How to prescribe and troubleshoot continuous renal replacement therapy: A case-based review

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Abstract

Continuous renal replacement therapy (CRRT) is the preferred dialysis modality for solute management, acid-base stability, and volume control in critically ill patients with acute kidney injury (AKI) in the intensive care unit (ICU). CRRT offers multiple advantages over conventional hemodialysis in the critically ill population such as greater hemodynamic stability, better fluid management, greater solute control, lower bleeding risk and a more continuous (physiologic) approach of kidney support. Despite its frequent use, several aspects of CRRT delivery are still not fully standardized or do not have solid evidence-based foundations. In this manuscript, we provide a case-based review and recommendations of common scenarios and interventions encountered during the provision of CRRT to critically ill patients. Specific focus is made on initial prescription, CRRT dosing, and adjustments related to severe hyponatremia management, concomitant extracorporeal membrane oxygenation support, dialysis catheter placement, use of regional citrate anticoagulation and antibiotic dosing. This case-driven simulation is made as the clinical status of the patient evolves and is based on step-wise decisions made during the care of this patient according to specific patient's needs and the logistics available at the corresponding institution.
Introduction

Acute kidney injury (AKI) affects up to half of critically ill patients admitted to intensive care units (ICU).\textsuperscript{1,2} In patients with AKI and hemodynamic instability, continuous renal replacement therapy (CRRT) is the preferred dialysis modality for solute management, acid-base stability, and volume control. ICU mortality in this vulnerable population is as high as 75\% but kidney recovery occurs in up to two-thirds of survivors.\textsuperscript{1-3} Several factors contribute to these deleterious outcomes, including overall severity of acute illness, multi-organ failure, or the pathophysiologic effects of AKI itself.\textsuperscript{4,5}

CRRT is a lifesaving RRT modality for critically ill patients with AKI.\textsuperscript{6} CRRT removes toxins and excessive fluid, and replenishes substances that are needed. It offers multiple advantages over conventional hemodialysis in the critically ill population such as greater hemodynamic stability, better fluid management, greater solute control, lower bleeding risk and a more continuous (physiologic) approach of kidney support. In the recent years technology for the provision of CRRT to critically ill patients has evolved and some standardization in practice has been achieved, such as the consensus on delivered effluent flow rates of 20-25 ml/kg/h\textsuperscript{7}; however, several aspects of CRRT delivery are still not fully standardized or do not have solid evidence-based foundations.\textsuperscript{8} Therefore there is wide heterogeneity in clinical practice for the provision of CRRT and in some cases, suboptimal care for patients.\textsuperscript{9,10}

In this manuscript, we provide a case-based review and recommendations of common scenarios encountered during the provision of CRRT to critically ill patients, with focus on initial prescription and iterative adjustments as the case evolves which somehow simulates real-time scenarios encountered frequently at the bedside.
Case Vignette

LC is a 68-year-old woman (weight prior to hospitalization 120 kg) with past medical history of hypertension, coronary artery disease status post percutaneous coronary intervention, and gastroesophageal reflux who was transferred to a tertiary care center for extracorporeal membrane oxygenation (ECMO) consideration after being treated for acute respiratory failure at an outside hospital for 7 days. Two weeks prior to admission, she developed upper respiratory symptoms and was prescribed an antibiotic, which she took without improvement. At the outside hospital, she required intubation and mechanical ventilation and had worsening hypoxia despite antibiotics, steroids, diuretics, and inhaled epoprostenol, prompting her transfer for ECMO support. She had a CT scan with intravenous contrast prior transfer that showed bilateral ground glass opacities. Nephrology was consulted 24 hours after ECMO cannulation for oliguric AKI.

At time of consultation, she was intubated, mechanically ventilated, on VV-ECMO and systemic heparin. She was on a norepinephrine infusion and treated with azithromycin, piperacillin-tazobactam, vancomycin, and oseltamivir. She had been anuric for the past 12 hours despite high dose diuretic challenge. Admission sodium was 130 mEq/L and had been slowly drifting down over hospital course. See Table 1 for summary of clinical data.

