Continuous Renal Replacement Therapy: Reviewing Current Best Practice to Provide High-Quality Extracorporeal Therapy to Critically Ill Patients

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Continuous renal replacement therapy (CRRT) use continues to expand globally. Despite improving technology, CRRT remains a complex intervention. Delivery of high-quality CRRT requires close collaboration of a multidisciplinary team including members of the critical care medicine, nephrology, nursing, pharmacy, and nutrition support teams. While significant gaps in medical evidence regarding CRRT persist, the growing evidence base supports evolving best practice and consensus to define high-quality CRRT. Unfortunately, there is wide variability in CRRT operating characteristics and limited uptake of these best practices. This article will briefly review the current best practice on important aspects of CRRT delivery including CRRT dose, anticoagulation, dialysis vascular access, fluid management, and drug dosing in CRRT.
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INTRODUCTION

Continuous renal replacement therapy (CRRT) has been evolving briskly over the last 40 years.[1] While in some circles, there remains a robust debate on the merits and role of CRRT compared to other methods of renal replacement therapy (RRT) such as intermittent hemodialysis (IHD), prolonged intermittent RRT, and peritoneal dialysis, for many reasons, CRRT has become the dominant modality of acute RRT in critically ill patients in resource-rich areas throughout Europe, North America, Asia, and Australia.

This article will not wade into these important issues or questions regarding modality of acute RRT, but rather will attempt to summarize best practice in the delivery and application of CRRT. While many readers will have strong opinions on whether CRRT provides more benefit than struggle, hopefully, we can all agree that when CRRT is prescribed, it is our duty to optimize and target therapy to achieve the desired goals by using the best available evidence and guidelines.

DEFINING HIGH-QUALITY CONTINUOUS RENAL REPLACEMENT THERAPY

Many countries define quality metrics for chronic IHD for end-stage kidney disease patients, yet, in the United States at a minimum, there are no current reportable quality metrics for acute RRT or CRRT. As a result, there has been little unified or systematic effort to improve CRRT quality in the United States yielding a striking variability in practice patterns between both experienced centers and providers.

Providing high-quality CRRT is a complex endeavor that involves a multidisciplinary team with a unified vision. For example, clinician experts must consider mode of clearance (convective, diffusive, or both), small solute clearance rate, fluid removal targets, CRRT circuit anticoagulation strategies, and vascular access to name a few. Nurses deliver CRRT therapy making sure to setup and maintain the machine with the prescribed operating characteristics (using the proper solutions, etc.) while attempting to meet fluid removal targets and troubleshoot vascular access and the CRRT circuit to decrease CRRT circuit failures. Nutrition and pharmacy support colleagues need to adjust medication dosing and nutrition support needs.

Failures anywhere along this complex tree lead to suboptimal CRRT, failure to achieve the individualized goals of therapy, and can negatively impact patient outcomes. While critical care medicine specialists are increasingly experienced with CRRT, we endorse that there remains a broad role for collaborating nephrologists to assist in the management of acute kidney injury (AKI) and acute RRT in the critically ill patient.[2] Highlighting the multidisciplinary nature of CRRT, Table 1 describes a six-step framework for delivering high-quality CRRT, and facilitating high-quality CRRT with a tailored precision medicine approach was the subject of the 17th Acute Dialysis Quality Initiate (ADQI) International Consensus Conference.[1]

Given the complexity of CRRT, it is impossible to employ a single metric to define and benchmark high-quality, precision CRRT or monitor a programs performance. Table 2 outlines possible metrics and benchmarks that could be used in CRRT.

Hard end points such as survival, and kidney function recovery (in AKI) to liberation from RRT are more difficult to benchmark because multiple patient factors competitively influence these outcomes in the intensive care unit (ICU) and there are large differences in expected mortality rates based on the type of patient and severity of illness (both of which differ between various subspecialized ICUs and hospitals). Precision CRRT certainly requires attention to both CRRT modality and total effluent flow rate targets ("CRRT dose") when prescribing therapy. Yet, there is ample data that support a gap between prescribed and achieved/delivered CRRT dose,[3,4] suggesting

that a benchmark of prescribed dose alone is an inadequate metric. While fluid overload is now clearly recognized as contributing to poor outcomes in ICU patients,[5-11] fluid balance targets must be individualized for each patient based both on disease process and stage of illness thus making it difficult to benchmark across different ICUs or institutions.

