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Continuous Renal Replacement Therapy in Adult Patients with Acute Renal Failure: Systematic Review and Economic Evaluation

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Canadian Agency for Drugs and Technologies in Health

Continuous Renal Replacement Therapy in Adult Patients with Acute Renal Failure: Systematic Review and Economic Evaluation

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Conflicts of Interest

Dr. Ravindra L. Mehta has had consulting agreements with companies providing dialysis equipment and solutions (Gambro, DSI, RenaMed). He has received grant support from companies involved in acute renal failure (Lilly). Dr. Mehta has been on advisory boards of dialysis companies (RenaMed, DSI), and has organized an annual conference on CRRT that was supported by continuous renal replacement therapy and intermittent hemodialysis manufacturers (Gambro, Fresenius, B. Braun, NxStage, Edwards, Baxter).

REPORT *IN BRIEF*

June 2007

Continuous Renal Replacement Therapy in Adult Patients with Acute Renal Failure: Systematic Review and Economic Evaluation

Technology and Condition

Continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD) in critically ill adult patients with acute renal failure (ARF). There are 2,445 cases of ARF requiring dialysis among critically ill Canadian patients per year.

Issues

CRRT is a more costly therapy that has theoretical advantages over standard therapy with IHD, but there is uncertainty about whether these translate into patient-relevant outcomes. CRRT is popular among some Canadian intensivists, but there are wide variations in its use across Canada.

Methods and Results

A systematic review of the clinical literature was conducted. Thirteen RCTs and large ($n \geq 100$) controlled trials comparing CRRT with IHD were selected for review. We also identified three trials comparing the submodalities of IHD and 10 trials comparing the submodalities of CRRT. A cost-utility analysis was conducted from the perspective of a Canadian third-party payer. A Markov model followed a theoretical cohort of Canadian patients for a lifetime. The systematic review did not reveal statistically significant differences in clinical outcomes between IHD and CRRT. Economic models suggested that IHD could be cost-saving or lead to additional downstream costs. Cost-effectiveness is influenced by small differences in patient survival and need for long-term dialysis.

Implications for Decision Making

- **The benefit from CRRT is yet to be proven.** Compared to IHD, observed differences in clinical outcomes after CRRT (dialysis dependence at study end, number of hospitalization days) were not statistically significant, but had wide confidence intervals, suggesting that meaningful clinical differences could exist. Available evidence suggests similar rates of mortality between modalities.
- **IHD reduces acute-care costs.** Given current CRRT usage rates of 26% to 68%, selectively funding IHD when either technology is appropriate would save $2.1 million to $6.1 million in acute-care costs. If no improvements in clinical outcomes are obtained with CRRT, its use leads to equal QALYs and an additional cost of $3,679 compared with IHD. If IHD leads to reduced mortality, it produces 0.07 QALYs and additional costs of $8,541 per patient largely due to the additional downstream costs of more long-term dialysis.
- **Decisions about optimal therapy should be revisited as more information becomes available.** If future studies suggest that CRRT leads to better clinical outcomes, especially a reduced risk of dialysis dependence among survivors, the cost-effectiveness of CRRT should be revisited.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): Tonelli M, Manns B, Wiebe N, Shrive F, Pannu N, Doig C, Klarenbach S. *Continuous renal replacement therapy in adult patients with acute renal failure: systematic review and economic evaluation.*

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EXECUTIVE SUMMARY

Issue

Acute renal failure (ARF) occurs in 20% to 25% of patients who are admitted to an intensive care unit (ICU). It is associated with high in-hospital mortality (40% to 65%) and health care costs. ARF in critically ill ICU patients can be managed with intermittent hemodialysis (IHD) or continuous renal replacement therapy (CRRT). CRRT is a newer therapy that has theoretical advantages. Whether these translate into a meaningful clinical advantage for patients is controversial. Given CRRT's higher cost, its popularity among some intensivists (doctors who are critical care board-certified and who specialize in treating seriously ill patients) in Canada and elsewhere, and evidence that most critically ill patients with ARF can tolerate CRRT or IHD, further examination of this issue is worthwhile.

Objectives

Our objectives were to conduct a systematic review of the efficacy and harm of CRRT and IHD, and to conduct an economic evaluation and budget impact analysis comparing these strategies in critically ill adult patients with ARF.

Systematic Review

Methods: Using MEDLINE®, EMBASE®, all EBM Reviews, ProQuest Dissertations & Theses, and 35 grey literature sources, we conducted a comprehensive search to identify all randomized and large non-randomized ($n \geq 100$) controlled adult trials of renal replacement therapies. We assessed study quality using condensed versions of the Chalmers Index, and the Black and Downs checklist. All steps of the review process were performed in duplicate. In addition to demographic and clinical characteristics, we extracted the following clinical outcomes: mortality, length of stay, health-related quality of life, dialysis dependence, the number of dialysis treatments, and complications. Because of the differences expected between trials, we decided a priori to combine results in a conservative fashion using a random effects model. Statistical heterogeneity was quantified using the I^2 statistic. We conducted submodality comparisons before undertaking the main comparison of CRRT versus IHD. This facilitated additional analyses where only the best practices for each modality were used.

Results: We found 10 trials (with 1,298 participants) comparing the submodalities of CRRT. Few of these trials were powered to detect differences in clinical outcomes. There was some evidence for favouring hemodiafiltration over hemofiltration, favouring higher doses (45 mL/kg/h and 35 mL/kg/h versus 20 mL/kg/h) in hemofiltration, and favouring bicarbonate over lactate buffers. Although we found three trials (with 233 participants) comparing the submodalities of IHD, we reached no conclusions about its clinical benefit.

We found 13 trials (with 1,259 participants) that compared CRRT with IHD. The quality of the trials was generally poor. About half met each quality criterion. We found no evidence of significant differences between CRRT and IHD for the clinical outcomes. The relative risk (RR) of the mortality associated with CRRT was similar to unity (RR 1.02, 95% CI 0.93 to 1.12). There was little heterogeneity between studies for the RR of mortality due to dialytic modality (I^2=10%). The estimates of RR associated with other clinical outcomes (dialysis dependence at study end, number of hospitalization days) were largely non-significant, but had wider confidence intervals, suggesting that meaningful clinical differences could exist.

Economic Analysis

Methods: The objective of the economic analysis was to determine the cost-effectiveness of CRRT versus IHD in the treatment of critically ill adults with ARF in Canada. We conducted a systematic review of economic evaluations comparing CRRT with IHD for the treatment of ARF in critically ill patients and found none. A decision model was created to model events occurring from the start of renal replacement therapy in the ICU, until death or discharge from the index hospitalization. Survivors then entered a Markov model for the transition between the following clinical states: "alive requiring dialysis," "alive without dialysis," and "death." Observational data taken from a Canadian setting and the results of the systematic review were used in the model. We used the perspective of the Canadian publicly funded health care system and modelled the cost-effectiveness of CRRT over a lifetime horizon.

The model outputs were quality-adjusted life-years (QALYs), life-years gained, health care costs, and the cost per QALY gained. QALYs were calculated by multiplying the time spent by the average patient in each clinical state, by the utility associated with that state. We performed base case analyses using Markov cohort analysis and used Monte Carlo simulation for probabilistic sensitivity analysis.

Results: In the a priori defined economic analysis (model 1), which used the point estimates for the RR of death and dialysis dependence taken from the systematic review and meta-analysis, IHD was associated with a reduction in acute dialysis costs. It was also associated with an increase in total health care costs, given that more patients receiving IHD survived to hospital discharge – a proportion of whom needed long-term dialysis. Patients who were treated with IHD had increased QALYs compared with those treated with CRRT. QALYs increased by 0.07 and costs increased by $8,541, resulting in an incremental cost per QALY gained of $125,960 for IHD compared with CRRT.

The secondary analysis (model 2) used a RR of 1.0 for mortality and dialysis dependence, because no evidence of benefit was found between the two therapies in the systematic review. This resulted in CRRT being dominated by IHD, with IHD leading to equal QALYs and immediate cost savings of $3,679 (all savings resulting from the lower dialysis costs for ARF). Scenarios evaluating practices where the costs of providing CRRT and IHD varied had small effects on the incremental cost-effectiveness ratio (ICER). The RR of dialysis dependence had the most significant effect on the ICER in the one-way sensitivity analysis. Using model 2, CRRT was dominated by IHD in all sensitivity analyses except when the RR of mortality or dialysis dependence was set at the extremes of their respective 95% confidence intervals. These two parameters seemed to have the greatest influence on the ICER in models 1 and 2.

Health Services Impact

Using Canadian 2001 Census data for the total adult population, it is estimated that there are 2,445 cases of ARF requiring dialysis in critically ill Canadian patients per year. Assuming that CRRT is performed in 26% of critically ill patients with ARF across Canada, reducing its use to 0% or 1.6% would result in cost savings of $2.1 million to $2.3 million. Because the extent of CRRT use in Canada is unclear, other scenarios were calculated for Canada. For example, if CRRT is used for 68% of patients, $6.1 million could be saved by providing IHD only.

These results can be modified to represent a region or centre by considering the baseline use of CRRT and the population in the catchment region. For example, in 2002, the Calgary Health Region

(catchment population of 1.3 million patients) used CRRT to treat approximately 68% of critically ill patients with ARF. By providing IHD only, this region could expect to save $357,000 annually.

Conclusions

Although CRRT is more costly than IHD, available data do not support the hypothesis that, compared with IHD, CRRT results in clinically meaningful improvements in outcomes for critically ill adults with ARF. The quality of the studies identified in the literature review was generally poor. Evidence from additional large trials would be needed to exclude a clinically relevant benefit associated with either therapy.

Because the costs incurred in providing CRRT were low compared with the cost of downstream complications in survivors (especially the cost of providing chronic dialysis), this conclusion should be revisited if future studies suggest that CRRT improves clinical outcomes, especially the risk of dialysis dependence in survivors.

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ABBREVIATIONS

APACHE	Acute Physiology and Chronic Health Evaluation
ARF	acute renal failure
CI	confidence interval
CKD	chronic kidney disease
CRRT	continuous renal replacement therapy
CVVHD	continuous venovenous hemodialysis
CVVHDF	continuous venovenous hemodiafiltration
CVVHF	continuous venovenous hemofiltration
HD	hemodialysis
HDF	hemodiafiltration
HF	hemofiltration
ICER	incremental cost-effectiveness ratio
IHD	intermittent hemodialysis
IHF	intermittent hemofiltration
IRRT	intermittent renal replacement therapy
Kt/V	an index of dialysis dose, with larger numbers representing higher doses
MAP	mean arterial (blood) pressure
PD	peritoneal dialysis
QALY	quality-adjusted life-years
RCT	randomized controlled trials
RR	relative risk
RRT	renal replacement therapy
SLEDD	slow low-efficiency daily dialysis

1 INTRODUCTION

1.1 Background in Canada

The provision of care to critically ill patients consumes a disproportionate amount of health care resources. Although intensive care unit (ICU) beds form a small fraction of hospital beds, they consume 8% of the total inpatient cost and 0.2% of the gross national product in Canada.[1] In the US, ICU beds account for 20% of the total inpatient cost and 0.8% of the gross national product. A day in a North American ICU costs between three and six times as much as one day in a non-ICU setting.[1] As health care budgets become constrained, the use of resources for critically ill patients must be optimized.