Scenario # 1: Initial CRRT prescription

LC is critically ill with multi-organ failure including respiratory failure, shock, and anuric AKI. In addition, evolving fluid overload at a level consistently associated with mortality (>10%)\textsuperscript{11-14} and biochemical abnormalities such as metabolic acidosis prompt CRRT initiation.\textsuperscript{15} In the case of this patient, CRRT will be added in tandem to the ECMO circuit so there will be no need to place an additional catheter for CRRT. Beyond access, the initial considerations when prescribing CRRT include:
1- **What CRRT modality?** Continuous veno-venous hemofiltration (CVVH – convective clearance) vs. continuous veno-venous hemodialfiltration (CVVHD – mostly diffusion) vs. continuous veno-venous hemodiafiltration (CVVHDF – diffusion and convection). Despite diffusion and convection being distinct dialysis physiological processes ([Figure 1](#)), in terms of hard clinical outcomes (e.g., mortality or kidney recovery), there is no evidence to support one modality as more beneficial over the other for the overall CRRT population. Therefore, one should decide according to the available protocols, expertise, and logistics of the specific hospital in which CRRT is being delivered. *For our patient, LC, we will prescribe CVVHDF.*

2- **What effluent dose?** The effluent fluid rate is a surrogate of solute clearance provided by CRRT and is reported in milliliters per hour and adjusted by the patient’s weight in kilograms (ml/kg/hr). When determining CRRT dose, it is recommended to use the most updated patient weight (at the time of prescribing CRRT) as it theoretically accommodates acute increases in volume of distribution due to fluid overload. The recommended average delivered effluent dose is 20 to 25 ml/kg/hr for patients with AKI requiring CRRT based on data from the ATN and RENAL trials. However, one should recognize that the prescribed dose is not always delivered due to multiple patient-related reasons such as off-room diagnostic procedures, interventions, or CRRT-related downtime due to replacing filters, bags, tubing, or catheter malfunction problems. Therefore, a patient on CRRT requires an iterative evaluation of goals of care (solute and volume control) to adjust CRRT dose and prescription as needed. When prescribing high dose CRRT (>30 ml/kg/hr), careful monitoring of electrolyte disturbances (e.g., hypophosphatemia), nutritional deficits, and drug dosing (e.g., antibiotics) is necessary to prevent complications. *For our patient, LC, we will prescribe an effluent dose of ~30 ml/kg/hr (4000 ml/hr) accommodating for an*
expected 5-10% downtime and the pre-dilution factor. Table 2 summarizes similar effluent dose under different CRRT modalities, including the adjustment for pre-dilution if needed.

3- **What net UF?** Due to objective data of fluid overload in our patient (e.g., cumulative fluid balance, CT chest, and respiratory status), tailored fluid removal is recommended to improve the chance of patient’s survival and organ recovery. However, data on the rate of fluid removal are mostly observational and likely confounded by indication.\textsuperscript{21-23} Given the lack of clinical trials addressing this important aspect of the CRRT prescription, as well as the lack of fully validated methods of predicting and assessing fluid removal tolerance and need, significant heterogeneity in practice exists.\textsuperscript{24} Although the prescription of net ultrafiltration (net UF or UF\textsubscript{net}) is highly dynamic and commonly individualized, it is recommended not to exceed 1.5-2.0 ml/kg/hr of net UF as a general rule. *For our patient, LC, we will prescribe a net ultrafiltration rate to achieve a goal of negative 50 ml/hr until she is re-assessed later in the treatment course.*

4- **What blood flow?** A minimum blood flow of 150 ml/min maximizes clearance for pre-filter replacement fluid rates of up to 1500 ml/hr and dialysis fluid rates of up to 3600 ml/hr.\textsuperscript{25,26} *For our patient, LC, we will prescribe a blood flow of 200 ml/min.*

5- **What anticoagulation?** Our patient is currently on systemic anticoagulation with heparin\textsuperscript{27} at therapeutic levels prescribed for veno-venous ECMO, therefore we will not use regional citrate anticoagulation (RCA)\textsuperscript{28} at this time for CRRT.

