

The Case for Increased Renal Replacement Therapy Dosing in ICU Patients with Acute Renal Failure: Re-Examining Current Evidence

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The adoption of continuous renal replacement therapies (CRRT) represents one of the more substantial advancements in the management of critically ill patients in the intensive care setting.¹ Not a single treatment but a spectrum of modalities, CRRT includes continuous hemofiltration, continuous hemodialysis, and continuous hemodiafiltration.² By providing clearance and fluid removal continuously for 24 hours a day, and at a much slower rate than intermittent hemodialysis (IHD), the CRRT therapies are better-matched to the metabolic and hemodynamic needs of critically ill patients with acute renal failure (ARF) who are prone to fluid overload, diuretic resistance, hemodynamic instability, and azotemia.³

Despite present CRRT technologies that allow continuous hemodialysis (diffusive clearance, e.g. CVVHD), continuous hemofiltration (convective clearance, e.g. CVVH), or a hybrid of the two: continuous hemodiafiltration (CVVHDF), there is no evidence that any one of these therapies provides a survival advantage over the other. There is, however, an increasing body of evidence that the dose of clearance provided by each of these modalities does affect survival.⁴ Conventional thrice weekly dosing of IHD for patients with ARF in the intensive care unit (ICU), accepted as adequate for many years, was originally extrapolated from standard practices that were employed in stable out-patients with end-stage renal disease (ESRD).⁵ However, the alarmingly high rate of mortality associated with ARF in critically ill patients receiving dialysis, often exceeding 50%, caused nephrologists to re-examine the criteria for optimized renal support, including dosing and its impact upon renal function and patient survival in ARF.⁶

Starting in 2000, there have been three randomized, single-center trials, the published results of which have led a paradigm shift in our approach to the renal replacement therapy prescription for the patient with acute renal failure in the ICU.⁷⁻⁹ Each of these studies was designed to test the hypothesis that patient survival could be improved by increasing the dose of clearance. Each one has a different method of clearance, from continuous hemofiltration, to continuous hemodiafiltration, to daily hemodialysis. Despite these methodological differences, each study provided the same conclusion by demonstrating a survival improvement with an increase in dose.⁴

The early study of Ronco and associates (2000), considered by many a landmark study, looked directly for the first time at high-volume versus low-volume continuous veno-venous hemofiltration (CVVH).⁷ Over a five-year period, 425 patients with ARF were randomized to one of three treatment arms based upon hemofiltration rates of 20 ml/kg/hr, 35 ml/kg/hr, or 45 ml/kg/hr (for a 70 kg patient, this requires daily hemofiltration amounts of 34 L, 59 L, and 76 L, respectively). Using an intention to treat analysis, survival 15 days after discontinuation of CVVH was 41% in the lowest dose arm compared to 57% and 58% in the intermediate and highest dose arms, respectively (p = 0.001).

The study of Schiffel and associates (2002), examined the effect of frequency (daily or alternate day) of hemodialysis upon survival.⁸ One hundred and

sixty critically ill patients with severe ischemic or nephrotoxic acute tubular necrosis were alternately assigned to daily or every other day hemodialysis. All-cause mortality 14 days after the last hemodialysis session was 46% in the alternate day treatment group compared to 28% in the daily treatment group (p = 0.01). This study provided important support for the concept that a dose-response relationship exists for standard hemodialysis in patients with ARF and suggests that the traditional ESRD-based prescription patterns result in inadequate levels of clearance.

In 2006, Saudan and associates examined the effect of adding a “dose” of dialysis to continuous veno-venous hemofiltration (lower dose CVVH versus higher dose CVVHDF) on survival of patients in the ICU with ARF.⁹ In this single-center controlled study in two intensive care units, the investigators randomized 206 patients to either CVVH at a rate of 1 – 2.5 l/h of replacement fluid or to CVVHDF using the same rate of hemofiltration but with the addition of dialysate at a rate of 1 – 1.5 l/h. Survival rates at 28 days and 90 days were significantly higher with CVVHDF than CVVH (59% vs. 39%, P = 0.03, and 59% vs. 34%, P = 0.0005, respectively). When comparing the results of Saudan and Ronco, despite the partial differences in clearance technique utilized, the similarities in dose and outcome are worth noting: Dose levels, Saudan 25 ml/kg/h vs 42 ml/kg/h, Ronco 20 ml/kg/hr v 35–45 ml/kg/hr; Patient survival (Saudan 34% vs 59%, Ronco 41% v 57%).