Acute renal failure (ARF) occurs in as many as 25% of patients who are admitted to an ICU, and a significant proportion of these will need acute dialysis treatment.[2] This subset of critically ill patients has a high rate of in-hospital mortality (40% to 65%)[3-5] and high health care costs during the acute phase of their illness.[1] In addition, 5% to 30% of such patients who survive and are discharged from hospital will stay on long-term dialysis without renal recovery.[1] Thus, the optimal management of ARF in critically ill patients can improve health outcomes and influence health care costs.

1.2 Overview of Technology

When kidneys fail, toxins, excess salts, and fluid build up in the body. Without renal replacement therapy (RRT), patients will die. Different types of RRT can be used in patients with acute kidney failure. Each differs in the way that it removes toxins and fluids, and in the resources that it consumes. Renal replacement can be achieved by diffusion (hemodialysis or HD), convection (hemofiltration or HF), or a combination of these methods (hemodiafiltration or HDF).

In HD, blood is removed from the body and passed through a semi-permeable membrane. Clean dialysate fluid (with no toxins) passes on the other side of the membrane, allowing equilibration of the patient's blood with dialysate. Toxins in the blood move into the dialysate.

During HF, blood is removed from the body and passed through a semi-permeable membrane. Hydrostatic pressure is used to force fluid, toxins, and salts from the blood, and across the membrane, resulting in the convective loss of solutes and water. The fluid removed in this process is replaced intravenously ("replacement fluid") to prevent iatrogenic acidosis, electrolyte depletion, and excessive fluid removal.

HDF combines diffusive and convective clearance. While HD, HF, and HDF all efficiently remove small molecular weight substances such as urea, creatinine and potassium, middle and larger molecular weight substances are more efficiently removed using HF and HDF.

1.3 Options in ICU for Renal Replacement

ARF in the ICU can be managed intermittently with HD – known as intermittent hemodialysis (IHD) – or continuously using HD, HF, or HDF – known as continuous RRT (CRRT).

In IHD, HD is performed using venovenous access for a few hours at variable intervals (typically four hours, three to four times per week).[2] Typically, the same equipment and staff that are involved in treating chronic kidney failure are involved in IHD. Therefore, the capital and training expenditures associated with establishing an IHD program are often low. Slow, low-efficiency daily dialysis (SLEDD) or extended daily dialysis are variants or submodalities of IHD where the duration of dialysis is extended to between eight and 12 hours, blood flow is reduced, fluid removal is more gradual, and solute clearance slower. SLEDD is associated with less hemodynamic instability than IHD and has excellent solute control.[6]

CRRT is performed continuously (i.e., approximately 24 hours per day) through arteriovenous or venovenous vascular access. Arteriovenous access, which was used more extensively in the past, involved simultaneous cannulation of the femoral artery and the femoral vein. The patient's cardiac output drove blood through the dialysis circuit. This method has recently fallen out of favour because of the high rate of complications and the development of external circuit pumps. The most commonly applied submodalities of CRRT are continuous venovenous hemofiltration (CVVHF), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF) (Appendix 1 Table 1). Regardless of the method used, CRRT involves specialized equipment and training for staff, generally consumes additional supplies (especially replacement fluids) compared with IHD, and is generally performed only in an ICU.

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 IHD. Because fluid is removed more slowly using CRRT, in theory, it may be better tolerated hemodynamically than IHD. Its continuous nature might allow for enhanced toxin removal, including solutes of large molecular weight (such as cytokines), which may contribute to the adverse outcomes associated with critical illness.[7,8] On the other hand, CRRT requires continuous anticoagulation (which might predispose patients to bleeding) and involves continuous exposure to an extracorporeal circuit (which might lead to adverse consequences, including complement activation or infection). On balance, the theoretical benefits seem to favour CRRT.

See Appendix 1 Table 2 for a comparison of intermittent versus continuous dialysis therapies.

1.4 Current Practices for Renal Replacement in ICU

There is regional variation in the management of ARF among critically ill adults in Canada.[9] For example, CRRT is not used in Nova Scotia, but it is the predominant mode of renal replacement for critically ill patients treated at certain facilities in Montreal. Internationally, there is similar variation, and in some settings (such as Australia), CRRT is the only dialysis modality used.[9-11]

The factors that govern the choice of modality are poorly described, but may include availability, cost, physician's expertise or preference, indication for renal replacement (fluid removal versus solute clearance), availability of trained nursing staff, and perceptions about the theoretical benefits of each therapy. For instance, it is believed that CRRT is better tolerated in hemodynamically unstable patients,[12] although a large randomized trial suggests that this is not the case.[13] There are no North American or European clinical practice guidelines that address the choice of dialytic modality in ARF, although many opinion-based review articles have been published on this issue over the last two decades.

2 THE ISSUE

ARF in critically ill ICU patients can be managed with intermittent hemodialysis (IHD) or continuous renal replacement therapy (CRRT). CRRT is a newer therapy that has several theoretical advantages. Whether these translate into a meaningful clinical advantage for patients is controversial. Given the higher cost of CRRT, its popularity among intensivists in Canada and elsewhere, and evidence that most critically ill patients with ARF can tolerate CRRT or IHD, further examination of this issue is worthwhile.

3 OBJECTIVES

Our objectives were to perform a systematic review of the efficacy and harm of CRRT and IHD, and to conduct an economic evaluation and budget impact analysis comparing these strategies in critically ill adult patients with ARF.

For all objectives, CRRT was compared with IHD, which may be administered with varying frequency (daily and thrice weekly) and duration (≥4 hours).

- Compared with thrice-weekly or daily IHD, what is the clinical effectiveness of CRRT in adult patients with ARF requiring dialysis?
- Compared with IHD, does CRRT reduce mortality?
- Compared with IHD, does CRRT reduce the total number of days in the ICU or in hospital?
- Compared with IHD, does CRRT reduce the risk of chronic renal impairment or the requirement for chronic dialysis treatment?
- Compared with IHD, does CRRT improve health-related quality of life?
- Compared with IHD, does CRRT reduce the risk of dialysis-related complications?
- Compared with IHD, what is the cost per QALY gained by the use of CRRT in adult patients with ARF requiring dialysis? Compared with IHD, what is the cost per life-year (LY) gained by the use of CRRT in patients with ARF requiring dialysis?
- What is the role of CRRT in ARF? Are there any subgroups in which CRRT might be more effective or more cost-effective than IHD?
- What is the potential economic impact of CRRT use in Canada?

4 SYSTEMATIC REVIEW

4.1 Methods

This study was conducted and reported in accordance with available guidelines.[14,15] The primary objective was to compare the safety and efficacy of treating ARF in critically ill adults with CRRT versus IHD. Because there can be variability between CRRT submodalities and between IHD submodalities, we designed our search strategy to include studies comparing different submodalities (e.g., low dose versus high dose CRRT). This was done to aid the interpretation of the findings for CRRT and IHD.

4.1.1 Literature search

We conducted a comprehensive search to identify all the relevant controlled trials of renal replacement therapies in ARF patients. Articles in all languages were considered, regardless of publication status. MEDLINE® (1966 to June 27, 2006), EMBASE® (1988 to June 27, 2006), all EBM Reviews, the ProQuest Dissertations & Theses, and grey literature sources (n=35) were searched (Appendix 2 Table 1). Each citation or abstract was screened by a subject specialist (MT, SK) and another reviewer (MO, DA). Any trial that was considered to be relevant by one or two reviewers was retrieved for review. The reference lists of included trials and relevant reviews were studied for pertinent trials. We contacted RRT manufacturers (Appendix 2 Table 2) and the authors of included studies for information about further studies. Neither of the latter two sources identified additional trials.

4.1.2 Study selection

Each potentially relevant study was independently assessed by two reviewers (MO or DA, ST) for inclusion in the review using predetermined eligibility criteria (Appendix 7 Form 1). An initial set of 10 articles was used to calibrate the assessment of eligibility between reviewers. For assessing efficacy and harm, trials meeting the following criteria were eligible:

- randomized controlled trials (RCT) with any number of participants or prospective controlled trials with ≥100 allocated participants
- population of adults with ARF, as determined by study authors
- RRT used as intervention
- another RRT used as comparator
- clinical outcomes (e.g., mortality, length of stay, dialysis dependence).

Disagreements were resolved by a third party (NW) through consensus. Disagreements arose with 8% of the articles (kappa=0.77). The disagreements were about design (n=8), outcome (n=3), and whether an article was a duplicate publication (n=1).

4.1.3 Quality assessment

We assessed the study quality of all controlled trials using a condensed version of the Chalmers Index.[16] We looked for characteristics known to be associated with study quality (e.g., method of allocation concealment,[17] randomization technique, double-blinding, and description of withdrawals or dropouts[18]) (Appendix 7 Form 2). For non-randomized studies, we determined the likelihood of selection bias using the checklist described by Black and Downs.[19] Finally, we extracted data on funding sources, given their potential to introduce bias.[20]

We report the quality of all included studies in trial design (selection of participants, description of treatment, allocation of participants, blinding), statistical analysis (estimation of sample size, types of models, adjustment for potential confounding, handling of missing data), and presentation of results (access dates, confidence intervals, reports of adverse events). Two reviewers (MO or DA, ST) assessed each included study independently. An initial set of 10 included trials was used to calibrate the assessment of study quality between reviewers. Disagreements were resolved with a third party (NW) through consensus.

4.1.4 Data extraction

We used a standard data extraction method to record the following properties of each trial: characteristics (country, design, sample size, setting, duration of follow-up); participants (age, gender, presence of liver failure or systemic inflammatory response syndrome), illness severity [serum creatinine and urea; Acute Physiology and Chronic Health Evaluation (APACHE II or III) score; need for mechanical ventilation, 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, whether the outcome was ascertained for all patients or just survivors); and results. One reviewer extracted the data (MO or DA), and a second (DA or MO) checked for accuracy. A statistical reviewer (NW) checked the numerical results for accuracy.