6- **Summary of CRRT prescription (Table 3):** CVVHDF, blood flow rate 200 ml/min, dialysate fluid rate 2000 ml/hr, pre-blood pump (pre-filter replacement fluid) 1000 ml/hr, post-filter replacement fluid 1000 ml/hr, net ultrafiltration goal of net negative 50 ml/hr, solutions composition: sodium 140 mEq/L, potassium 4 mEq/L, chloride 113 mEq/L, calcium 2.5 mEq/L, lactate 3 mEq/L, bicarbonate 32 mEq/L, glucose 110 mg/dL, osmolarity 300 mOsm/L.
Scenario # 2: Addressing rapid correction of serum sodium in patients on CRRT

Patients with chronic hyponatremia and kidney failure who require RRT pose a special therapeutic challenge. Rapid correction of serum sodium concentration places these patients at risk for osmotic demyelination syndrome.\textsuperscript{29,30} Although serum sodium concentration increase with CRRT is less rapid than hemodialysis, it can far exceed recommended correction limits (≤ 8 mEq/L) if factors affecting sodium change are ignored.\textsuperscript{31} Therefore, the CRRT prescription may need to be individualized based on the duration and/or severity of hyponatremia if the anticipated change exceeds the recommended therapeutic targets.

1) What is the expected rise in serum sodium at 24 hours with the above CRRT prescription?

Sodium kinetic models have been shown to predict end-dialysis plasma water sodium concentration.\textsuperscript{32} Some reported equations are complex and may be prohibitive for daily use. Instead, a single-pool, fixed-volume, sodium kinetic equation may be used in a manner similar to urea kinetics for the quantification of sodium changes during CRRT (Figure 2). The patient’s serum sodium at 24 hours from CRRT initiation can be estimated using equation 1 in patients with negligible non-isotonic fluid gains or losses.\textsuperscript{31,33} Bedside application of the single-pool, fixed-volume sodium kinetic model has been reported by several groups since first described by Yessayan and colleagues.\textsuperscript{31,34,35}

\[
N_a(t) = N_a_0 + (N_{a_{dial/RF}} - N_a_0) \times \left(1 - e^{-\frac{D t}{V}}\right)
\]

where $N_{a_{dial/RF}}$ is the dialysate/replacement fluid sodium concentration, $N_a_0$ is the initial serum sodium concentration, $D$ is the effective sodium dialysance, which is nearly equal to effective urea clearance, $t$ is the time elapsed since CRRT initiation and $V$ is the total body water volume. An estimate of $V$ can be calculated using the Watson formula applied to the patient’s euvolemic weight (prior to hospitalization) and adding to this any estimated edema volume. In our case, the $N_a_0$ is 119 mEq/L, $N_{a_{dial/RF}}$ 140 mEq/L, $D$ is roughly equal to the sum of dialysate and
replacement fluid rates (4 L/hr), V is ~60 L (45 L of total body water estimated through the Watson formula applied to her dry weight and 15 L of edema). By applying the above sodium kinetic model and substituting for patient and CRRT prescription variables, the predicted serum sodium concentration at 24 hours with the above prescription will be ~136 mEq/L and thus will exceed the recommended limits of correction:

\[
Na(t) = 119 + (140 - 119) \times \left(1 - e^{-\frac{4 \times 24}{60}}\right) = 136 \text{ mEq/L}
\]

2) **What strategies could be used to avoid serum sodium overcorrection and maintain the serum sodium within a desired range?**

Strategies to avoid overly rapid correction of chronic hyponatremia include using hyponatremic CRRT solutions, using separate hypotonic infusions, and regulating the overall and hourly clearance delivered by CRRT using kinetic principles.\(^{33}\) In those with concomitant clinically significant abnormalities of other solutes (e.g., hyperkalemia, metabolic acidosis), decreasing the CRRT dose should be avoided. Although these strategies are helpful in predicting the rate of change in serum sodium level, frequent laboratory confirmation is still advised. Clinical factors that affect serum sodium may change over time, and readjustment of the approach may be necessary.\(^{33}\)