Despite the challenges of benchmarking, clinicians should be encouraged that there is an expanding evidence base to inform best practice and consensus statements which should guide decision making for individual patients while also fostering for programmatic quality assurance (QA) and improvement (QI) at the institutional level.

Continuous Renal Replacement Therapy Mode

Recognizing that with advancing technology came variability in nomenclature, Villa and colleagues[12] recently published an expert consensus statement to clarify CRRT nomenclature. Historically, there has long been teaching, bordering on dogma, that there is a significant difference in the middle molecule clearance between convective (hemofiltration) vs diffusive (hemodialysis) modes of clearance.[13] However, in continuous venovenous (CVV) hemofiltration (CVVH), the middle molecule clearance may be as great as 20 mL/min, while only 8-12 mL/min with CVV hemodialysis (CVVHD).[14] There is no increase in middle molecule clearance with CVV hemodiafiltration (CVVHDF), either. There remains no definitive randomized data comparing survival with continuous hemofiltration vs hemodialysis. Wide variability in practice remains around the world, and no clear consensus statements have been published on this topic.

Certainly, purely convective modes of therapy such as CVVH will always have a higher filtration fraction (FF) compared to purely diffusive clearance as in CVVHD when blood flow, hematocrit, and total effluent flow rates are held constant.[9,15] Increasing FF should negatively correlate with CKRT circuit survival, and one small pilot data set may corroborate this trend toward fewer circuit exchanges in CVVHD vs CVVH, but this data do not reach statistical significance due to small sample size.[16] Of course, CVVHDF allows for a combination of the two modalities and whose FF lies between CVVH and CVVHD depending on the relative contribution of convection and diffusion to the total effluent flow rate. It should be noted that while using a prefilter replacement fluid strategy in CVVH or CVVHDF does decrease FF marginally, it would be naïve to assume that this alone resolves the concern of elevated FF on circuit failures and comes at the expense of decreasing small solute clearance.

At this time, the data cannot strongly support one mode of CRRT over another. We support that mode selection should be guided with the intent to maximize CRRT circuit survival and by considering planned anticoagulation practice and other factors. As will be discussed below further, standardization of certain aspects of CRRT (such as mode) can decrease variability and improve quality.

Continuous Renal Replacement Therapy Dose

Based on both the VA/NIH ATN[17] and RENAL[18] trials, clear consensus has emerged regarding CRRT dose—specifically that "high-dose" CRRT has no apparent additive benefit compared to usual dose as a standard of care. As a result, the Kidney Disease Improving Global Outcomes (KDIGO) and ADQI recommend achieving a target CRRT effluent flow rate of at least 20-25 mL/kg/h.[19,20]

However, approaching CRRT dose as a static concept is certainly not appropriate for all patients. Rather, our practice is a dynamic approach to CRRT dose focused on achieving specific daily goals but maintaining a floor of 20-25 mL/kg/h effluent flow. This individualized approach allows for a more precise approach to serve a critically ill patient's evolving needs.[15,20,21] For example, when CRRT is first initiated, severe acidemia may warrant a more aggressive CRRT dosing approach. Subsequently, CRRT effluent flow rates can (and should) be decreased to a more standard CRRT dose when homeostasis is reached to avoid the negative impacts of high-dose CRRT on nutritional status especially.

CLINICAL SUMMARY

- High-quality continuous renal replacement therapy is a complex procedure requiring a collaborative multidisciplinary team-based approach to maximize patient outcomes.

- Use best available evidence to employ best practices in prescribing continuous kidney replacement therapy.

- Measure performance and adherence to best practices for quality assurance and quality improvement.

Anticoagulation

Anticoagulation of the CRRT circuit is recommended by KDIGO[19] as a strong grade 1B recommendation, and multiple studies have shown a benefit to circuit survival with a variety of different anticoagulation methods when compared to no anticoagulation.[22] The optimal anticoagulation strategy should be (1) readily available, (2) prolong filter life by preventing clotting, (3) have minimal systemic affects, and (4) have low bleeding risk. Regional citrate anticoagulation (RCA) and systemic heparin protocols are the two most widely used strategies globally. Meta-analyses and multiple additional studies support RCA as providing superior circuit survival with lower bleeding complications when compared to systemic heparin.[23-27] We believe that current best practice supports anticoagulation for CRRT circuit survival and improves the prescribed to delivered CRRT dose ratio. RCA has proven safe and effective and should be considered as a default approach. There are many published RCA protocols nicely reviewed by Morabito and colleagues[28] in 2014. It is important to note that the US FDA has yet to approve citrate use in CRRT circuits. Despite this, off-label RCA in CRRT is quickly expanding in the United States.