We assessed the following outcomes: mortality (ICU, hospital, any other point), length of stay (ICU, hospital), length of mechanical ventilation, health-related quality of life, dialysis dependence, subsequent chronic renal insufficiency, number of dialysis treatments, dialysis dose (Kt/V, urea reduction ratio), hyperkalemia, acidosis, change in mean arterial pressure, hypotension, and complications. We classified complications into filter clotting, hemorrhagic complications, hemodynamic instability or arrhythmia, metabolic abnormalities, and other complications.

4.1.5 Data analysis

We analyzed data using Review Manager 4.2.7 (Oxford UK) and Stata 8.2 (College Station TX). We pooled the results of trials that compared CRRT to IHD. Because of the differences expected between trials, we decided a priori to combine the results using a random effects model.[21] For dichotomous outcomes (e.g., mortality), we used the relative risk (RR) to pool outcomes. For complications that had many zero event cells, we used the risk difference. When complications were reported more than once in the same category, we used the maximum number of events as the total number to keep our rate estimates conservative.

We used the weighted mean difference to pool results for analyses that evaluate the difference in change-from-baseline in mean arterial blood pressure (MAP). The standard deviation for this estimate was calculated using a correlation of 0.5 (between the baseline and final measures of MAP) when neither this parameter nor the observed correlation were reported.[22] Other continuous outcomes (length of stay and number of dialysis treatments) were generally associated with right-skewed distributions and were not pooled. Measures of central tendency, spread, tests and corresponding p values were extracted for each intervention and reported in evidence tables.

Where the results were pooled, the statistical heterogeneity was quantified using I^2.[23,24] The I^2 statistic approximates the percent of total variation (in and between studies) due to between-study variation. We planned to use meta-regression[25] to examine whether certain variables (age, gender, baseline serum creatinine, illness severity, and study quality) influenced the association between treatment (CRRT versus IHD) and clinical outcomes, but too few trials were identified to permit meta-regression. In sensitivity analyses, we compared CRRT and IHD based on the type of vascular access (venovenous only versus all forms); era (before or after the median publication year of 2004); and study quality (RCT versus clinical controlled trials, intention-to-treat, loss to follow-up, and funding). We assessed the publication bias[26] using weighted regression.[27]

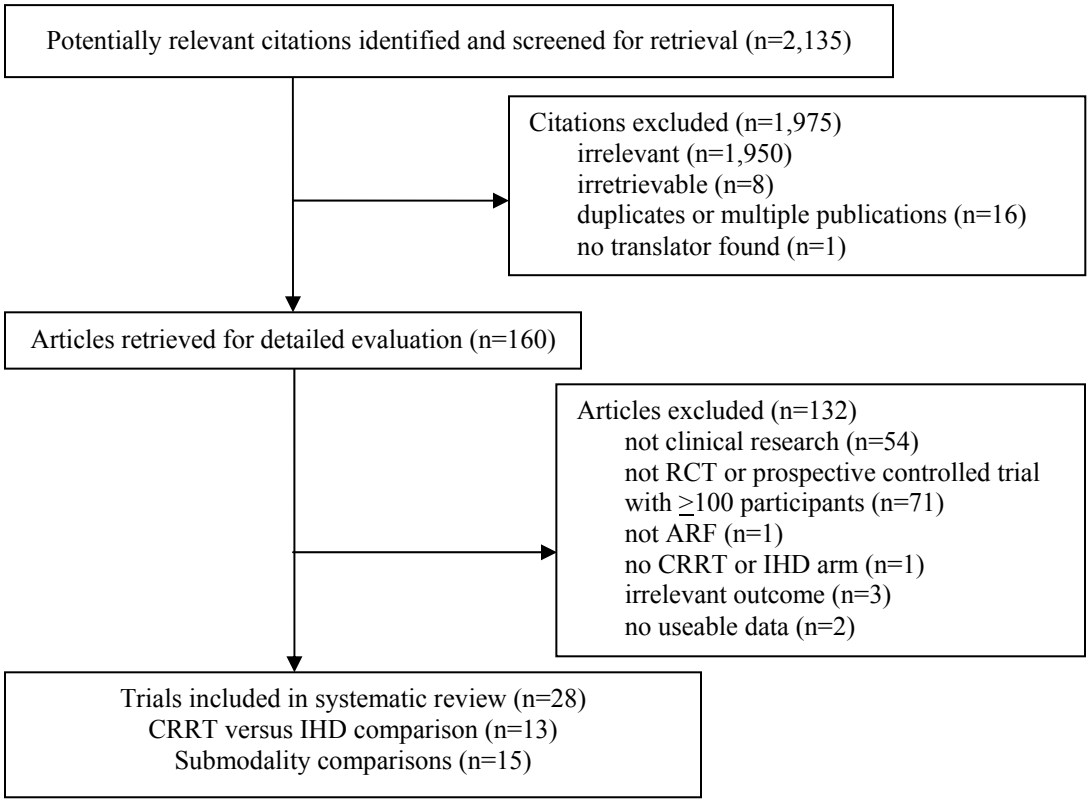
Although we identified multiple studies that compared the submodalities of each dialytic method, there were too few trials in each comparison to pool systematically. The findings of these studies are presented in an evidence table, which includes outcomes of interest for our review, particularly – when they were reported – mortality, dialysis dependence, and the authors' conclusions on clinical outcomes.

4.2 Results

4.2.1 Quantity of research available

Figure 1 shows the trial selection. From 2,135 citations, 160 potentially relevant articles were retrieved for review. Of these, 132 were excluded because they did not meet the selection criteria. Most were irrelevant. Three trials[28-30] were excluded because they did not report a clinical outcome that was relevant to this review. One trial[31] was excluded because the intermittent therapy that it studied was plasma exchange rather than dialysis. One prospective controlled trial was excluded because there were <100 participants (53 participants).[32] Of the 28 eligible controlled trials, 13 compared CRRT and IHD.[13,33-44] Thus, they were used to perform the comparison of primary interest. Among the other 15 controlled trials, 10 compared the submodalities of CRRT,[12,45-53] three compared the submodalities of IHD,[54-56] and two compared CRRT or IHD with peritoneal dialysis.[57,58]

Figure 1: Studies Considered for Inclusion



4.2.2 Submodality comparisons of CRRT

Because submodality comparisons could inform the findings of the main review, our protocol specified that these comparisons should be performed first. Our objective was to identify whether certain forms of CRRT were superior to others. Similar analyses were performed for IHD. This would allow us to perform additional analyses comparing CRRT with IHD when only best practices for each were used (assuming that the submodality comparisons were useful for this purpose).

In the 10 publications of controlled trials comparing submodalities of CRRT, there was a total of 1,298 participants (Appendix 3 Table 1). Three trials compared CRRT techniques. The largest and highest quality of these (Saudan *et al.*,[53] Appendix 3 Table 2) compared HDF with HF in 206 participants and found a significant reduction in mortality at 28 days favouring HDF over HF (RR 0.63, 95% CI 0.48 to 0.82; Appendix 3 Table 3). Two studies[45,50] comparing HD with HF found no differences in mortality. These studies included a total of 44 participants, so they were not powered to detect a difference in clinical outcome. The pooled results were non-significant (1.37, 0.77 to 2.43; I^2=39%).

Two trials[45,51] compared prescribed dialysis flow rates (2.5 L/h and 1.5 L/h versus 1 L/h) in a total of 80 participants. Neither found a significant difference in mortality or was adequately powered to detect such a difference.

Two trials with 531 participants compared different doses of HF. The larger study[12] (425 participants) was of moderate quality, because the concealment of treatment allocation was unclear, and the methods and results were inadequately described (inclusion and exclusion criteria, therapeutic regimens, ineligible patients, and complications). The paper reported that the doses of 45 mL/kg/h and 35 mL/kg/h reduced mortality compared with the dose of 20 mL/kg/h (RR 0.72, 95% CI 0.56 to 0.91; and 0.73, 0.58 to 0.93 respectively). No difference was noted in the likelihood of dialysis dependence among survivors at the end of the study. The second study[46] (106 participants) found a non-significant trend towards reduced mortality with higher HF volumes, and no difference in the likelihood of dialysis dependence or in the number of mechanical ventilation days. The pooled results for mortality were significant and favoured higher doses (0.74, 0.63 to 0.88; I^2=0%). The pooled results for dialysis dependence were non-significant (1.20, 0.27 to 5.32) and non-heterogeneous (I^2=19%).

Two trials compared an earlier to a later start of HF in a total of 134 participants. In the larger trial[46] (n=106), "early" dialysis was started after 6 h of urine output <30 cc/h. No significant differences were found in mortality, dialysis dependence in survivors, or the number of mechanical ventilation days. The smaller study[52] found a large reduction in mortality, but had several markers of poor quality (no intention-to-treat design; no reported sample size calculation; and failure to report loss-to-follow-up, confidence intervals, or the incidence of complications by treatment arm). In addition, this trial used unusual definitions of "early" and "late" initiation of dialysis (urine output <30 cc/h for 3 h and urine output <20 cc/h for 2 h respectively), which would be difficult to implement in routine clinical practice.

Two trials with a total of 249 participants compared different buffer (base) solutions (bicarbonate, acetate, and lactate) in patients receiving CRRT. Neither found significant differences in mortality. One trial[47] reported a significantly reduced risk of the primary outcome – cardiovascular events (RR 0.39, 95% 0.20 to 0.79) – with the use of a bicarbonate rather than a lactate buffer. This trial had

several design characteristics that may have introduced bias (no sample size calculation, not an intention-to-treat design, losses to follow-up not reported).

One additional study was eligible for the review based on the inclusion and exclusion criteria. The study suggested that the spontaneous modes of arteriovenous CRRT (i.e., those driven by the patient's blood pressure) were inferior to pump-driven CRRT (arteriovenous or venovenous).[49] Because spontaneous arteriovenous CRRT is not used in clinical practice, the findings of these studies did not inform our review.

4.2.3 Submodality comparisons of IHD

We identified three controlled trials with a total of 233 participants that compared the submodalities of IHD (Appendix 3 Table 1). Two of these trials compared the higher doses of dialysis with conventional (every second day) HD. One trial[54] (n=146), which compared an intensive (daily) schedule of IHD with the conventional schedule, found significantly lower mortality (RR 0.59, 95% CI 0.39 to 0.91; Appendix 3 Table 3) in the daily treatment arm. Intensive therapy in another trial[56] (34 participants) was defined by HD performed as often as necessary to maintain blood urea nitrogen <21 mmol/L and serum creatinine <440 µmol/L (resulting in daily HD for all but two participants in the intensive therapy arm). This study found a non-significant trend towards lower mortality with conventional HD. The pooled overall RR for mortality associated with more intensive IHD was non-significant (0.83, 0.40 to 1.72) and heterogeneous (I^2=73%). Both trials had potentially significant design limitations, because neither concealed treatment allocation, and both used quasi-randomized designs (Appendix 3 Table 2). The third trial[55] (n=39), which compared intermittent HDF with intermittent HD, found no significant difference in mortality between treatment groups.

