Overview of Continuous Renal Replacement Therapy in Adult Patients with Acute Renal Failure
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June 2007

We thank Lisa Hum for her assistance in creating this overview from a longer report authored by Tonelli, et al.

This overview is based on the Technology Report commissioned by CADTH: Continuous renal replacement therapy in adult patients with acute renal failure: systematic review and economic evaluation. 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≥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.
1 Introduction

Acute renal failure (ARF) occurs in 20% to 25% of patients who are admitted to an intensive care unit (ICU). A significant proportion of these patients will need acute dialysis treatment.1 These critically ill patients have a high rate of in-hospital mortality (40% to 65%)2-4 and high health care costs during the acute phase of their illness.5 In addition, 5% to 30% of such patients who survive and are discharged from hospital will stay on long-term dialysis without renal recovery.5

Different types of renal replacement therapy (RRT) can be used for patients with ARF. Each differs in the way that it removes toxins, excess salts, and fluid that build up in the body; 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 and HF, blood is removed from the body and passed through a semi-permeable membrane. In HD, clean dialysate fluid (with no toxins) passes to the other side of the membrane, allowing the equilibration of the patient’s blood with dialysate. Toxins in the blood move into the dialysate. During HF, 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 that is removed is replaced intravenously to prevent iatrogenic acidosis, electrolyte depletion, and excessive fluid removal. HDF combines diffusive and convective clearance. HD, HF, and HDF all efficiently remove small molecular weight substances. Larger molecular weight substances are more efficiently removed by HF and HDF.

ARF in the ICU can be managed with intermittent hemodialysis (IHD) or continuously using HD, HF, or HDF [continuous renal replacement therapy (CRRT)]. IHD is performed using venovenous access for a few hours at variable intervals (typically four hours, three to four times per week).1 CRRT is performed continuously (approximately 24 hours per day) through arteriovenous or venovenous vascular access. The most commonly applied submodalities of CRRT are continuous venovenous hemofiltration (CVVHF), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). Regardless of the method used, CRRT requires specialized equipment and training for staff, usually consumes more supplies than IHD, and is generally performed only in an ICU.

Compared with intermittent therapies, CRRT provides slower solute clearance per unit time, but over a 24-hour period, 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. Also, 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.6,7 On the other hand, CRRT requires continuous anticoagulation, which might predispose patients to bleeding complications, 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.

There is regional variation in the management of ARF among critically ill adults in Canada.8 For example, CRRT is not used in Nova Scotia, but it is the predominant mode of renal replacement among critically ill patients who are treated at certain facilities in Montreal. Internationally, there is similar variation. In some countries, such as Australia, CRRT is the only dialysis modality that is used.8-10 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.

There are no North American or European clinical practice guidelines that address the choice of dialytic modality in ARF. 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.

2 Objectives

The objective is 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 the two strategies among critically ill adult patients with ARF.

There are four research questions.

• What is the clinical effectiveness of CRRT among adult patients with ARF requiring dialysis, compared with thrice-weekly or daily IHD?
• What is the cost per quality-adjusted life-year (QALY) gained by the use of CRRT among adult patients with ARF requiring dialysis, compared with IHD? What is the cost per life-year (LY) gained by the use of CRRT among patients with ARF requiring dialysis, compared with IHD?
• What is the role of CRRT in ARF? Are there 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?

3 Clinical Review

Methods

Published and unpublished literature was obtained by searching MEDLINE®, EMBASE®, all EBM Reviews, ProQuest Dissertations and Theses, and other grey literature sources. Studies were included if they were randomized controlled trials (RCTs) or prospective controlled trials with ≥100 participants, involved adult participants with ARF, compared one RRT with another RRT, and assessed clinical outcomes. The reference lists of included trials and relevant reviews were reviewed for pertinent studies. The manufacturers of RRT and authors of included trials were contacted for additional information. Two reviewers independently screened studies and applied the selection criteria. Disagreements occurred with 8% of articles (kappa=0.77) and were resolved by a third party through consensus.

