright, ³² 2000	IHD membrane	IHD (NA)	PS (NA)	B	NA	500-550 mL/min or URR 44% (NA)	IHD (NA)	CA (low)	B	NA	500-550 mL/min or URR 44% (NA)
Barenbrock, ³³ 2000	CRRT buffer	CVWHF (NA)	NA (NA)	B	H	1 L/h	CVWHF (NA)	NA (NA)	L	H	1 L/h
Gastaldello, ³⁴ 2000 ^b	IHD membrane	IHD (NA)	PS (high)	B	NA	500 mL/min (3 h/daily)	IHD (NA)	PS/CDA (low)	B	NA	500 mL/min (3 h/daily)
Ronco, ³⁵ 2000 ^c	CRRT dose	CVWHF (variable)	PS (NA)	L	H	20 mL/kg per h	CVWHF (variable)	PS (NA)	L	H	35 and 45 mL/kg per h

(continued)

Table 2. Characteristics of Dialytic Support in Included Studies (cont)

Source	Comparison	Intervention					Control				
		Technique (Device)	Membrane Material (Flux)	Buffer	Anti-coagulant	Dosage (Schedule)	Technique (Device)	Membrane Material (Flux)	Buffer	Anti-coagulant	Dosage (Schedule)
Randomized Controlled Trials											
Jörres, ³⁶ 1999	IHD membrane	IHD (NA)	PMMA (low)	B	NA	500 mL/min (NA)	IHD (NA)	C (low)	B	NA	500 mL/min (NA)
Bret, ³⁷ 1998	IHD buffer	IHD (MONITRAL Bio)	PAN (high)	Acetate-free	H	500 mL/min (4 h/session) ^d	IHD (MONITRAL S)	PAN (high)	B	H	500 mL/min (4 h/session) ^d
Himmelfarb, ³⁸ 1998	IHD membrane	IHD (NA)	PMMA/PS (low)	NA	NA	NA (NA)	IHD (NA)	Cellulose-based (low)	NA	NA	NA (NA)
Jones, ³⁹ 1998 (study 2)	CRRT membrane	CVVHD (NA)	PAN (high)	L	H	2.1 L/h	CVVHD (NA)	PS (high)	L	H	2.1 L/h
Kurtal, ⁴⁰ 1995	IHD membrane	IHD (AK 100)	PA (high)	B	NA	NA (4 h/session daily)	IHD (AK 100)	C (low)	B	NA	NA (4 h/session daily)
Hakim, ⁴¹ 1994	IHD membrane	IHD (NA)	PMMA (low)	NA	NA	NA (NA)	IHD (NA)	C (low)	NA	NA	NA (NA)
Schiffli, ⁴² 1994	IHD membrane	IHD (NA)	PAN (high)	B	NA	500 mL/min (3-4 h/alternate days)	IHD (NA)	C (low)	B	NA	500 mL/min (3-4 h/alternate days)
Davenport, ⁴³ 1993	CRRT vs IHD	CAVHF/CAVHDF (Gemmini)	PAN (high)	L	H/none	0.9-1.4 L/h or UCI 17-24 mL/min	IHF (NA)	PA (high)	L	H/none	17 L in 4 h (3.5-4.5 h/session daily)
Gillum, ⁴⁴ 1986	IHD schedule	IHD (Century II)	C (low)	NA	H/none	Target predialysis BUN <60 mg/dL ^e	IHD (Century II)	C (low)	NA	H/none	Target predialysis BUN <100 mg/dL ^e
Prospective Cohort Studies											
Uchino, ⁴⁵ 2007	CRRT vs IHD	CVVHF/CVVHDF/CVVHD (NA)	NA (NA)	NA	NA	2 L/h	IHD/IHDF/ISLED/ISLEDF/IHF (NA)	NA (NA)	NA	NA	NA (3 h/session)
Liu, ⁴⁶ 2006	Time of dialysis initiation	69% CRRT (NA)	NA (NA)	NA	NA	NA	43% CRRT	NA (NA)	NA	NA	NA
Noble, ⁴⁷ 2006	CRRT vs IHD	CXVHDF (NA)	PS (high)	B	H/P	NA	IHD (NA)	C (low)	B/A	H	NA (4 h/daily)
Swartz, ⁴⁸ 2005	CRRT vs IHD	CVVHF/CVVHDF (NA)	NA (NA)	B	H	NA	IHD (NA)	PS/CTA (high)	B	H	URR 65%-70% (NA)
Brause, ⁴⁹ 2003	CRRT dose	CVVHF (ADM 08)	PS (high)	L	H	1.5 L/h or BUN 50 mg/dL	CVVHF (ADM 08)	PS (high)	L	H	1 L/h or BUN 70 mg/dL
Guérin, ⁵⁰ 2002	CRRT vs IHD	CVVHF/CVVHDF (BSM 22/Prisma)	No cuprophan	NA	NA	NA	IHD (NA)	No cuprophan	NA	NA	NA (NA)
Morgera, ⁵¹ 1997	CRRT buffer	CVVHF (BSM 22)	PS (NA)	L	H	NA	CVVHF (BSM 22)	PS (NA)	A	H	NA
Neveu, ⁵² 1996	CRRT vs IHD and membrane	CXVHD/CXVHF/CXVHDF (NA)	C/PAN/PS/CA/PA (high/low)	NA	NA	NA	IHD/IHF (NA)	C/PAN/PS/CA/PA (high/low)	NA	NA	NA (NA)