Certainly, RCA protocols are more complex than alternatives and require monitoring for potential adverse effects including systemic hypocalcemia, metabolic alkalosis,

Table 1. Six Steps for Providing Optimal Acute RRT (CRRT)

1. Close collaboration between CCM and nephrology
2. Define the primary goal of CRRT daily (ie, fluid removal, acid/base control, small solute clearance, etc)

    Daily goal informs individualized CRRT prescription

3. Keep CRRT running—maximize delivered vs prescribed CRRT ratio

    Establish and maintain high functioning dialysis vascular access

    Anticoagulation—regional citrate anticoagulation vs heparin vs other

4. Review appropriateness medication dosing daily (especially antimicrobial agents)

    Large changes in effluent flow rates should prompt consideration to increase or decrease medication dosing

5. Ensure appropriate nutrition support for CRRT—augmented protein intake recommended
6. Avoid CRRT-related complications

    Severe hypophosphatemia (ie, <2.0 meq/L)

    Frequent CRRT circuit failures → increased blood transfusion needs

    Minimize risk of CRRT therapy errors through standardization and consistency of machine, modality, anticoagulation strategies, and education

Abbreviations: CCM, Critical Care Medicine; CRRT, continuous renal replacement therapy; RRT, renal replacement therapy.

or systemic citrate toxicity. RCA requires systemic calcium supplementation to avoid life-threatening hypocalcemia, and there are many published calcium replacement protocols.[28] Citrate toxicity occurs when there is systemic accumulation of unmetabolized citrate that has both escaped removal by the CRRT circuit and whose metabolism by muscles and liver is impaired by liver failure or severe malperfusion states. Given these complexities, it is extremely important that all members of the multidisciplinary

Table 2. Possible Quality Metrics (Based on Current Best Practices, Data, and Consensus Guidelines)

CRRT Modality (If Standardized)
Prescribed CRRT dose = total prescribed effluent flow rate/h/weight (kg)
Delivered CRRT dose = total achieved effluent flow rate/d (or per hour)/weight (kg)/24 hours (if necessary)
Ratio of delivered dose/prescribed dose = total daily effluent volume achieved (in 24 hours)/total effluent volume prescribed
Time between CRRT circuit exchanges (required and/or unplanned)
Effective CRRT treatment time (in 24-hour period) = 24—number of downtime hours or 1440—number of downtime minutes
Vascular access site, size, length, and depth—is the access of appropriate length?
Mortality (or survival)—specifically in those with AKI requiring RRT
Kidney functional recovery to dialysis liberation

Abbreviations: AKI, acute kidney injury; CRRT, continuous renal replacement therapy; RRT, renal replacement therapy.

CRRT team have education and demonstrate competencies to accurately and safely use RCA.

Dialysis Vascular Access

KDIGO 2012 guidelines recommend a nontunneled temporary dialysis catheter for dialysis vascular access.[19] However, precious little data exist comparing catheter sites, lengths, or size. General guidelines by KDIGO[19] and others regarding estimated catheter length for each access site do not individualize insertion based on a patient's height. In an important single-center study, Morgan and colleagues[29] demonstrated that deeper catheter insertion to target the right atrium (RA) (or caval atrial junction) vs higher position in the superior vena cava significantly improved CRRT circuit survival and delivered dose of CRRT without increasing risk of complications. This was achieved by using 20-cm catheters at the right internal jugular and 24 cm catheters at the left internal jugular position rather than 15 and 20 cm, respectively. Czepizak and colleagues.[30] demonstrated that a height-based formula can more accurately predict the proper length of CVL insertion to achieve superior vena cava positioning. To date, there are no reports of a systematic height based formula to achieve RA insertion depth specifically for dialysis catheter insertions. However, in the authors' clinical experience, insertion 1-2 cm beyond the depth suggested by Czepizak [right internal jugular depth = height (cm)/10 and left internal jugular depth = (height {cm}/10) + 4 cm] yields a preferred tip location at the caval atrial junction or in the RA in vast majority of cases serving as a starting point. Notably, these formulas are more accurate for subclavian catheters compared to right internal jugular ones.