4.2.4 Other comparisons informing dialysis modality selection in ARF

In peritoneal dialysis (PD), the peritoneum is used as a semi-permeable membrane for diffusive removal of solutes. It is an effective treatment modality for patients with chronic renal failure, and outcomes appear similar to those associated with HD.[59,60] PD is valuable in pediatric critical care, where vascular access is challenging and peritoneal surface area is larger than in adults.[61] The use of PD is limited by practical considerations. Acute PD requires the surgical insertion of a peritoneal dialysis catheter. It is often complicated by catheter leakage and malfunction. The use of PD is limited by low solute clearance in hypercatabolic patients and potential pulmonary restriction due to the expansion of the peritoneal cavity. It is contraindicated in post-operative patients who need abdominal surgery or surgical drains.[57] A study comparing PD with CRRT in critically ill septic patients with ARF[57] showed more rapid correction of acidosis, better solute clearance, and significantly improved survival with CRRT. A second study[58] compared PD and IHD, and found no differences in solute clearance. Because acute PD is not widely used to treat ARF in Canada, these findings do not influence the conclusions of this review.

4.2.5 Findings from submodality comparisons

Limited data suggest that CRRT should be performed with a bicarbonate buffer and the use of HDF rather than HF. Higher doses of HF (45 mL/kg/h or 35 mL/kg/h) are preferable to lower doses (20 mL/kg/h), although it is unclear whether higher filtration volumes are beneficial with HDF. Little information was available from randomized trials to inform best practices for IHD.

4.2.6 CRRT versus IHD comparisons

We identified 13 controlled trials with a total of 1,259 participants (Appendix 3 Table 4). The median sample size was 80 (five trials enrolled >100 participants). All were RCTs, except for Noble *et al.,*[43] which combined non-randomized pilot data with data from an RCT. For continuous therapy, seven trials[35,36,38-41,44] studied HF, four[13,33,37,43] looked at HDF, and two[34,42]examined HD. The vascular access for continuous therapies was venovenous in all cases except in two small, older trials[40,41] (37 patients combined), which used arteriovenous accesses exclusively; and in two larger trials,[37,43] which used a combination of both types. Arteriovenous accesses were used in fewer than 98 of the patients treated with CRRT (16%), although one report does not give exact numbers. For intermittent therapy, extended HD of six to 12 hours' duration was used in two studies.[35,42] HF was used in two small trials[40,41] (n=37). The remaining nine studies used standard HD.

The information on dialysis dose was largely incomplete and the method used to quantify it varied among trials that reported it. Different HD membranes were used, although the use of cellulosic membranes was rare,[37] and most were high flux. Most studies used a bicarbonate-based buffer with heparin-based anticoagulation.

The mean age of participants in the 13 trials ranged from 53 to 67 years, except in the two small trials evaluating arteriovenous HF, where the mean ages were 31 and 35 years, and all had liver failure. The percentage of males in each trial ranged from 53% to 87%. The mean baseline serum creatinine ranged from 329 µmol/L to 608 µmol/L. The mean reported APACHE II scores ranged from 21 to 34, representing moderate to severe illness severity. These data were available in seven of the13 trials. From 0% to 100% of patients in each trial had systemic inflammatory response syndrome.

Appendix 3 Table 5 reports the findings of quality assessment. Of the13 trials, five adequately reported selection criteria, including a definition of ARF. One trial reported that an adequate method was used to conceal treatment allocation; three used inadequate methods of concealment; and the method of allocation concealment was not reported in the remainder. Fewer than half of the studies (six) adequately described the dialytic regimens they studied [by reporting dialytic technique, filter type, prescribed blood and dialysate flows, and at least one index of dialysis dose (treatment schedule, Kt/V, or urea reduction ratio)]. A sample size calculation was reported in four of the 13 trials. An intention-to-treat design was used in three trials. Eight reported the adjusted association between treatment assignment and outcome rather than unadjusted results alone. Two trials reported a description of recruited but ineligible patients, six reported losses to follow-up (which was <10% in all cases), five reported confidence intervals or a measure of deviation from the central tendency for nonparametric analyses, and six reported information on rates of complications. Four studies reported a public source of funding, one reported a private source, and one reported funding from public and private sources. The remaining seven did not report any source of funding.

a) Publication bias

To assess the potential for publication bias, we used the results from analyses comparing mortality between treatment groups, using the latest time-point from each trial. Publication bias is often assessed using a funnel plot. A funnel plot is a simple scatter plot of a measure of each study's precision (y-axis) against each study's treatment effect (x-axis). Precision may be the inverse of the study's standard error or sample size. Because precision is directly related to sample size, the scatter plot of precision versus sample size should form an inverted funnel. An asymmetrical funnel plot may be due to the absence of small negative studies (i.e., if these studies have been conducted but not published) resulting from publication bias. Other causes of funnel plot asymmetry[26] include trial

diversity, language bias, and multiple publication bias. Our funnel plot was asymmetrical (Appendix 4 Figure 1), but the weighted regression test detected no statistical evidence of publication bias (bias=0.44, p=0.56).

b) Mortality

Six controlled trials with 549 participants reported all-cause mortality before discharge from the ICU. The overall RR of mortality due to CRRT was non-significantly different from that due to IHD (1.10, 95% CI 0.95 to 2.08; Appendix 4 Figure 2), with small heterogeneity due to between-study variance (I^2=8%). There was no significant difference in the RR of in-hospital mortality for CRRT recipients (1.05, 0.92 to 1.20 compared to IHD; I^2=36%; Appendix 4 Figure 3), based on findings from six trials with a total of 901 participants. One study[13] with 359 participants reported mortality in all patients at 60 and 90 days. The results were not significantly different for CRRT compared with IHD at either time-point (0.98, 0.85 to 1.14; and 0.98, 0.86 to 1.12 respectively). We pooled the mortality results from all trials using the final reported time-point. The RR was non-significant (1.02, 0.93 to 1.12; 10 trials; 1,142 participants; Appendix 4 Figure 4) and the between-study heterogeneity was small (I^2=10%).

In the sensitivity analyses, we compared mortality between treatments in strata that were defined by potential confounders. Analyses stratified on the 2004 median publication year found similar mortality for CRRT and IHD in studies published in 2004 and later (RR due to CRRT 0.97, 0.89 to 1.08; I^2=0%; 5 studies; 735 participants). There was non-significantly higher mortality due to CRRT when only studies published before 2004 were included (RR due to CRRT 1.14, 0.96 to 1.35; I^2=8%; five studies; 407 participants). The results did not differ from those of the primary analysis for any of the other stratified analyses. For instance, the RR of mortality due to CRRT was 1.01 (95% CI 0.92 to 1.11; I^2=0%; seven studies; 852 participants) when only studies using venovenous access were included. One trial[13] reported private funding. Stratified analyses were not informative.

The exclusion of one trial[43] in which treatment allocation was incompletely randomized or quasi-randomized decreased the between-study heterogeneity (6%; RR 1.05, 0.95 to 1.15; nine studies; 1,025 participants). The statistical between-study heterogeneity increased when only intention-to-treat trials (51%; 1.09, 0.93 to 1.29; four studies; 709) or trials that reported loss to follow-up (38%; 1.02, 0.89 to 1.16; five studies; 797 participants) were included.

Prompted by our findings from the submodality comparisons, we tried to identify trials using CRRT best practices, such as HDF, bicarbonate buffer, and higher filtration volumes. No trials reported a comparison of high dose CRRT with IHD (the dose was poorly reported in the studies). The pooled RR results for overall mortality in trials where the CRRT arm used HDF exclusively (RR 1.02, 95% CI 0.87 to 1.20; I^2=54%; four studies, 767 participants) or a bicarbonate buffer exclusively (0.96, 0.87 to 1.06; I^2=0%; three studies; 556 participants) did not differ from the findings of the main analysis.

c) Duration of RRT and risk of chronic kidney disease

Two trials with 413 participants reported the mean or median number of dialysis treatment days needed during the hospital stay. The results were skewed, so we report statistical summaries in Appendix 3 Table 6. Both between-study comparisons were non-significant, and the mean and median numbers of treatment days were similar between treatment groups and across trials.

Five trials reported the frequency with which chronic dialysis treatment was required (implying end-stage renal disease) in 308 participants who survived to ICU or hospital discharge. The results were

non-significant, although the number of events was small (RR of chronic dialysis dependence for CRRT versus IHD 0.91, 0.56 to 1.49; I^2=0%; Appendix 4 Figure 5). The results were similar when patients who died before ICU or hospital discharge were included in the estimate (RR of dialysis dependence due to CRRT 1.01, 0.80 to 1.28; I2=72%; four trials; 423 participants; Appendix 4 Figure 6). One trial[37] (n=166) reported that chronic renal insufficiency [serum creatinine≥176 μmol/L] at hospital discharge was significantly lower in CRRT recipients (RR 0.21, 0.06 to 0.70).

d) Total duration of ICU stay and hospitalization

Three RCTs (650 participants) reported the length of ICU stay (Appendix 3 Table 7). The summary statistics indicated right-tailed skewness. Therefore, we did not pool the results. All trials reported non-significant p values when tested for differences between treatments, although one used an appropriate statistical test for skewed outcomes. The mean and median estimates were similar between groups, but varied across trials (range six days to 20 days). Four RCTs (643 participants) reported length of stay in hospital (Appendix 3 Table 6). These results were skewed, and the estimates of mean and median length of stay ranged from 16 days to 32 days. Two trials reported non-significant differences between RRT groups. One trial[37] (n=166) reported a significant mean difference of 9.2 days (P<0.01) favouring shorter stays in the CRRT group. The statistical test used was inappropriate, given the skewed nature of the data. A second trial[42] (n=54) reported a median difference of 8.5 days favouring IHD, but did not report the results of significance testing. No trials reported days on mechanical ventilation.

e) Metabolic control

No studies compared Kt/V, urea reduction ratio, incidence of hyperkalemia, or incidence of severe acidosis between treatments.

f) Blood pressure and hypotension

Two trials with 389 participants compared the incidence of hypotension between treatment groups. One study[38] defined hypotension as the cumulative incidence of a decrease of >20% in MAP at 24 hours. The second[13] defined hypotension by the cumulative incidence of ≥50 mm Hg decrease in systolic arterial blood pressure from baseline or a value of ≤80 mm Hg at any time, and was assessed at ICU discharge. The pooled results showed no significant difference between treatments (RR of hypotension due to CRRT 0.87, 0.68 to 1.12; I^2=0%; Appendix 4 Figure 7). Three trials measured the mean arterial pressure at 24 hours or ICU discharge. The pooled change from baseline, involving 212 participants, was 4.6 mm Hg (95% CI 0.4 to 8.9; Appendix 4 Figure 8). It significantly favoured CRRT, and the between-study heterogeneity was 22%.

g) Health-related quality of life

No trials compared health-related quality of life between treatment groups during acute illness or in long-term follow-up.

h) Dialysis-related complications

Five trials with 543 participants compared the incidence of complications between treatment groups (Appendix 4 Figure 9). The pooled analyses of these five trials showed no significant differences. The overall risks of filter clotting and hemorrhagic complications were non-significantly higher for CRRT (risk difference for filter clotting 12% higher, 95% CI −7 to 31, I^2=82%, 149 participants; and 2% higher for hemorrhagic complications, −3 to 7, I^2=0%, 424 participants). The pooled risk of hemodynamic instability or arrhythmia was non-significantly lower for CRRT (risk difference 3% lower, −20 to 14, I^2=77%, three trials, 469 participants). The risk difference for the incidence of metabolic abnormalities was 0% between treatments (−6 to 5, one trial, 359 participants).