Abbreviations: A, acetate; B, bicarbonate; C, cuprophan; CA, cellulose acetate; CAVHDF, continuous arteriovenous hemodiafiltration; CAVHF, continuous arteriovenous hemofiltration; CDA, cellulose diacetate; CRRT, continuous renal replacement therapy; CTA, cellulose triacetate; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; CVVHF, continuous venovenous hemofiltration; CXVHDF, continuous arteriovenous or venovenous hemodiafiltration; E, enoxparin; H, heparin; Hi, hirudin; IHD, intermittent hemodialysis; IHDF, intermittent hemodiafiltration; IHF, intermittent hemofiltration; L, lactate; N, nadroparin; NA, not available (not reported or not applicable); P, prostacyclin; PA, polyamide; PAN, polyacrylonitril; PMMA, polymethylmethacrylate; PS, polysulfone; P2SH, newly developed high-flux membrane; RC, regional citrate; TC, trisodium citrate; UCI, urea clearance; URR, urea reduction ratio.

^aRandomized participants into 3 groups: early initiation and high dose, early initiation and low dose, late initiation and low dose.

^bRandomized participants into 3 membrane groups.

^cRandomized participants into 3 dosage groups.

^dPlus ultrafiltration rate.

^eAs required to achieve dose.

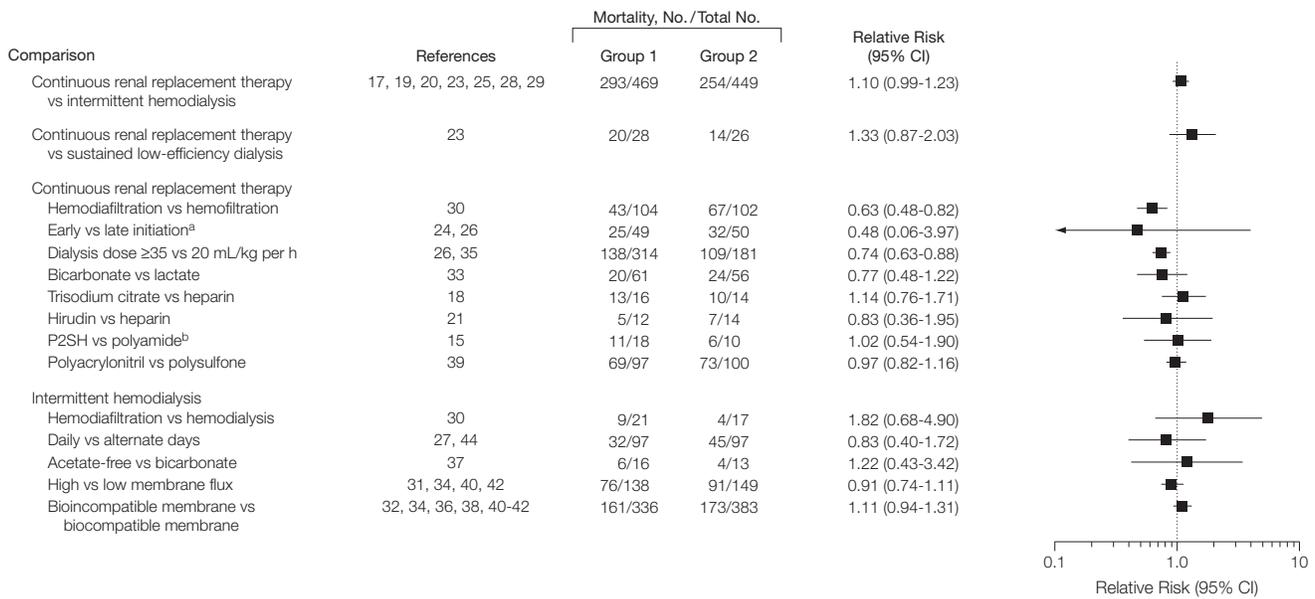
hemofiltration, continuous venovenous hemodialysis, and continuous venovenous hemodiafiltration (BOX). CRRT provides slower solute clearance per unit of time compared with intermittent therapies, but over 24 hours, the total clearance may exceed that provided by intermittent hemodialysis, especially for larger solutes such as cy-