Validity assessment was performed by two reviewers independently using condensed versions of the Chalmers Index11 and the Black and Downs checklist.12 Data on funding sources were extracted. The following outcomes were assessed: mortality, length of stay, length of mechanical ventilation, health-related quality of life, dialysis dependence, subsequent chronic renal insufficiency, number of dialysis treatments, and complications. The results of trials that compared CRRT to IHD were
pooled. Because of the differences expected between trials, a decision was made a priori to combine
the results using a random effects model.\textsuperscript{13} The relative risk (RR) was used to pool dichotomous
outcomes and the risk difference was used for complications that had many zero event cells. Where
results were pooled, statistical heterogeneity was quantified using the I$^2$ statistic.\textsuperscript{14,15} Submodality
comparisons were performed before undertaking the comparison of CRRT with IHD.

4 Results

The literature search yielded 2,135 citations, of which 160 were retrieved for detailed evaluation. Of
the 160 reports, 28 were included. Thirteen trials compared CRRT and IHD, and 15 trials compared
the submodalities (10 of CRRT, three of IHD, and two of CRRT or IHD with peritoneal dialysis).
Because acute peritoneal analysis is not widely used to treat ARF in Canada, the findings from these
studies\textsuperscript{16,17} did not influence the conclusions of our review.

Submodality Comparisons

The 10 trials comparing the submodalities of CRRT involved a total of 1,298 participants.\textsuperscript{18-27} Few
had sufficient statistical power to detect the differences in clinical outcomes. There was evidence
favouring HDF over HF,\textsuperscript{27} favouring higher doses (45 mL/kg/h and 35 mL/kg/h versus 20 mL/kg/h)
in HF,\textsuperscript{18,20} and favouring bicarbonate over lactate buffers.\textsuperscript{21} Three trials\textsuperscript{28-30} (with 233 participants)
compared the submodalities of IHD, but no conclusions about clinical benefit could be made.

CRRT versus IHD Comparisons

Thirteen controlled trials (n=1,259 participants) were identified.\textsuperscript{31-43} All were RCTs except one.\textsuperscript{42}
The validity of the individual trials was generally poor (about half met each individual validity
criterion). For CRRT, seven trials\textsuperscript{34,35,37-40,43} studied HF, four\textsuperscript{31,32,36,42} looked at HDF, and two\textsuperscript{33,41}
examined HD. Vascular access was venovenous in all cases except in two small, older trials,\textsuperscript{39,40}
which used arteriovenous access, and two larger trials,\textsuperscript{36,42} which used a combination of both types.
In total, arteriovenous access was used in <98 patients (16%). For IHD, two studies\textsuperscript{34,41} used
extended HD (six to 12 hours duration) and two small trials\textsuperscript{39,40} (n=37) used HF. The remaining nine
used standard HD.

Mortality

There was no evidence of significant differences between CRRT and IHD based on all-cause
mortality before discharge from the ICU (n=549, RR 1.10, 95% CI: 0.95 to 2.08),\textsuperscript{32,35-37,40,42} in-
hospital mortality (n=901, RR 1.05, 95% CI: 0.92 to 1.20),\textsuperscript{31-33,36,41,42} and pooled mortality (n=1,142,
RR 1.02, 95% CI: 0.93 to 1.12, I$^2$=10%).\textsuperscript{21-33,35-37,40-43} The results of analyses that were stratified on
potential confounders did not show differences in mortality between CRRT and IHD. The pooled
mortality results from trials where the CRRT arm used HDF exclusively (n=767, RR 1.02, 95% CI:
0.87 to 1.20, I$^2$=54%) or a bicarbonate buffer exclusively (n=556, RR 0.96, 95% CI: 0.87 to 1.06,
I$^2$=0%) did not differ from the findings of the main analysis. No trials compared high-dose CRRT
with IHD.

Length of ICU and Hospital Stay

Three trials (n=650)\textsuperscript{31,32,36} reported the length of ICU stay. The results were skewed and not pooled.
In each trial, the mean and median estimates were similar between CRRT and IHD groups. Across
trials, the estimates ranged from six to 12 days. Four RCTs (n=643) reported the length of hospital stay.31,32,36,41 These results were also skewed and not pooled. The mean and median lengths of stay ranged from 16 to 32 days. Two trials reported non-significant differences between RRT groups. One trial36 reported shorter stays in the CRRT group. A second trial41 reported shorter stays in the IHD group. In both trials, the statistical tests were inappropriate or not reported.