Femoral dialysis catheters should only be used when an IJ catheter at a proper depth cannot be obtained at either location for any reason. It is important to note that catheters at least 24 cm in length should be used for all femoral venous insertions in adults. Increased risk of catheter-associated bacteremia with the femoral venous catheters has been noted for people with body mass index >28 kg/m^2.[31]

Timing of Acute Renal Replacement Therapy Initiation

Despite numerous prior trials, to date, there is little consensus on when to initiate acute RRT. Historically, studies have used blood urea nitrogen (BUN) or creatinine levels as surrogates for severity of AKI from which to randomize to early vs late RRT initiation. However, most agree that BUN and creatinine are not the determinants of outcomes for patients with CRRT. This was corroborated by Liboria and colleagues[8] in 2015 who described that most of the excess mortality associated with AKI in the critically ill is the result volume overload, hyperkalemia, and metabolic acidosis that complicates AKI.

Two studies—AKIKI[32] and ELAIN[33]—were published in 2016 but reached divergent conclusions. AKIKI randomized patients at KDIGO stage 3 to immediate initiation vs to wait for a life-threatening indication and demonstrated

no difference in outcomes.[32] However, it should be noted that only approximately 50% of the delayed group actually received acute RRT and the vast majority of all RRT was with IHD. When one compares the patients who actually received dialysis, there was a marked improvement in survival in the early group supporting the concern that awaiting a life-threatening complication of AKI before starting RRT is putting patients at risk for death. ELAIN randomized patients at KDIGO stage 2 AKI to either immediate start vs to wait until either KDIGO stage 3 or life-threatening indication developed.[33] In this single-center study, all patients received CVVHDF and only 9 of 118 in the delayed group did not receive acute RRT. Mortality at 90 days was lower in the early RRT group (39.3%) vs the delayed group (54.7%, $p = 0.03$) with HR for death of 0.66 (95% confidence interval 0.45-0.97) in the early group. Two large multicenter trials (STAART-AKI and IDEAL-ICU) are both enrolling with similar methods to ELAIN and AKIKI, respectively, which will hopefully shed further light on this topic. However, concern remains that making decisions regarding timing of RRT initiation on the basis of BUN or creatinine (ie, stage of AKI) may not be the most appropriate study design. For example, perhaps, a protocol based on volume status in an oliguric patient may be a more realistic real-world study.

Thus, at this time, our practice remains largely unchanged—we start acute RRT early in the setting of oliguria especially with high obligate fluid intake, established volume overload, metabolic acidosis, or electrolyte derangements—when metabolic demand exceed the capacity of the injured kidney. Failure to respond to a formalized furosemide stress test strongly predicts patients who will progress to severe AKI (KDIGO stage 3)[34] and is often valuable in helping to decide whether to initiate RRT early. However, in the less common circumstance whereby isolated asymptomatic azotemia has developed in isolation, it remains reasonable to consider delaying dialysis. This is paradigm that is endorsed also by ADQI 17.[35]

Fluid Removal
On the basis of copious data, there is a growing acceptance that volume overload is detrimental to critically ill patients with and without AKI contributing to both mortality[5-8,11,36,37] and increased ICU length of stay, time on mechanical ventilation,[10] intra-abdominal hypertension,[38,39] and other morbidities.

It is well accepted that CRRT provides a superior platform for fluid removal in hemodynamically unstable patients,[5] and fluid management and removal is increasingly the main objective of CRRT. Achieving the targeted daily fluid balance using CRRT should be considered one of the most important daily goals in those receiving CRRT to allow for either (1) prevention of further fluid accumulation or (2) return to euvolemia. To accurately manage fluid status and balance, and frequent reassessment of goals, tolerance for fluid removal is required and accurate documentation of input and output in near real-time is essential.

Medication Dosing
Advanced pharmacokinetic (PK) studies of drugs in patients receiving CRRT remain rare with large studies including 20-40 people only.[40-43] Many historical drug dosing recommendations have proven inaccurate for many reasons—rare historical PK data generated with different CRRT operating characteristics (ie, low CRRT effluent flow rates thereby low clearance, low surface area, and low-flux, low-efficiency dialyzers, etc.) or were simply extrapolated from data in IHD in generated in outpatient settings.