tokines.^{78,79} While fluid is removed more slowly using CRRT, it requires continuous anticoagulation (thus creating the potential for bleeding) and involves continuous exposure to an extracorporeal circuit (which might lead to depletion of nutrients, subtherapeutic levels of antimicrobial agents, or infection).

CRRT vs Intermittent Hemodialysis. The effect of dialytic modality on outcomes in ARF has only been directly studied in critically ill patients. We identified 9 RCTs* (989 total participants) that compared CRRT with intermittent hemodialysis. Of these, 7

*References 17, 19, 20, 22, 23, 25, 28, 29, 43.

Figure 2. Pooled Effects From Randomized Controlled Trials of Various Interventions on Mortality

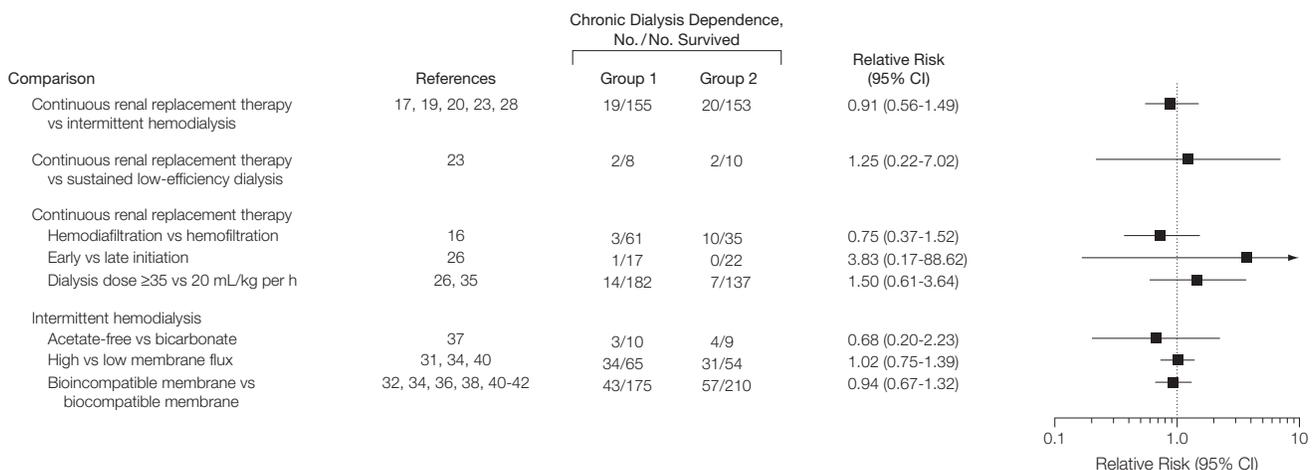


CI indicates confidence interval.

^aPooled estimate should be viewed with caution ($I^2=90\%$).

^bP2SH is a newly developed high-flux membrane.

Figure 3. Pooled Effects From Randomized Controlled Trials of Various Interventions on Chronic Dialysis Dependence in Survivors



CI indicates confidence interval.

trials^{17,19,20,23,25,28,29} (918 participants) reported all-cause mortality at discharge from hospital, discharge from the ICU, or 28 days. When the latest follow-up available from each trial was considered, the RR of death due to CRRT was nonsignificant compared with intermittent hemodialysis (RR, 1.10; 95% CI, 0.99-1.23; $I^2=0\%$). Results were similar for ICU mortality and in-hospital mortality (data not shown). Data from prospective cohort studies were generally consistent with those from trials: all 4 such studies^{45,48,50,52} that we identified found significantly higher unadjusted mortality among CRRT recipients (who tended to be more severely ill), but of the 3 that reported adjusted summaries, none suggested a significant difference between modalities. One additional (partially randomized) study⁴⁷ found no significant difference in unadjusted mortality between modalities.