**Health-related Quality of Life**

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

**Number of Dialysis Treatments, Dialysis Dependence, Risk of Chronic Kidney Disease**

Two trials (n=431) reported the number of dialysis treatment days required during the hospital stay.31,41 The results were skewed and not pooled. They showed no differences between treatment groups or between studies. The results from several trials reported no differences between groups in their requirement for chronic dialysis treatment (implying end-stage renal disease), whether among patients who survived to ICU or to hospital discharge (n=308, RR 0.91, 95% CI: 0.56 to 1.49),31-33,36,41 or who died before ICU or hospital discharge (n=423, RR 1.01, 95% CI: 0.80 to 1.28).32,33,36,41 One trial36 reported that chronic renal insufficiency (serum creatinine ≥ 176 µmol/L) at hospital discharge was significantly lower among CRRT recipients (n=166, RR 0.21, 95% CI: 0.06 to 0.70).

**Metabolic Control, Blood Pressure, and Dialysis-related Complications**

No studies compared Kt/V, urea reduction ratio, incidence of hyperkalemia, or incidence of severe acidosis between treatments. The pooled results from two trials31,37 showed no significant difference in the incidence of hypotension between treatment groups. Three trials measured mean arterial pressure at 24 hours or ICU discharge. The pooled (n=212) change from baseline significantly favoured CRRT (4.6 mm Hg, 95% CI: 0.4 to 8.9).32,33,40 The meta-analyses of five trials31,33,34,37,38 (n=543) showed no significant differences between treatment groups in the incidence of complications, including filter clotting and hemorrhagic complications, hemodynamic instability or arrhythmia, and metabolic abnormalities.

## 5 Economic Evaluation

**Literature Search**

All studies identified in the clinical systematic review (n=2,135) were screened for inclusion in the economic review. Two reviewers applied the inclusion criteria. Studies were included if they:

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

Of 2,135 citations, 49 were identified as potentially relevant, and full-text articles were reviewed. Disagreements occurred in 14% of articles (kappa=0.44) and were resolved by consensus.

After examination, none of the articles identified were deemed to meet all inclusion criteria. Two articles had some elements of an economic evaluation and provided a contextual framework for our evaluation. The first was a multi-centre RCT of CRRT versus IHD in ICU patients with ARF.36
Adjusted analyses showed no statistically significant differences between treatment groups in mortality, duration of ICU stay, and renal recovery. The direct costs of CRRT and IHD treatment were US$543 and US$282 respectively. The total per-patient treatment costs were US$3,946 and US$3,077 respectively. The second study, which was non-randomized, measured health care resource use among patients with ARF receiving CRRT or IHD in the ICU. In-hospital and one-year post-discharge health care costs were measured. The study reported significantly higher costs to provide CRRT than IHD (difference of C$1,342 per week in 1999 dollars). Most of the difference was due to supplies and replacement fluid cost (C$416 per day for CRRT compared to C$68.30 per run of IHD). The cost was offset somewhat by the nursing costs required for IHD (C$149 per run). Other costs were comparable between the treatments. Patients who survived but required ongoing chronic dialysis therapy incurred incremental costs of C$62,081 during the post-discharge year compared to survivors not requiring dialysis. Clinical outcomes were captured, but the non-randomized study design precluded insights into clinical benefits, and the investigators did not try to determine the incremental cost-effectiveness.

**Primary Economic Evaluation**

The cost-effectiveness of CRRT compared with that of IHD was determined by adapting an economic decision model to represent events from the start of RRT in the ICU until death or discharge from hospital. Survivors entered a Markov model that modeled the transitions between “alive requiring dialysis,” “alive without dialysis,” and “death.” The analysis was continued until <1% of the original cohort remained alive. The model used observational data from a Canadian setting and results from the systematic review. The analysis was performed from the perspective of the Canadian publicly funded health care system and modeled the cost-effectiveness of CRRT over a lifetime horizon. The base-case analysis included patients ≥18 years old with ARF requiring treatment with RRT and candidates for CRRT or IHD. The analysis assumed the most commonly used of each modality in Canada – that IHD would be provided from 3.5 to 4.5 hours, 3.9 days per week, and that CRRT would be delivered through CVVHDF. The model outputs were QALYs, LYs gained, health care costs, and cost per QALY gained. The base-case analyses were conducted using Markov cohort analysis, and Monte Carlo simulation was used for the probabilistic sensitivity analysis.