A fourth study (which failed to show a survival advantage to an increase in clearance dose) requires mentioning. Bouman and associates (2000) assigned 106 critically ill patients to three intensity groups: early high-volume hemofiltration (72 to 96 L/24 h), early low-volume hemofiltration (24 to 36 L/24 h), and late low-volume hemofiltration (24 to 36 L/24 h).¹⁰ These investigators found no difference in terms of renal recovery or 24-hour mortality. However, this study has been generally considered to be underpowered. In addition, the overall mortality in the study cohort was significantly lower than in other published series, suggesting that the study population may not have been representative of that observed at other reporting centers.⁴

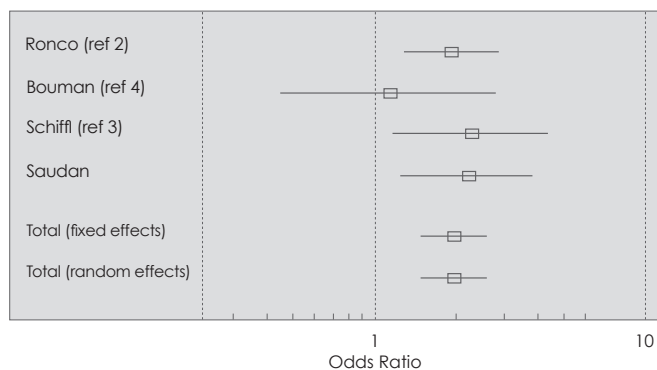
Synopsis of Studies

	Ronco (425 pts)	Bouman (106 pts)	Schiffel (206 pts)	Saudan (206 pts)
Base Modality/ Dose	Hemofiltration 20ml/kg/hr	Hemofiltration 24-36 l/24 hr	Hemodialysis 3X/wk	Hemofiltration 1-2.5 l/hr
Increased Dose	35ml/kg/hr	72-96 l/24 hr	6X/wk	Hemodiafiltration 1-2.5 l/hr HF 1-1.5 l/hr HD
Survival	Improved	No Change	Improved	Improved

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There are 2 major multi-centered trials presently underway designed to specifically test the dose hypothesis. The Acute Renal Failure Trial Network (“ATN trial”) is based in the U.S. and utilizes various clearance modalities based on patient stability, with randomization to “conventional” or “intensive” clearance goals. The Randomized Evaluation of Normal versus Augmented level of renal replacement therapy (RRT) (“RENAL trial”) is based in Australia and New Zealand and is comparing CVVHDF at 25ml/kg/hr versus 40 ml/kg/hr. Hopefully, these studies will give us definitive guidelines as to our treatment goals of the various methods of RRT for these critically ill ICU patients with ARF.⁴

Supplementary Figure 1:
Forest plot pooling trials of RRT dose¹¹



Study	n	Treatment Groups
Ronco (ref 2)	425	CVVH 20/h vs. 35-45 ml/kg/h*
Bouman (ref 4)	106	CVVH 20 ml/kg/h* vs. 48 ml/kg/h
Schiff (ref 3)	160	Alternate day vs. daily hemodialysis
Saudan	206	CVVH 25 ml/kg/h vs. CVVHDF 42 ml/kg/h

*For purposes of analysis the two high-dose arms in Ronco were combined, as were the two low-dose arms in Bouman. If these groups are removed the odds ratio is unchanged (1.94; P<0.001).

In the meantime, the “case” for increasing clearance goals in critically ill patients with ARF has been strengthened by a recent editorial by John Kellum, M.D., *Professor of Critical Care Medicine at the University of Pittsburgh*.¹¹ He showed that the pooled results from the four previously mentioned studies demonstrated a large effect on survival in favor of higher dosing with an odds ratio of 1.95 (95% CI 1.48 – 2.58, P < 0.001 see figure 1).

Based on these data he stated his belief that the best evidence to date supports the use of at least 35 ml/kg/h for CVVH, CVVHDF, or daily dialysis. He also concluded that the lower dose prescriptions that we utilized in the past should now be considered suboptimal.

Summary

The body of evidence to date is highly supportive that “more is better” when we consider RRT dosing of ICU patients with ARF. It also appears that how much clearance we provide is more important than how we provide it. Clearly, the ESRD thrice-weekly IHD model is inadequate for this different and unique patient population and we need to be more aggressive in our prescription.

When increasing the dose of clearance, there are a number of practical aspects which may impact the success of delivering what we prescribe. Hemofiltration volumes of >50 liters/day (for CVVH) requires large amounts of “intravenous-grade” replacement fluid which can be costly and difficult for hospital pharmacies to provide. Pre-mixed bagged dialysate is readily available and cheaper and thus CVVHD and CVVHDF may afford an economic and logistic advantage.

The vascular access has long been described as the “Achilles’ heel” of out-patient hemodialysis and this dependence is no different for the continuous renal replacement therapies (CRRT). The best CRRT machine is only as good as the access allows it to be. Obtaining, and maintaining, a vascular access that affords adequate blood flow without excessive pressures and subsequent machine alarms is paramount to a successful therapy. While venous access sites include the subclavian, internal jugular, and femoral veins, the optimal site in any given patient may be determined by the risk of thrombosis, infection, and by the ease of placement. Adequacy of function (blood flow), however, often takes precedence. Ultrasound guidance and catheter placement by specialized/experienced vascular access teams may reduce failure and complication rates. In the end, it is often only diligence that separates access success from failure.

Finally, the CRRT machine itself, including pumps, tubings and filter, must have performance characteristics that can accommodate higher dosing. With larger volume therapies, these increased clearance goals require higher pump flow rates and fluid exchange rates. Clinicians should be able to tailor the therapy delivered (volume, frequency, duration and/or location) to the patient’s needs. Importantly, the equipment must be easy to set up, operate and maintain. This includes minimizing the complexities and risks associated with water processing and disinfection.

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