Available RCTs did not suggest that dialytic modality influenced the frequency with which chronic dialysis treatment (implying end-stage renal disease) was required in survivors (RR for CRRT vs intermittent hemodialysis, 0.91; 95% CI, 0.56-1.49; $I^2=0\%$ [5 trials, 308 participants]). Results were similar when the composite of death or dialysis dependence in survivors was considered (RR, 1.11; 95% CI, 0.87-1.42;

$I^2=66\%$ [4 trials, 425 participants]). Data from 4 RCTs (643 participants) were inconclusive as to the effect of dialytic modality on hospital length of stay.^{17,19,23,28} Two prospective cohort studies^{45,48} suggested substantially lower risk of dialysis dependence in survivors who received CRRT (RR, 0.48; 95% CI, 0.25-0.90 and RR, 0.43; 95% CI, 0.30-0.62), but CRRT recipients in these studies were substantially more likely to die and therefore survivorship bias may have influenced these results. This is supported by the fact that the risk of the composite outcome of dialysis dependence or death among CRRT recipients was significantly⁴⁸ and non-significantly⁴⁵ higher, respectively, in these studies, compared with intermittent hemodialysis recipients.

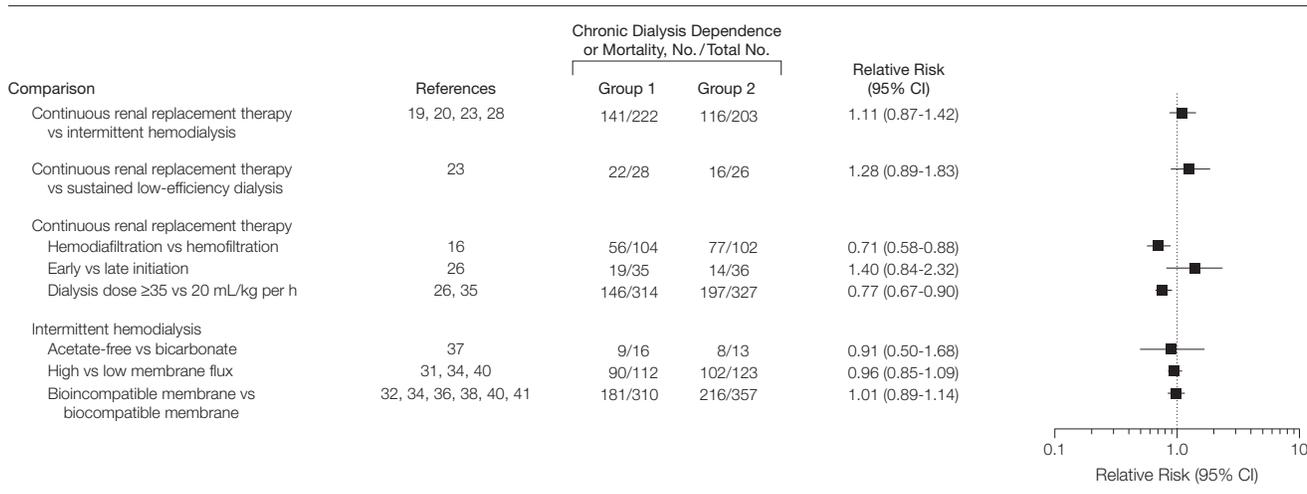
Four trials (274 participants) measured MAP at various points. In 3 RCTs with no heterogeneity ($I^2=0\%$), the pooled change in MAP from baseline was no different in patients treated with CRRT or intermittent hemodialysis (mean decrease in MAP, 2.5 mm Hg smaller with CRRT; 95% CI, 1.0 greater to 6.0 smaller). Results of the fourth RCT were substantially different than those of the other 3 (I^2 after including this study increased to 99%) and suggest that patients treated with CRRT may have a slightly higher MAP over

the course of treatment (increase in MAP, 0.4 mm Hg; 95% CI, 7.2 greater to 8.0 smaller). Additionally, the pooled risk of hypotension did not significantly differ between treatments (RR of hypotension with CRRT, 0.87; 95% CI, 0.68-1.12; $I^2=0\%$ [2 trials, 389 participants]). The sole relevant eligible prospective cohort study suggested a lower risk of hypotension among CRRT recipients (RR, 0.68; 95% CI, 0.52-0.87), despite the higher illness severity of patients in this group.⁴⁵

In summary, data from 9 RCTs suggest no difference in survival between CRRT and intermittent hemodialysis, while data from a subset of these RCTs suggest no significant difference in the frequency with which chronic dialysis treatment was required in survivors or in the incidence of hypotension.