**a) Base Case Analyses**

The primary a priori-defined economic analysis (model 1) used the point estimates for the RR of death and dialysis dependence from the systematic review and meta-analysis. Compared with CRRT, IHD was associated with increased total health care costs and QALYs. 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. Although the dialysis costs were C$3,679 less per patient with IHD compared with CRRT, the overall health care costs increased because of the higher proportion of patients who survived and required HD. The second analysis (model 2) used a RR of 1.0 for mortality and dialysis dependence. CRRT was dominated by IHD, with IHD leading to equal QALYs and early cost savings of C$3,679.

**b) Scenario Analyses**

Scenarios evaluating practices where the costs of providing CRT and IHD were varied, had small effects on the incremental cost-effectiveness ratio (ICER). When the risk of developing various clinical outcomes was varied by era and setting, the ICER ranged from C$109,698 to C$164,554 per QALY for model 1, while CRRT remained dominated by IHD in model 2. The costs associated with RRT were varied, depending on the method of delivery and setting. In model 1, the cost-utility of IHD compared with CRRT ranged from C$93,283 to C$150,619 per QALY. Model 2’s results
remained unchanged, with IHD dominating CRRT in all scenarios. Because surviving patients may incur high costs for hospitalization and subsequent health care, therapies that improve survival would be expected to increase downstream costs. The effect of this trade-off on cost-utility was evaluated. When the need for chronic dialysis was assumed not to influence the long-term costs among survivors, CRRT was dominated in model 1. In the scenario where the non-dialysis related costs of the index hospitalization were identical, regardless of clinical outcome, there was minimal impact on the ICER (model 1).

c) Sensitivity Analyses
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 for models 1 and 2. Other variables, such as the daily cost of providing CRRT, had a smaller impact.

6 Limitations

Large, good quality RCTs that address the clinical effectiveness of CRRT are scarce. The findings and the strength of this review are limited by the lack of available evidence. The pooled results were prone to the limitations inherent in meta-analyses, although measures were taken to reduce the likelihood of bias.

The economic evaluation model and results were limited by the lack of available evidence and the requirement to model all relevant clinical and economic consequences. Non-dialysis-dependent chronic kidney disease (CKD) was excluded in the model. Patients with CKD have worse clinical outcomes and increased health care costs compared to those without CKD. By necessity, the use of observational data to assign costs is a common practice in economic models. Ideally, an RCT would have been used to assess the extent to which health care resource use influences the results in this model, by including these as a specific outcome measure. Such an RCT was unavailable.

Much of the information, including information on costs and quality of life, was obtained from small studies, and a significant number of studies were performed in one region of Canada. These factors may limit the generalizability of results. No information was available on indirect and productivity costs. These may be substantial if survival and functional status are influenced by therapy. The incremental costs and incremental effectiveness were small, and may lead to instability of the ICER.

7 Health System Implications

The current practices of providing RRT vary across Canada and seem to be changing. In future, CRRT could be used in Canada all the time, some of the time, or not at all. Based on the 2001 Canadian census data for the adult population, it is estimated that there are 2,445 cases of ARF requiring dialysis among 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 C$2.1 to C$2.3 million. If CRRT is performed in 68% of patients, C$6.1 million could be saved by providing IHD only.
While the economic model indicated that survivorship and dialysis dependence had a significant impact on health care costs, there was no evidence to suggest that CRRT significantly influenced these outcomes. The cost savings due to reduced dialysis dependence among survivors were excluded in the budget impact analysis. If future studies suggest that CRRT is associated with a lower risk of dialysis dependence, then the cost savings should be included in future budget impact analyses.

The human resources required to perform CRRT and IHD in the ICU may differ, but the net impact of using either therapy on human resources is likely to be health care centre-specific. CRRT is typically performed by ICU nurses. It is resource-intensive, and additional ICU nurses may be required, depending on the number of patients. 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. The total health care costs may be lower with IHD, but the scarcity of human resources may be a limiting factor.

The most significant capital costs are due to the equipment used to provide IHD and CRRT. The RRT equipment that is typically used can provide IHD or CRRT, but not both. The cost difference between a machine that can provide CRRT rather than IHD is not large (~$36,000 versus $28,000 list prices respectively for CRRT and IHD machines) (J. Foster, Project Manager, Northern Alberta Renal Program: personal communication, 2007). An IHD machine can also be used to provide chronic HD – a procedure that is commonly performed at 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 consider what additional equipment may be required.

8 Conclusion

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

9 References