5 ECONOMIC ANALYSIS

5.1 Review of Economic Studies

We conducted a systematic review of economic evaluations comparing CRRT with IHD for the treatment of ARF in critically ill patients.

5.1.1 Methods for review of economic studies

A protocol for the systematic review was written a priori and followed throughout the process.

a) Literature search strategy

Given the broad search terms used for the clinical systematic review, we screened all the studies identified in that search for eligibility in our economic review. A total of 2,135 articles were deemed to be potentially relevant using the search criteria in Appendix 2 Table 1.

b) Study selection criteria

A study was eligible for inclusion in the systematic review of economic evaluations if it:

- was a complete economic evaluation that evaluated the incremental impact of CRRT on costs and benefits
- examined a cohort of adult patients with ARF requiring supportive RRT in intensive care
- compared CRRT to any IHD regimen (i.e., of any frequency and duration).

The protocol specified that analyses based on RCTs or conducted in Canada would receive higher priority when formulating conclusions.

c) Selection method

Two reviewers (SK, FS) applied the eligibility criteria to the title and abstract of each citation. Full-text articles were obtained for citations that could not be excluded using the title and abstract. The full-text articles were assessed using a form (Appendix 7 Form 3). For inclusion in the review, the study had to satisfy all the selection criteria. Disagreements between the reviewers were resolved by consensus. Disagreements arose with 14% of the articles (kappa=0.44).

d) Data extraction

The protocol specified that two reviewers (SK, FS) would use a standard form to independently extract and document relevant information on author, title, type of program, intervention, comparators, study population and size, study design, time horizon, perspective, data sources for effects, data sources for costs, discounting, health-related quality of life, currency, year, base-case incremental cost-effectiveness ratio results or incremental net benefit, sensitivity analysis, and conclusions.

e) Study quality assessment

The protocol specified that the quality of each included study would be independently assessed by two reviewers (SK, FS) using a checklist adapted from the *BMJ*[62] and the Consensus on Health Economic Criteria (CHEC).[63]

f) Data analysis methods

We anticipated a priori that only a small number of articles would be identified. Therefore, we planned a qualitative synthesis of included trials. This would highlight the impact of CRRT

compared with IHD, considering health outcomes, costs, and the incremental cost per quality-adjusted life-year (QALY) or life-year gained. It would also assess the applicability of the findings to a Canadian setting.

5.1.2 Results

Out of 2,135 citations, 49 were identified as potentially relevant, and the full-text articles were reviewed. After evaluation, none of these articles met all the criteria for inclusion. No studies were true economic evaluations. None assessed the incremental costs and incremental benefits of CRRT versus IHD in a cost-effectiveness, cost-utility, or cost-minimization framework.

Some of the 49 citations reviewed criteria 2 and 3, and had elements of an economic evaluation (criterion 1), but reviewers agreed that they did not meet the full criteria (Appendix 6 Figure 1).

5.1.3 Discussion

No true economic evaluations – where the incremental benefits and costs of CRRT compared with IHD were presented as a cost-minimization, cost-effectiveness, or cost-utility analysis – were identified in our search. The discussion of two articles that had some elements of an economic evaluation provides a contextual framework for our economic evaluation.

The first article described a multi-centre RCT of CRRT versus IHD in ICU patients with ARF conducted by Mehta *et al*.[37] In this study, CRRT was associated with a statistically significant increase in mortality in the ICU and other hospital settings. The odds of death were non-significantly different between the two groups when multivariate analysis was performed to account for imbalances between treatment arms, which occurred despite randomization. Other secondary outcomes, such as duration of ICU stay and renal recovery, did not differ between groups, with or without adjustment. This study collected resource utilization data, but only for in-hospital dialysis treatment costs. The direct cost of CRRT treatment compared with IHD treatment was US$543 versus US$282, and the total per patient treatment costs were US$3,946 versus US$3,077. Other costs that were related to ICU care, hospital stay, or post-discharge health care were not reported. While this study was based on one RCT, it contained some of the information needed to conduct a cost-effectiveness or cost-minimization analysis.

The second article described a high-quality, micro-costing study of a Canadian cohort.[1] It measured health care resource utilization for patients receiving CRRT or IHD in the ICU for ARF. In addition to capturing in-hospital costs, including those for delivering the dialysis therapies, the health care costs for one-year post-discharge were measured for surviving patients. This study reported significantly higher costs to provide CRRT than IHD (a difference of C$1,342 per week in 1999 dollars). Most of the difference is due to supplies and replacement fluid cost (C$416/day for CRRT compared to C$68.30 per run of IHD). This cost is offset somewhat by the nursing costs required for IHD (C$149 per run). Other costs are comparable between the two treatments. The patients who survived but needed ongoing chronic dialysis therapy incurred incremental costs of C$62,081 in the post-discharge year compared to the survivors who did not require dialysis. While clinical outcomes were captured, this observational study acknowledged that it could not provide meaningful insights into clinical benefits because of the non-randomized study design. This study did not try to determine the incremental cost-effectiveness.

5.2 Clinical Data Relevant to Economic Analysis

The data required to perform our economic evaluation can be divided into:

- baseline event rates and clinical outcomes
- modification of clinical outcomes due to use of alternative delivery methods of RRT in intensive care
- resource use and costs, which can be divided into costs specific to renal replacement modality, other costs associated with ICU and hospital stay, and health care costs incurred after discharge from the index hospital stay (such as costs associated with chronic dialysis therapy).

Our a priori plan specified that the economic analysis would use point and variance estimates of effectiveness obtained from the formal systematic review and meta-analysis.[64,65] These would be applied to baseline risks and clinical events in the economic evaluation, which was informed by observational data from a representative Canadian context.

5.2.1 Baseline event rates and clinical outcomes

To make our findings relevant to Canada, we used high-quality observational data from one region to inform the model parameters and transition probabilities for the IHD arm. These included the risk of mortality in the ICU and hospital stay, recovery of renal function, length of stay in the care settings, frequency of IHD, and long-term outcomes of dialysis dependence and death after the episode of ARF (Appendix 5 Table 1). As a sensitivity analysis (to ensure the generalizability of this data source), we used alternative estimates based on pooled data from the IHD arms of RCTs included in the clinical systematic review. In the CRRT arm, these model parameters and transition probabilities were modified based on the estimates of effectiveness.

5.2.2 Estimate of effectiveness of CRRT

When multiple RCTs exist, it is recommended that the summary measures of efficacy from high-quality systematic reviews and meta-analyses be used for the decision model estimates of effectiveness.[64,65] We obtained data on relevant clinical and economic outcomes from the systematic review, focusing on those that might be influenced by dialytic modality (mortality, dialysis dependence, hospital and ICU length of stay, complications, and quality of life).

5.2.3 Resource use and costs

High-quality Canadian costing studies comparing the resource utilization of CRRT, IHD, and SLEDD were used[1,66] to calculate the costs of providing RRT. The total index hospitalization costs were calculated by adding the cost of RRT to the product of length-of-stay and per diem costs for each care setting.[1] Data from this study on health care costs for surviving patients (stratified by the need for chronic dialysis therapy) at one year of follow-up were incorporated.

5.3 Economic Evaluation

5.3.1 Methods

a) Objective

Our objective was to determine the cost-effectiveness, in a Canadian context, of CRRT versus IHD in the treatment of critically ill adults with ARF.

b) Population

In the base-case analysis, we evaluated a simulated cohort of adult patients (≥18 years old, average age of approximately 60 years) with ARF, requiring treatment with RRT in a Canadian intensive care setting, who are candidates for treatment with IHD or CRRT.

c) Treatment comparators

As IHD and CRRT techniques vary, we assumed that the most commonly used of each modality in Canada would be used for the base case, which is consistent with most of the trials included in the systematic review.[1,9] IHD would be provided from 3.5 hours to 4.5 hours, 3.9 days per week, and CRRT would be delivered through continuous venovenous hemodiafiltration (CVVHDF). Standard heparin anticoagulation was assumed for both modalities.

The techniques for CRRT and IHD can be modified in delivery and potentially affect health care costs and outcomes. The systematic review did not identify submodalities with differences in efficacy. Therefore, the economic analysis did not vary the estimate of effectiveness across submodalities. Nevertheless, variations in technique may significantly affect costs [e.g., IHD may be provided more frequently or for a longer duration per day (with SLEDD), and citrate anticoagulation may be used for CRRT].

d) Analytic approach

To determine the cost-effectiveness of CRRT compared with IHD, we adapted an existing economic decision model[67] to represent the events occurring from the start of RRT in the ICU, until death or discharge from the index hospital. At that point, the survivors entered a Markov model that represented biannual transitions between the following clinical states: "alive requiring dialysis," "alive without dialysis," and "death." The analysis was continued until <1% of the original cohort remained alive (Appendix 6 Figure 2).