Techniques for Intermittent Hemodialysis and CRRT. One small trial³⁰ (39 participants) compared hemodiafiltration with hemodialysis in patients treated with intermittent hemodialysis and found no significant differences in clinically relevant outcomes, although statistical power was low. One high-quality trial¹⁶ compared hemodiafiltration with hemofiltration in 206 participants treated with CRRT and found a significant reduction in mortality at 28 days favoring hemodiafiltration over

Figure 4. Pooled Effects From Randomized Controlled Trials of Various Interventions on the Composite Outcome of Chronic Dialysis Dependence or Mortality



CI indicates confidence interval.

hemofiltration (RR, 0.63; 95% CI, 0.48-0.82). However, participants in the hemodiafiltration group also received a substantially higher dose of RRT than those in the hemofiltration group, making it impossible to determine if submodality (rather than differences in RRT dose) was truly responsible for the better outcomes. In a sensitivity analysis, the pooled results for overall mortality in trials in which the CRRT group used hemodiafiltration exclusively (RR, 1.07; 95% CI, 0.85-1.35; $I^2=62\%$ [3 studies, 650 participants]) did not differ from the findings of the main analysis.

SLED vs Other Dialytic Techniques. We identified 2 RCTs^{22,23} that compared SLED (6-11 h/d; 6-7 d/wk) with a continuous modality (continuous venovenous hemofiltration or hemodialysis) with respect to the surrogate outcomes of hemodynamic stability and uremic clearance. No differences were found, although statistical power was low. To our knowledge, no study has compared SLED with conventional intermittent hemodialysis.

In summary, there was no evidence that either CRRT or intermittent hemodialysis was superior for reducing mortality, resource use, or the risk of chronic dialysis dependence in patients with ARF. Although cohort data suggest a lower risk of hypotension among CRRT recipients, this finding was not confirmed by the data reported within the available randomized trials.

Dialysis Dose

Urea clearance is widely used to quantify chronic dialysis dose, and it is tempting to use similar techniques to quantify dose in acute intermittent hemodialysis. However, patients with ARF are frequently catabolic and have highly variable fluid volumes, which violates several of the assumptions on which chronic dialysis dosing is based. Since there is no consensus as to how intermittent hemodialysis dose should be quantified, it is often prescribed in terms of duration (hours per treatment, typically 4 to 6 hours); frequency (typically 3 to 7 treatments per week), and blood flow rate (150 to 400 mL/min).

Box. Modalities of Continuous Renal Replacement Therapy

Continuous Venovenous Hemofiltration (CVVHF)

Ultrafiltrate produced is replaced with a replacement solution
Ultrafiltration in excess of replacement results in patient volume loss
Solute removal is through convection

Continuous Venovenous Hemodialysis (CVVHD)

Dialysate solution is delivered across membrane countercurrent to blood flow
Blood flow rates are 100 to 200 mL/min
Dialysate flow rates are 1 to 2 L/h
Fluid replacement is not routinely administered
Solute removal is by diffusion

Continuous Venovenous Hemodiafiltration (CVVHDF)

Dialysate solution is delivered across membrane countercurrent to blood flow
Typical dialysate flow rates are 1 to 2 L/h
Ultrafiltration volumes are optimized to exceed desired weight loss and enhance solute clearance from convection
Fluid losses are replaced in part or completely with replacement solution
Solute removal is both diffusive and convective

Since urea equilibrates rapidly across the dialysis membrane, urea clearance in CRRT is essentially equivalent to the volume of effluent dialysate (including any ultrafiltered fluid), and therefore CRRT dose is commonly expressed as L/kg per hour of effluent.

CRRT. Two trials with 531 participants compared different doses of hemofiltration. The larger study³⁵ (425 participants) found that doses of 45 mL/kg per hour and 35 mL/kg per hour reduced mortality compared with the dose of 20 mL/kg per hour (RR, 0.72; 95% CI, 0.54-0.94 and RR, 0.73; 95% CI, 0.56-0.96, respectively). No difference was noted in the likelihood of dialysis dependence among survivors, although the composite outcome of mortality and dialysis dependence was significantly less frequent in patients receiving higher hemofiltration volumes. The second trial²⁶ (106 participants) found a nonsignificant trend toward reduced mortality with higher hemofiltration volumes but no difference in the likelihood of dialysis dependence in survivors or in the composite of the 2 outcomes. In pooled analyses of these 2 studies, the risk of mortality (RR, 0.74; 95% CI, 0.63-0.88; $I^2=0\%$) and of the composite of mortality or dialysis dependence (RR,