Several antimicrobial PK studies in the modern era of CRRT have shown a disturbingly high number of patients failing to meet desired therapeutic drug levels as a result of both augmented CRRT clearance and non-CRRT clearance in critically ill patients.[40,41,43]

Given the current lack of data on most drugs in CRRT, many have recommended dosing medications at least for the estimated CRRT clearance based on total effluent flow rate (by converting mL/h effluent flow to mL/min) and by having a low threshold to dose more aggressively especially with drugs with wide therapeutic index as the incidence of overt drug toxicities (ie, seizures from carbapenem overdose) is exceedingly low in patients on CRRT suggesting that patients are not achieving toxic drug levels.

Nutrition Support
Small studies suggest that amino acid removal with CRRT is robust and, obviously, CRRT dose dependent. The American Society of Enteral Parenteral Nutrition recommends augmented protein/amino acid intake in those on CRRT up to 2-2.5 g/kg/d.[44] Several publications note that vitamin and micronutrient deficiencies are common in patients with CRRT as well and supplements are recommended.[45,46] However, it should be noted that the there is precious little prospective data on vitamin and micronutrient deficiencies in critically ill patients on CRRT and even less regarding whether supplements improve outcomes. That being said, based on small studies, such as by Sgambat and Moudgil,[47] some centers do routinely supplement B complex multivitamins, Vitamin C, copper, and/or carnitine in those on CRRT especially prolonged CRRT.

PRECISION CONTINUOUS RENAL REPLACEMENT THERAPY AND QUALITY MONITORING
Providing high-quality CRRT in an individualized and precise fashion to all patients should be the goal for all CRRT programs. Achieving this laudable goal remains challenging and requires commitment from all stakeholders including at an institutional level. QI and QA do require that we develop systems to monitor current and future performance and search for avenues for improvement which initially requires measuring the current state of the CRRT program (Table 2).[20] Admittedly, developing these reporting mechanisms remains challenging and has, unfortunately, not become easier with the widespread adoption of electronic medical records. Institutional administrative support is required to prioritize CRRT QA and QI.

While ADQI 17[9,20] and we endorse an individualized approach to CRRT dose and fluid removal, there are several aspects of high-quality CRRT that do lend themselves to standardization across a given health system. CRRT modality and anticoagulation are two such aspects. Standardizing CRRT modality and anticoagulation strategy system-wide (especially if using an RCA protocol) allows for a consistency in CRRT circuit setup which supports nursing education and decreases errors by improving accuracy in delivery of a complex procedure. Furthermore, hospital-level decisions regarding which CRRT device to employ may be informed by and/or modify the standard CRRT modality and anticoagulation plans.

Similarly, a standard approach to dialysis vascular access site, depth, and type/size preferences will certainly lead to improved CRRT circuit performance[29] and decrease risk of access-related complications as clinicians (ie, those responsible for insertion) and nursing (those responsible for using and maintaining the access) will benefit from a consistent equipment and standard catheter insertion and care procedures.

Individualization of CRRT therapy is encouraged when determining CRRT dose and fluid removal targets as patients' weight, fluid balance, and clinical conditions inform these decisions and these factors can fluctuate frequently in the critically ill patient and require frequent reassessment and modification. However, this does not absolve the CRRT program of the need to monitor performance through measurable metrics as suggested in Table 2. We cannot just assume that by standardizing CRRT modality, anticoagulation, and access will yield appropriate CRRT circuit function without ongoing monitoring and training. Furthermore, monitoring adherence to standard protocols and understanding reasons for deviations provides ongoing insight into further opportunities for improvement.

CONCLUSION

As the incidence of AKI and AKI requiring RRT continues to increase and that the costs to both the patient and the health system for AKI continue to accelerate, we can only hope that there will be a growing interest by health systems, payors, researchers, and care providers to provide the resources necessary to improve the care of AKI patients in the ICU and after discharge from the ICU.[48,49] Despite vast advances in CRRT device technology, there remains wide variability in practice patterns and suboptimal uptake of best practices by the wider nephrology and critical care community. In general, too few health systems and CRRT programs engage in systematic monitoring of performance for CRRT QA and QI.

While many important questions regarding CRRT remain, there are increasing areas of agreement and consensus based on medical evidence to inform best practice benchmarks especially surrounding CRRT dose, fluid balance, vascular access, and CRRT anticoagulation protocols. In an effort to improve and maximize our patients chances of survival, clinicians and CRRT programs are encouraged to accelerate the adoption of the current best practice as we have outlined and to build programs for ongoing QI.

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