The model outputs were quality-adjusted life-years (QALYs), life-years gained, health care costs, and the cost per QALY gained. QALYs were calculated by multiplying the time spent by the average patient in each clinical state, by the utility associated with that state. We performed base case analyses using a Markov cohort analysis and used Monte Carlo simulation for a probabilistic sensitivity analysis. All analyses were performed using TreeAge Pro 2005 (Williamstown MA).

e) Audience and perspective

The target audience of this study includes regional intensive-care and renal programs that provide care to critically ill patients with ARF. The primary perspective is that of the Canadian publicly funded health care system, which is consistent with CADTH guidelines.[65] There may be differences in productivity and patient-related costs if a treatment strategy leads to differences in long-term functional status. For example, patients who need maintenance HD may be less likely to work. Given the paucity of information on employment status in this patient population (with an average age of approximately 59 years), lack of information on personal and productivity costs, and methodological uncertainty as to how to incorporate them,[68,69] a societal perspective was not considered.

f) Time horizon

The primary analysis used a lifetime time horizon, which is consistent with CADTH guidelines.[65]

g) Clinical events in patients with ARF treated with IHD

The baseline transition probabilities and events were based on a population-based analysis of two cohorts of Canadian patients with ARF admitted to ICUs in the Calgary Health Region. The region

provides services to a referral population of 1.3 million.[1,70] All adult ICU patients with ARF requiring RRT were included in two observational cohorts (April 1996 to March 1999 and May 1999 to April 2002). Additional data were obtained from hospital survivors in the first cohort (n=261) to determine the incidence of death and dialysis dependence after a follow-up of four years.

During the period of observation in this region, intensive care settings were closed units and managed by qualified intensive-care physicians. RRT included IHD and CRRT, and either could be used at the discretion of the attending physician. As bias by indication is probable, data from all patients (regardless of renal replacement modality) were used to inform baseline model parameters for the IHD arm. We evaluated the validity of this assumption by making a comparison with pooled estimates from the IHD arm of the RCTs in the systematic review (Appendix 5 Tables 1 and 4).

h) Efficacy of CRRT

The estimates of efficacy and effectiveness of CRRT were based on the results of the systematic review and meta-analyses included in this report.

Mortality

We used the RR of all-cause overall mortality for CRRT compared with IHD at the last reported period, to model the survival differences. This was calculated using the last time-point for the determination of mortality (ICU mortality for three studies, in-hospital mortality for five, 90-day mortality for one, and unknown but presumed in-hospital mortality for one). The re-examination of the point estimate using 28-day instead of 90-day mortality for the paper that reported this[13] did not change the point estimate (RR 1.04, 95% CI 0.95 to 1.14). This estimate and other timeframes for assessing mortality (ICU and in-hospital, Appendix 4 Figures 3 to 5) were evaluated in sensitivity analyses. The RR of overall mortality was applied to the interval between the start of dialysis in the ICU and hospital discharge, which is the period when the greatest mortality occurs and which is most commonly used in clinical trials.

The model specified that post-discharge mortality was determined by the patient's clinical state (alive on dialysis or alive without dialysis dependence) and not directly influenced by the initial dialysis modality.

Renal recovery

The recovery of renal function – defined as the patient's independence from ongoing dialysis therapy – was determined from the systematic review. The pooled RR for dialysis dependence among surviving patients is 0.91 favouring CRRT (Appendix 4 Figure 5). While the confidence intervals for this estimate of RR overlap 1.0, this point estimate was used in the primary model, as established in the a priori plan.

Duration of ICU and hospital stay

The delivery of continuous dialysis, compared with intermittent dialysis, may theoretically influence the length of stay in care settings. While the data extracted from the systematic review on length of stay in the ICU and hospitalization could not be reliably pooled, there was no indication of a difference between the two treatments (Appendix 3 Table 7). The maximum reported differences in hospital stay (9.2 days favouring CRRT and 8.5 days favouring IHD) were explored in a sensitivity analysis.

Duration of RRT

The duration for which RRT is required was examined in the systematic review. While infrequently reported, we found no differences in the duration of dialysis between treatment arms (Appendix 3 Table 6).

Quality of life

None of the identified studies determined differences in quality of life over the short timeframe of the index hospitalization (where differences would be unlikely and of little importance given the short duration of critical illness).

We performed a focused literature search to obtain the estimates of utility for patients who survive critical illness, including those who do or do not require ongoing chronic dialysis therapy. Hamel *et al.*[71] reported the utility estimates in this patient population for six months after enrolment. The summary estimate included all surviving patients (dialysis-dependent or not). For technical reasons, this report may underestimate the utility of surviving patients. We obtained utility scores for patients receiving chronic HD from a Canadian cohort of similar patients.[72,73] Because patients recovering from ARF in the ICU may have different severities of illness and co-morbid illness, we may have over- or under-estimated the utility. The ranges for both these estimates were explored in a sensitivity analysis, as was an analysis where only life-years were considered. A discount of 5% was applied.

Complications

No significant differences in complications were found between CRRT and IHD in the systematic review (Appendix 4 Figure 9). While a trend for increased filter clotting was noted for CRRT, the cost of managing this complication is captured in the cost of providing CRRT.

Hemodynamic instability could lead to greater difficulty in providing IHD compared with CRRT. While some trials excluded patients with low mean blood pressures,[37] a RCT by Vinsonneau *et al.*[13] provided recommendations to maintain hemodynamic stability (high sodium concentration, low temperature dialysate, isovolemic connections). IHD was provided every other day, and three patients or 1.6% were switched to CRRT for hemodynamic instability, suggesting that this condition does not preclude treatment with alternate-day IHD in most critically ill patients. Alternative modes of delivering IHD (such as SLEDD, where IHD is provided for eight hours, six days per week, in the hope of improving hemodynamic stability) are explored in scenario analyses.

i) Costs

We identified a high-quality micro-costing study enumerating health care resource use and costs of this Canadian patient population to inform costs.[1] All costs were inflated to 2005 Canadian dollars using the general Consumer Price Index. The inflation factor was applied for the year of the reported cost. The Bank of Canada's exchange rate of the reported year was applied to all foreign currency. The costs were then inflated to 2005 Canadian dollars and discounted at 5%.

CRRT and IHD costs

The costs of providing IHD and CRRT, including the submodalities of CRRT and methods of anticoagulation for each, are taken from Manns *et al*.[1] (Appendix 5 Table 2). For the scenario analysis comparing SLEDD with CRRT, the costs reported in a Canadian study by Berbece and Richardson[66] were used. These costs included the costs of staffing and supplies (Appendix 5 Table 5). Average daily costs were used, and the duration of treatment for both modalities was taken from the systematic review as described for the clinical outcomes.

ICU and hospital costs

Per diem costs for care settings were obtained from Canadian sources (Kim Walker, Capital Health, Edmonton: personal communication, 2007),[74] and the number of days spent in each care setting was obtained from Canadian data.[1] As in the systematic review, we assumed that there was no difference in the length of stay by modality in the primary analysis, although it differed depending on the patient's clinical state (Appendix 5 Table 2).

Long-term costs of surviving patients

The direct health care costs incurred by surviving ARF patients for one year after discharge from hospitalization were taken from Manns *et al*.[1] In the sensitivity analysis, we considered the scenario where the cost differences between patients requiring or not requiring dialysis were only related to the dialysis treatment.[75]

j) Assumptions

- No difference in quality of life exists for surviving patients treated with IHD or CRRT during the hospital admission for ARF.
- Patients who continue to require chronic dialysis after recovery from a critical illness have a quality of life similar to that of typical Canadian HD patients.
- The RRT used to treat ARF (CRRT versus IHD) may influence short-term outcomes (such as in-hospital survival and renal recovery), but does not affect long-term outcomes for any given health state. For example, the post-discharge mortality risk for survivors of the hospital admission would be dictated by their clinical state (dialysis or non-dialysis dependent) and not the therapy used to initially treat ARF.
- No subgroups of patients exist where the clinical and economic impact of CRRT versus IHD differs from that of the base case. As a result, one general cohort of patients was examined.
- All patients who started on IHD can tolerate this therapy and do not require the use of CRRT for hemodynamic stability. Patients with hemodynamic instability on IHD are managed by increasing the duration and frequency of IHD.
- The estimates of efficacy are unaffected by the submodality of CRRT or IHD used.
- The non-dialysis dependent chronic kidney disease occurring after critical illness does not alter the clinical outcomes or costs. Although the presence and degree of chronic kidney disease after hospital discharge among those not requiring dialysis can be relevant, its importance in this scenario is unclear. Furthermore, individual trials used various methods to measure and classify kidney function. As a result, we excluded chronic kidney disease not requiring dialysis as a clinical state in this model.
- Given the lack of data on clinical and economic outcomes in different age groups, we assumed that the baseline event rates and outcomes would be similar to those from observational data (average age 59.3 and 62.7 years)[1,70] and effectiveness data (weighted mean 60.8, mean 59.5, range 53 to 67, from studies included in the systematic review).

k) Scenario analysis

Effectiveness of CRRT versus IHD

While point estimates from the systematic review were used in the primary analysis (model 1), the confidence intervals overlapped unity (RR of 1.0), even when considering the same outcome from various perspectives (e.g., overall mortality, ICU mortality, hospital mortality). Using a traditional statistical approach, we cannot reject the hypothesis of no clinical difference between CRRT and IHD. As a result, we included a second primary analysis that assumed a RR of 1.0 for CRRT on mortality and recovery of renal function (model 2).

Provision of CRRT and IHD

Although the systematic review found no evidence that the submodalities of CRRT or IHD influenced efficacy, they may affect costs and cost-effectiveness. Therefore, we considered several scenarios to determine their effect:

- delivery of IHD using slow, low-efficiency dialysis (SLEDD) for eight hours per day, six days per week
- daily delivery of IHD
- elimination of additional labour costs to provide dialysis (typically higher for IHD) which may be realized through the reorganization of dialysis delivery.[76]

Other considerations may influence the costs of providing CRRT or IHD, such as providing CRRT for a limited number of days (then switching to IHD), using CVVHF, using alternative anticoagulation methods, and using alternative data on costs (Appendix 5 Table 6).

Costs of maintenance dialysis and index hospitalization

There is controversy about which long-term health care costs to include in economic evaluations.[77] This is relevant in our analysis, because dialysis dependence — a chronic health state associated with ongoing resource consumption — is an outcome in this model. For the primary analysis, we considered all costs, including those due to ongoing dialysis. Because chronic dependence on dialysis is expensive, interventions that improve survival but lead to this state will be associated with a cost-utility ratio at least as great as that of dialysis. The magnitude of the cost-utility ratio for therapies that improve survival in patients with kidney failure may depend more on the estimate used for future dialysis costs than on the costs and benefits of the intervention.[77] The inclusion of such costs in economic evaluations (which is methodologically correct) may discourage the uptake of interventions that improve patients' survival. As a result, in the scenario analysis, we explored the cost per QALY gained when chronic dialysis-related costs were excluded.