0.77; 95% CI, 0.67-0.90; $I^2=0\%$) were significantly lower in patients treated with volumes of 35 mL/kg per hour or greater. Only 1 small prospective cohort study addressed this issue and did not find a significant difference between treatment groups, although statistical power was low.⁴⁹

Intermittent Hemodialysis. Two trials have directly compared higher doses of dialysis with conventional (every second day) intermittent hemodialysis. One trial²⁷ (n=160) found significantly lower mortality (RR, 0.59; 95% CI, 0.39-0.91) in patients treated daily, as compared with a conventional schedule. However, the dose of dialysis in the conventional-dialysis group was somewhat lower than expected (based on experience with chronic dialysis). Intensive therapy in another trial⁴⁴ (34 participants) was defined by hemodialysis performed as often as necessary to maintain levels of blood urea nitrogen less than 60 mg/dL (<21 mmol/L) and serum creatinine less than 5 mg/dL (<442 $\mu\text{mol/L}$) (resulting in daily hemodialysis for all but 2 participants in the intensive therapy group). This study found a nonsignificant trend toward lower mortality with conventional hemodialysis. The pooled overall RR for mortality associated with more inten-

sive intermittent hemodialysis was nonsignificant (0.83; 95% CI, 0.40-1.72) and highly heterogeneous ($I^2=73\%$). Given the methodological differences and low power, it is difficult to make firm conclusions; further RCTs are warranted.

Anticoagulation

Anticoagulation is essential for both intermittent hemodialysis and CRRT, because blood traveling through the extracorporeal circuit can lead to clotting of the filter, contributing to blood loss and reducing dialysis efficiency. On the other hand, excessive anticoagulation may result in bleeding complications.⁸⁰ Unfractionated heparin is the mainstay of anticoagulation for intermittent hemodialysis and CRRT,⁸¹ although the optimal intensity of heparinization is unknown. Low-molecular-weight heparin is infrequently used due to the need to monitor factor Xa levels.⁸² Alternatives to systemic anticoagulation in patients at high risk of bleeding include regular saline flushes or citrate infusion into the dialysis circuit.

In 1 small randomized trial¹⁸ (30 participants), citrate anticoagulation allowed longer filter life (hazard ratio for clotting, 0.37; 95% CI, 0.20-0.70) compared with standard unfractionated heparin and resulted in a lower risk of serious bleeding (RR, 0.06; 95% CI, >0-0.95). These advantages of citrate anticoagulation must be balanced against its increased complexity and potential for metabolic disturbances including hypocalcemia, metabolic alkalosis, and citrate toxicity. Hirudin may be an alternative to heparin in circumstances in which regional citrate anticoagulation is not available. In another small RCT²¹ (26 participants) comparing hirudin with unfractionated heparin, the filter life was nonsignificantly shorter in patients treated with hirudin ($P=.06$).

Dialysis Membrane

Membranes used for intermittent hemodialysis and CRRT are traditionally characterized in terms of flux (permeability to water and larger solutes) and biocompatibility (degree to which complement is activated by exposing

the membrane to blood). Biocompatible membranes are typically made of synthetic materials and are more expensive than bioincompatible membranes, which may be further subdivided into unsubstituted cellulose and cellulosic varieties.

Four trials^{31,34,40,42} compared the use of high-flux and low-flux membranes in intermittent hemodialysis and did not find any difference in the risk of mortality (RR, 0.91; 95% CI, 0.74-1.11; $I^2=16\%$ [287 participants]) or dialysis dependence in survivors (RR, 1.02; 95% CI, 0.75-1.39; $I^2=0\%$ [119 participants]). Since the increased permeability to water facilitates hemofiltration, high-flux membranes are generally recommended for CRRT. Two small trials compared different high-flux membranes in CRRT and found no effect on mortality.^{15,39}

Seven trials^{32,34,36,38,40-42} (719 participants) compared mortality in patients treated with bioincompatible vs biocompatible membranes. There was a borderline increase in the risk of death associated with bioincompatible membranes (RR, 1.11; 95% CI, 0.94-1.31; $I^2=7\%$) as compared with biocompatible membranes and no difference in the risk of dialysis dependence in survivors or the composite of these outcomes. The risk of death was significantly higher among patients treated with membranes made of unsubstituted cellulose (a subset of bioincompatible membranes) as compared with biocompatible membranes (RR, 1.23; 95% CI, 1.01-1.50; $I^2=0\%$ [5 trials, 494 participants]), and the risk of death or dialysis dependence was of borderline significance (RR, 1.07; 95% CI, 0.90-1.27; $I^2=0\%$ [4 trials, 442 participants]). These results, from 7 reasonable-quality RCTs, suggest that the use of unsubstituted cellulosic membranes should be avoided in ARF.

Dialysate Composition

Dialysate for intermittent hemodialysis is produced as needed by the dialysis machine by mixing specially treated water from the municipal supply with electrolytes. In contrast, dialysate/replacement solution for CRRT must be sterile and is either purchased or produced lo-

cally in hospital pharmacies. Options for correction of metabolic acidosis include acetate, lactate, and bicarbonate; the latter has become increasingly popular in recent years due to concern that acetate and lactate may not be adequately converted to bicarbonate in the setting of multiple organ failure.⁸³

One trial³³ with a total of 117 participants compared bicarbonate with lactate in patients receiving CRRT. The difference in mortality was not significant (RR, 0.77; 95% CI, 0.48-1.22), but a significantly reduced risk of cardiovascular events was found in patients treated with a bicarbonate rather than a lactate buffer (RR, 0.39; 95% CI, 0.20-0.79), suggesting that the former may be preferable in CRRT. No difference was found in the only RCT comparing buffers in patients with ARF treated with intermittent hemodialysis ($n=29$).³⁷ The sole eligible prospective cohort study⁵¹ identified by our search found no significant difference between lactate and acetate buffers on the risk of death (RR, 1.07; 95% CI, 0.75-1.52) in CRRT recipients.

Cost Implications of Selecting a Strategy for RRT

The same equipment and staff that provide chronic dialysis usually can be used to deliver intermittent hemodialysis to patients with ARF. Therefore, the capital and training expenditures associated with establishing an intermittent hemodialysis program are often low. Regardless of the submodality used, CRRT involves specialized equipment and training for staff, generally requires additional supplies (especially replacement fluids), and consumes greater health care resources than intermittent hemodialysis, a consistent finding regardless of country, scenarios of nursing care, and frequency of intermittent hemodialysis (including SLED).^{32,36,38,84} The weekly cost difference between intermittent hemodialysis and CRRT is estimated to be \$1100 to \$3700, depending on whether daily intermittent hemodialysis (or SLED) or thrice-weekly intermittent hemodialysis is compared with CRRT.^{32,38}

However, the incremental costs of providing RRT in critically ill patients are small compared with the large costs of the index hospitalization and beyond. While renal failure requiring provision of chronic dialysis is infrequent, it has substantial implications given its high costs.⁴¹ Patients who remain dialysis dependent are estimated to incur an additional \$60 000 in direct health care costs compared with those who recover renal function,³⁸ not including indirect or patient productivity costs. Thus, relatively costly interventions may be attractive if proven to improve these longer-term outcomes. Prior to widespread adoption of novel treatments for ARF, decision makers might find it valuable to consider the potential impact on resource utilization in the short and long term (including the index hospitalization and chronic dialysis).

Suggested Management Strategy

Our recommended management strategy for patients with severe ARF is presented below. The evidence for these recommendations was derived primarily from studies of critically ill patients and thus may not be generalizable to other populations. In the absence of evidence demonstrating clear superiority of one strategy over another, our recommendations have been guided by economic and practical considerations.

Starting RRT. The decision to initiate RRT in patients with severe ARF requires consideration of multiple factors, including assessment of intravascular volume, electrolyte and acid-base status, uremia, nutritional requirements, urine output, hemodynamic status, and the evolving clinical course of each patient. Potential advantages of earlier RRT initiation must be set against the hypothetical risks of treatment-induced renal injury, bleeding due to anticoagulation, and mechanical and infectious complications associated with central venous access.

Prescription of RRT. Available RCTs demonstrate no clear difference between continuous or intermittent modalities with respect to clinically relevant outcomes. Furthermore, the most

recently published randomized trial of intermittent hemodialysis vs CRRT demonstrated that even the sickest of patients could be safely treated with intermittent hemodialysis.¹⁷ Given the significantly higher cost of CRRT, intermittent hemodialysis may be preferable for patients with ARF who require RRT.