This is relevant for health care costs during hospitalization for critical illness. It has been observed that patients who die during their index hospitalization for ARF use fewer in-hospital health care resources and incur fewer costs than those who are alive and dialysis-dependent, or alive with renal recovery (C$29,425 versus C$56,035 and C$47,694 respectively, in 1999). As a result, treatment strategies leading to higher in-hospital mortality (i.e., CRRT in the primary analysis) will be associated with lower costs. While our base case incorporated the hospital costs of those who die and those who survive, we performed a scenario analysis that assumed hospital costs were identical regardless of outcomes.

I) Sensitivity analysis

We performed one-way sensitivity analyses by varying the values for uncertain parameters (Appendix 5 Tables 1 and 2). The estimates of effectiveness included point estimates from the meta-analysis in the base case (model 1), but given the lack of evidence of a statistically significant difference from unity, the RRs of 1.0 for mortality and dialysis dependence were also used (model 2). We performed a Monte Carlo simulation of 25,000 patients. Statistical distributions were created around all variables with significant measurement uncertainty and for which distributions could be estimated (Appendix 5 Table 1). The distributions were based on confidence intervals from the meta-analysis, ranges identified in the literature review, and common distributional forms.[78,79]

5.3.2 Results

a) Model validity

Before using this decision model and to be consistent with published guidelines,[64,80,81] we ensured that the results made sense and could be explained intuitively. We assessed for logical inconsistencies by evaluating our model under hypothetical conditions. We also confirmed that the mathematical calculations were accurate and consistent with the model's specifications (i.e., internal validity).

We determined that our model had predictive validity by comparing model outputs (a function of input variables and model structure) with observed data from a Canadian source[1,70] and outcomes from studies in the systematic review. This included a comparison of in-hospital outcomes (mortality, dialysis dependence, costs for patients in each clinical category), status at hospital discharge, and the long-term outcomes of mortality and dialysis dependence (Appendix 6 Figure 3). When we compared the modelled costs for in-hospital stay and the first post-discharge year for each health state (dead, alive on dialysis, or alive with renal recovery) with observational data,[1] we found similar values (data not shown).

b) Base case analyses

In the primary analysis (model 1), using point estimates for the RR of death and dialysis dependence from the systematic review and meta-analysis, IHD was associated with increased total health care costs and an increase in QALYs compared with CRRT. QALYs increased by 0.07, and costs increased by C$8,541, resulting in an incremental cost per QALY gained of C$125,960 for IHD (Appendix 5 Table 3). The QALYs and life-years are presented to two decimal places, but exact values are used to calculate the incremental cost per QALY. The dialysis costs were C$3,679 less per patient using IHD compared with CRRT, but the overall health care costs increased, given the higher fraction of patients surviving and requiring HD.

In the second analysis (model 2), we used a RR of 1.0 for mortality and dialysis dependence. This resulted in CRRT being dominated by IHD, with IHD leading to equal QALYs and an early cost savings of C$3,679.

c) Scenario analysis

Baseline clinical event probabilities

The risk of developing the clinical outcomes may vary by era and setting. We evaluated the use of event probabilities from a Canadian region for patients from 1999 to 2002[70] and a mean of the probabilities reported in the clinical studies from our systematic review. The incremental cost-effectiveness ratio (ICER) varied from $109,698 to $164,554 per QALY for model 1, while CRRT remained dominated by IHD in model 2.

Resource use and costs of CRRT and IHD

The costs associated with RRT may vary depending on the method of delivery and setting. We assessed the possible scenarios, including providing daily IHD, using alternative anticoagulation, providing SLEDD, using RRT from a different source,[76] and excluding staffing costs with IHD delivery (Appendix 5 Table 5). In model 1, the cost-utility of IHD compared with CRRT ranged from $93,283 to $150,619 per QALY. Model 2's results remained unchanged, with CRRT being dominated by IHD in all scenarios.

Other in-hospital costs and long-term costs of surviving patients
Surviving patients may incur high costs for hospitalization and subsequent health care. Therefore, therapies that improve survival would be expected to increase downstream costs. We wanted to assess the effect of this trade-off on cost-utility. As expected, the costs associated with providing chronic dialysis therapy had a significant impact on cost-effectiveness. When the need for chronic dialysis was assumed not to influence long-term costs in survivors, CRRT was dominated in model 1 (Appendix 5 Table 6).

In the scenario where the non-dialysis related costs of the index hospitalization were identical, regardless of clinical outcome (death, alive on dialysis, or alive with renal recovery), there was minimal impact on the ICER (model 1).

d) Univariate sensitivity analysis
Taking the RR of mortality to the extremes of its confidence interval leads to changes in the ICER and highlights the inverse relationship between survival and costs for survivors of critical illness (Appendix 5 Table 7). Decreasing the RR of survival to its lower bound of 0.93 leads to increases in QALYs gained (such that CRRT resulted in more QALYs than IHD) and higher costs, because surviving patients continue to use resources. This is shown in model 2 (where the RR of renal recovery is set to 1.0).

Varying the RR of renal recovery through the extremes of its 95% confidence interval leads to changes in the ICER. In model 2, where the RR of in-hospital mortality is set to 1.0, using the lower bound of 0.69 (less renal recovery in CRRT-treated patients) leads to CRRT being dominated by IHD, whereas using the higher bound leads to IHD being dominated by CRRT. This highlights the significant impact that the differential risks of long-term dialysis dependence has on the ICER of dialytic modality in ARF. A tornado diagram shows the impact on the ICER when the RR of mortality and the RR of renal recovery are varied throughout their 95% confidence intervals (Appendix 6, Figure 4).

Other one-way sensitivity analyses appear in Appendix 5 Table 8. CRRT remained dominated by IHD in all instances for model 2. The ICER for model 1 increased when the in-hospital mortality was set at its lowest value. It varied between $85,450 and $189,918 per QALY for IHD compared with CRRT (Appendix 6 Figure 5). The impact of other variables, including the daily cost of providing CRRT, has a smaller impact on the ICER.

e) Probabilistic sensitivity analysis
A scatter-plot of the second-order Monte Carlo simulation (Appendix 6 Figure 6) compares the incremental costs and QALYs of CRRT with those of IHD for 25,000 simulated patients. It demonstrates the significant uncertainty in the cost-effectiveness of CRRT when all included variables are uncertain and considered simultaneously.

The scatter points and the 95% confidence ellipse show that uncertainty exists, because a large fraction of points falls into each of the four quadrants of the cost-effectiveness plane. Approximately 67% of the simulations fall in the left half of the plane, where CRRT is less effective (less QALYs) than IHD. Approximately 62% of the simulations fall into the upper half of the plane, where CRRT is more costly than IHD.

6 HEALTH SERVICES IMPACT

6.1 Population Impact

The incidence of ARF requiring RRT in critically ill patients is estimated at 11.0 per 100,000 members of the general Canadian population per year.[70] No other population-based estimates were identified. Using Canadian 2001 census data for the total adult population, it is estimated that there are 2,445 cases of ARF requiring dialysis among critically ill Canadian patients per year.

The current practices of providing RRT vary across Canada and seem to be changing. A survey was conducted in 1999 of nephrologists at hospitals in Canada.[9] At that time, the most commonly used modality in the ICU was IHD (74%). In centres where CRRT was available, IHD was used in 54% of patients. The use of CRRT was reported to be increasing from 9% to 26% over a five-year period.[9] Other published data on RRT come from Alberta, where centres that have CRRT and IHD indicate that CRRT is used in 61% to 80% of patients.[1,70] The authors of this report are aware of centres that provide IHD only (Nova Scotia) and centres where CRRT is prescribed for most cases (Montreal). The basis for these variations is unclear and does not seem to be evidence-based.

In future, CRRT could be used in Canada all the time, some of the time, or not at all. Because some centres do not offer CRRT and data from two randomized trials suggest that most patients can tolerate IHD, the latter could be used exclusively. For instance, an RCT that did not exclude patients on the basis of hemodynamic stability reported that 1.6% of patients in the IHD arm were switched to CRRT because of persistent hemodynamic instability.[13] In another RCT where hemodynamic instability (mean arterial pressure <70 mm Hg) was an exclusion criteria, 20.9% of patients were excluded for this reason[37] and thus presumably received CRRT. An additional 22.1% of patients in this study were excluded at the discretion of the intensivist or nephrologist, although exclusions due to concerns about hemodynamic stability were reported in <4% of these patients. The exclusive use of CRRT is another option.

6.2 Budget Impact

We considered the annual costs of providing CRRT or IHD alone for a typical cohort of patients (using parameters for the base case, Appendix 5 Tables 1 and 2) from the health care provider's perspective. The cost of providing CRRT was estimated to be $3,454 more than that of IHD for an average patient. Most of the difference is due to supplies and replacement fluid cost ($416/day for CRRT compared to $68.30 per run of IHD). Labour costs (nursing care) are higher for IHD ($149 per run)[1]. For this to be relevant to centres using different practices, a range of baseline scenarios was considered, varying the proportion of patients receiving CRRT and specific characteristics of the CRRT treatment.

The cost estimate, based on existing practices and possible scenarios for using CRRT, is projected for the adult population of Canada in Appendix 5, Table 9. If CRRT is performed in 26% of critically ill patients with ARF across Canada,[9] reducing the use to 0% or 1.6% would result in cost savings of $2.1 to $2.3 million. If CRRT is performed in 68% of such patients, $6.1 million could be saved by providing IHD only.

These results can be modified to represent a region or centre by considering the baseline use of CRRT and the population in the catchment region. For example, the Calgary Health Region provides CRRT to 68% of critically ill patients and has a catchment population of 1.3 million. By providing IHD only, this region could expect to save $357,000 annually.

While the economic model indicates that survivorship and dialysis dependence have a significant impact on health care costs, there is no evidence to suggest that CRRT significantly influences these outcomes. As a result, the cost savings due to reduced dialysis dependence in survivors were excluded in the budget impact analysis. If future studies suggest that CRRT is associated with a lower risk of dialysis dependence, then these cost savings should be included in future budget impact analyses.

6.2.1 Human resource considerations

The human resources needed to perform CRRT and IHD in the ICU may differ, but the net impact on the use of either therapy on human resources is likely to be centre-specific. CRRT is typically performed by ICU nurses. Thus, it may not require additional human resources. Because CRRT is resource-intensive, additional ICU nurses may be required, depending on the number of patients receiving care. In many settings, IHD is provided by dialysis nurses who do not otherwise perform duties in the ICU. Thus, additional dialysis nurse time and associated costs may increase if IHD use in the ICU is increased. While total health care costs may be lower with IHD, the scarcity of human resources may be a limiting factor. We are aware of centres where CRRT and IHD are performed by ICU personnel, and labour resources are not a factor.