In otherwise stable patients, alternate-day dialysis treatments of 4 or more hours using blood flows of 250 mL/min or greater are usually sufficient in patients with or without concomitant critical illness. More frequent hemodialysis may be required in highly catabolic patients or to achieve treatment targets for fluid, electrolyte, or acid-base management, although data identifying how such targets should be set are limited. Despite the lack of data supporting its superiority and its higher cost, some clinicians may prefer to use CRRT in critically ill patients with ARF and severe hemodynamic instability. If CRRT is used, the target dose should be 35 mL/kg per hour (3 L/h in a 70-kg person).

Technical Considerations. Due to its low cost and wide availability, we recommend unfractionated heparin as the usual anticoagulant for dialysis in ARF, titrated to maintain activated partial thromboplastin time between 1 and 1.4 times the upper limit of normal. In patients at high risk of bleeding, regional citrate anticoagulation should be administered, although this technique is not recommended for usual care, given its substantially higher cost. Heparin-free dialysis with saline flushes may be used as an alternative, especially outside a critical care unit.

Dialysis membrane flux (high vs low) and surface area should be determined based on patient characteristics and treatment goals; unsubstituted cellulose membranes should not be used in patients with ARF. Dialysate composition should be determined by the treatment targets (correction of hyperkalemia, metabolic acidosis), and the use of acetate buffer should be avoided. Recently publicized errors in the preparation of CRRT fluids led to patient deaths due to hyperkalemia and massive hemo-

lysis.⁸⁵ These serious adverse events underscore the importance of quality assurance for the preparation of dialysate fluid, regardless of the composition that is selected for use. Given the potential for dialysis to reduce blood levels of vital medications (as well as the extensive list of medications that must be dose-adjusted or avoided in ARF), advice from an expert pharmacist should be sought for all patients with severe ARF.

COMMENT

To our knowledge, this is the most comprehensive review of options for renal replacement in ARF. Despite the wide variety of available techniques, we identified few good-quality data to guide best practice. Uncertainty remains about when RRT should be initiated, how much dialysis should be provided, and for how long treatment should continue. The design and execution of research in this area has been hampered by a number of factors, including (1) lack of consensus with regard to the definition of ARF and indications for dialysis; (2) limited understanding of the epidemiology of ARF; and (3) poorly designed and inadequately powered studies.

Perhaps the most problematic issue is the lack of a common metric for defining ARF. Changes in serum creatinine levels and urine output are relatively late events that provide little information about the etiology of ARF or the extent to which loss of kidney function is reversible, thus making even the most recently proposed definitions somewhat arbitrary. Future research efforts should be directed toward more specifically defining subsets of patients with ARF before considering interventional studies.

Second, the epidemiology of ARF is poorly understood. Relatively few data describe optimal dialytic support for patients with ARF who are not critically ill—patients who arguably may benefit the most from improved management, given their better overall prognosis. Much remains to be learned about how to improve outcomes after hospital discharge, such as renal recov-

ery, the development or acceleration of chronic kidney disease, and the need for chronic dialysis. Since such outcomes might drive the long-term costs and consequences of a renal replacement strategy, they should be addressed by future studies.

Finally, most studies of RRT in ARF have been small and of poor quality (80% of the Jadad scores were <3). Future studies should be adequately powered to detect differences in clinically meaningful outcomes and should also collect data on duration of hospitalization and use of resources. These objectives would be best achieved through collaborative multicenter studies such as the ARF Trial Network (ATN) study—an RCT of intensive vs conventional dosing of both intermittent hemodialysis and CRRT in critically ill US patients with ARF.⁸⁶ The multicenter Randomised Evaluation of Normal vs Augmented Level of Renal Replacement (RENAL) study is similarly comparing augmented with conventional dosing of CRRT in critically ill patients treated for ARF in Australia and New Zealand and is expected to complete enrollment in 2008.⁸⁷ These trials will provide useful guidance with respect to the dosing and frequency of RRT in patients with ARF as well as to establishing infrastructure that could be used to support future studies in this important clinical area.

Author Contributions: Dr Tonelli had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Pannu, Klarenbach, Wiebe, Manns, Tonelli.

Acquisition of data: Pannu, Wiebe, Tonelli.

Analysis and interpretation of data: Pannu, Wiebe, Manns, Tonelli.

Drafting of the manuscript: Pannu, Wiebe, Tonelli.

Critical revision of the manuscript for important intellectual content: Pannu, Klarenbach, Manns, Tonelli.

Statistical analysis: Wiebe.

Obtained funding: Tonelli.

Administrative, technical, or material support: Pannu, Wiebe.

Study supervision: Pannu, Wiebe, Manns, Tonelli.

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