6.2.2 Capital equipment considerations

The most significant capital costs are those for the equipment to provide IHD and CRRT. The renal replacement equipment typically used in Canada can provide IHD or CRRT, but not both. There is a cost difference between a machine that can provide CRRT rather than IHD, although it is not significant (approximately $36,000 versus the $28,000 list price for CRRT and IHD machines respectively) (J. Foster, Project Manager, Northern Alberta Renal Program: personal communication, 2007). An IHD machine can be used to provide chronic HD, a procedure that is commonly performed in most centres. Centres that are using CRRT for a large fraction of patients and that are considering moving some patients to IHD for the anticipated cost savings, should predetermine what additional equipment may be needed. The existing capital resources and the existence of trained personnel involved in providing chronic IHD may be involved in providing IHD for ARF, if they are not used to capacity. A centre that wished to adopt or expand the delivery of CRRT may need to acquire additional CRRT machines if current equipment is being used to capacity.

6.3 Efficiency versus Equity

The trade-offs between the goals of efficiency and equity, or fairness, occur when resource allocation decisions limit the use of potentially beneficial therapies. We found no evidence that CRRT is more effective than IHD. Therefore, no trade-off is needed. This may warrant further evaluation if future trials demonstrate a clinical benefit of CRRT.

7 DISCUSSION

7.1 Results

We identified 13 trials (1,259 participants) that compared CRRT and IHD for the risk of clinically relevant outcomes including death, dialysis dependence among survivors, and length of stay in hospital. Neither the results of individual studies nor the pooled results suggest that CRRT improves these clinical outcomes compared with IHD. Thus, the hypothesis that CRRT is better tolerated than IHD and results in clinically meaningful improvements in outcomes for critically ill adults with ARF is not supported by the evidence.

The results of the economic analysis show that CRRT is more costly than IHD and may require additional resource allocation. Unlike IHD, it requires specialized equipment that cannot be used to provide chronic HD. The magnitude of the increased costs of providing CRRT was low in comparison with potential downstream costs, such as the cost of chronic dialysis for survivors.

7.2 Systematic Review of CRRT's Clinical Effectiveness

Despite between-study variability in design, patient population, and dialytic techniques, the results of the systematic review were consistent with the results of individual trials. The point estimates for the RR of death and dialysis dependence due to CRRT treatment approached unity in all main analyses. The sensitivity analyses did not identify the subgroups of patients for whom CRRT was likely to be particularly beneficial. The non-significantly increased likelihood of death among CRRT recipients in trials published before 2004 suggests that recent outcomes may be better because of improved techniques, perhaps especially because of the availability of venovenous access. Even in more recently published studies, no benefit of CRRT therapy was seen. Although this analysis examined a subset of trials, the point estimate of the RR for mortality due to CRRT was close to one, making it unlikely that a clinically relevant benefit of CRRT in this subgroup was missed because of low statistical power.

Recovering sufficient kidney function to discontinue dialysis among patients with ARF is clinically relevant because acute and chronic dialysis are associated with adverse outcomes and high health care costs. Proponents of CRRT might argue that the slower fluid removal permitted by this technique may reduce ischemic renal injury and decrease the duration of dialysis dependence. The likelihood of renal recovery did not differ between treatment groups in any individual study or in the pooled analyses. Improved hemodynamic stability is often cited as an advantage of CRRT, although this hypothesis was not confirmed in any identified trial.

One trial[37] that compared the RR of chronic renal function impairment between treatment groups suggested a significant benefit with CRRT. This study had several potentially significant limitations, for example, chronic kidney disease and in-hospital mortality are competing risks among patients with critical illness. This study also found non-significantly increased mortality among CRRT recipients, which may have led to survivor bias and an increased risk of dialysis dependence in the IHD group. This issue is worthy of further study, because chronic kidney disease is associated with increased morbidity, mortality, and health care costs. It is unknown whether chronic kidney disease is independently associated with adverse outcomes in the long term among survivors of critical illness. Future studies should compare the risk of chronic renal insufficiency between treatment groups and

the implications of any increased risk of other clinically relevant outcomes such as mortality, chronic dialysis dependence, or hospitalization.

Available data were inconclusive as to whether CRRT reduces the length of hospital stay or improves the health-related quality of life. Given the short duration of critical illness, it is implausible that CRRT leads to clinically meaningful changes in quality of life before hospital discharge. Future studies that examine this issue should compare the quality of life over at least six to 12 months among survivors of critical illness who undergo CRRT or IHD.

The systematic review did not find any evidence of a clinically relevant benefit from CRRT relative to IHD.

7.3 Economic Evaluation

Despite the uncertainty and wide range of ICERs found in the economic evaluation, several conclusions can be reached. First, providing CRRT is more costly than providing IHD. The incremental costs of RRT in critical illness are small compared with the large costs of care during the index hospitalization and beyond. The risk of mortality and dialysis dependence are drivers of dialysis-related costs in hospital and post-discharge. Even small differences in risk lead to significant changes in the ICER. Given this finding and the lack of compelling evidence of benefit with CRRT from the systematic review, analyses using model 2 (where the RR of mortality and renal recovery are set to 1.0) are the most relevant. In most scenarios, this model resulted in IHD being associated with similar effectiveness and reduced costs compared with CRRT.

The risk of dialysis dependence had the most profound effect on the model outcomes. As maintenance dialysis is costly, even a small increase in this risk among surviving patients had an impact on the ICER. While there was no evidence that either therapy influenced the risk of chronic dialysis, a sensitivity analysis assuming a small benefit with either therapy resulted in changes in the ICER. Thus, future trials comparing dialytic modality in ARF should include long-term dialysis dependence as an outcome.

The impact of patients who survive versus those who die during the index hospitalization requires more discussion for an understanding of the potential effects on the numerator and denominator of the ICER. The point estimates from the meta-analysis non-significantly favour IHD for mortality. For dialysis dependence, the estimates non-significantly favour CRRT. These findings could be explained by the additional surviving patients in the IHD arm having a higher risk of permanent kidney failure (survivorship bias). While this leads to an increase in QALYs, it also has an impact on costs, given the high demand on health care resources by survivors, especially those requiring maintenance dialysis.

Our model considered overall mortality (RR 1.02) rather than ICU (RR 1.10) or hospital mortality (RR 1.05), and the point estimate for dialysis dependence evaluated survivors only (RR 0.91). An additional analysis evaluated the impact of CRRT on a composite endpoint of death and dialysis dependence, with this point estimate almost exactly at unity (RR 1.01, Appendix 4 Figure 6). While the point estimates used in model 1 were close to unity, these estimates led to increased QALYs and increased costs, as would be seen with this survivorship bias. While the most appropriate analysis is model 2, the lack of compelling evidence of effect, the possibility of competing risk (death or chronic dialysis), and survivorship bias should guide the interpretation of future studies.

Current data suggest that CRRT leads to equivalent patient outcomes at increased health care costs.

7.4 Limitations

7.4.1 Systematic review of clinical effectiveness of CRRT

This is the most comprehensive systematic review of the clinical and safety implications in selecting CRRT over IHD for the management of critically ill patients with ARF. Prior reviews have been narrative, were unable to include as many studies, or both. Our findings and the strength of our conclusions are limited by the available evidence. There is a paucity of large RCTs that address this topic, and the quality of the available trials is poor. More good-quality trials are needed.

Our pooled results may be prone to the limitations of meta-analysis. We took care to reduce the likelihood of bias by following recommendations for the conduct of systematic reviews, including an a priori review protocol using a defined comprehensive literature search strategy designed by an expert librarian, performing quality assessment and data extraction with duplicate reviewers, and using rigorous statistical methods. These steps have reduced our susceptibility to bias and have led to robust conclusions.

7.4.2 Economic evaluation of CRRT

As in most economic evaluations, our model and results are limited by available evidence and the requirement to model all relevant clinical and economic consequences. Our evaluation has been strengthened by its rigorous methods and our systematic review.

Non-dialysis dependent chronic kidney disease (CKD) was excluded in the model. While there is a lack of evidence that this is influenced by dialysis modality, patients with CKD have worse clinical outcomes and increased health care costs compared to those without CKD. This merits further study.

The use of observational data to assign costs is a common practice, by necessity, in economic models. Ideally, an RCT would have assessed the extent to which health care resource use influences the results in this model, by including these as an outcome measure, particularly the need for maintenance HD and its associated costs. Such an RCT is unavailable. Many sources of data, including studies observing costs and quality of life, were obtained from small studies with small sample sizes. A significant number of studies were obtained from one region of Canada. This may limit the generalizability of the results. Furthermore, no information was available on indirect and productivity costs. These may be substantial if survival and functional status are influenced by therapy. The lack of data on these outcomes and their modification with RRT preclude their incorporation here. Finally, the incremental costs and the incremental effectiveness were small and may lead to instability of the ICER, as shown in the Monte Carlo simulation.

Controversy exists regarding the suitability of IHD for all critically ill patients with ARF. The results of the economic analysis are relevant only to patients who can be appropriately treated with IHD or CRRT.

7.5 Health Services Impact

The impact of increasing or decreasing the use of CRRT in a region depends on the existing use of CRRT and the size of the catchment population. A reduction in CRRT use from baseline in the range of 26% to 68%, to 0% to1.6% would lead to cost savings of $2 million to $6 million in Canada.

7.6 Knowledge Gaps

Despite the large number of studies, the identification and treatment of ARF in the critically ill are challenges. Questions remain about when to start RRT, when to stop it, and whether the involvement of nephrologists in prescribing and providing dialysis has an influence on outcomes in critical care. Existing studies have not explored the impact of newer renal replacement therapies such as high volume HF compared with intermittent HD, the differences between convective and diffusive clearance, or the benefits of modified forms of IHD such as SLEDD. Given that a higher dialysis dose may have a favourable impact on clinical outcomes, future studies should focus on the potential benefits of higher hemofiltration volumes, perhaps in comparison with daily IHD. Whether changes to critical care practice or training programs would improve outcomes is also a potential topic for study. Finally, the evaluation of clinically and economically relevant outcomes requires further study, especially the frequency and impact of CKD among survivors.

8 CONCLUSIONS

Although CRRT is more costly than IHD, available data do not support the hypothesis that CRRT results in clinically meaningful improvements in outcomes for critically ill adults with ARF, compared with IHD. The quality of the studies identified in the literature review was generally poor. Additional large, carefully conducted trials would be needed to exclude a clinically relevant benefit that is associated with either therapy.

Because the magnitude of the increased costs incurred by providing CRRT was low compared with the cost of downstream complications among survivors (especially the cost of providing chronic dialysis), this conclusion should be revisited if future studies suggest that CRRT improves clinical outcomes, especially the risk of dialysis dependence among survivors.

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APPENDICES

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