3) **If you chose to use hyponatremic CRRT solutions as your strategy, what sodium concentration in the CRRT solutions should be used to maintain the patient’s serum sodium within a desired range of ≤8 mEq/L?**

Commercial hyponatremic CRRT solutions are lacking. Therefore, commercially available CRRT fluids need to be diluted with free water to achieve the desired sodium concentration. This approach can be adopted at institutions with adequate pharmaceutical support. A stepwise switch every 24 hours to CRRT solutions with higher sodium concentration than the patient’s current serum sodium can be considered. The CRRT solution sodium concentration needed to
maintain serum sodium within desired limits of correction can be estimated using the following formula.\(^\text{31}\)

\[
(2) \quad \text{CRRT solution } [Na^+] = \frac{\text{desired } \Delta \text{ serum } [Na^+]}{\left(1 - e^{-\frac{D \times 24 \text{ hr}}{V}}\right)} + \text{ initial serum } [Na^+]
\]

For a desired change of 8 mEq/L at 24 hours, and an initial serum sodium of 119 mEq/L and sodium dialysance of 4L/hr, a CRRT solution with sodium concentration of 129 mEq/L will be required. The approach of using solutions with successively higher sodium concentration may be reliable in avoiding any overcorrection in serum sodium due to CRRT. The dilution can be achieved by injecting free water into the CRRT solution bag or exchanging a volume of CRRT solution with an equivalent volume of water. Both dilution methods have been described in detail previously.\(^\text{31}\) **Tables 4 and 5** demonstrate the effect of adding different volumes of sterile water to a 5 L dialysate/replacement fluid bag or exchanging different volumes of a 5 L dialysate/replacement fluid bag with sterile water on sodium and other electrolyte concentrations.

**4) Your hospital does not have adequate pharmaceutical support to dilute the CRRT solutions. At what rate should 5% dextrose water solution be administered to maintain the patient’s serum sodium within a desired range of ≤8 mEq/L?**

Infusing electrolyte free water as a 5% dextrose water (D5W) solution into the patient or into the return limb (venous return port) of the CRRT blood circuit is another approach to decrease the rate of correction of serum sodium. Safety concerns with this technique include the theoretical risk of worsening hyponatremia with filter clotting and rapid correction of sodium if consecutive D5W bags run out while the CRRT continues. The D5W infusion rate to maintain serum sodium below a desired target level could be estimated using the following formula:\(^\text{33}\)

\[
3) \quad \text{D5W rate} = \frac{\text{CRRT solution } [Na^+] - \text{ target serum } [Na^+]}{\text{CRRT solution } [Na^+]} \times \text{ desired clearance}
\]
For example, in this patient with initial serum sodium of 119 mEq/L, CRRT solution [Na+] of 140 mEq/L, effluent rate or clearance of 4.0 L/hr, the D5W infusion should be administered at a rate 0.314 L/hr (314 mL/hr) in order to keep the serum sodium concentration at or below 127 mEq/L. The net UF setting should be increased by the rate of the D5W infusion (314 ml/hr). In the case of our patient, we will dilute the CRRT solutions (dialysate and replacement fluid) to an initial sodium concentration of 129 mEq/L in the first 24 hours with anticipated successive adjustment of sodium concentration in CRRT solutions according to the most current patient’s serum sodium in the following 24 hours.

**Scenario # 3: Considerations of ECMO-CRRT in tandem connections**

Use of ECMO has increased over the last decade as techniques, technology, and protocols have advanced. ECMO may be considered for patients with severe acute hypoxemic and/or hypercapnic respiratory failure who fail conventional mechanical ventilation. The most common ECMO modality utilized for respiratory failure is veno-venous support. Less commonly, veno-arterial ECMO or a hybrid method of support may be utilized. Several studies have been performed over the last decade examining ECMO for respiratory failure, with mixed results. Two prospective, multi-center trials of ECMO for severe respiratory failure or ARDS (CESAR and EOLIA) showed: (1) a survival benefit with early referral to a tertiary ECMO center; and (2) no difference in 60-day mortality when ECMO was compared to conventional mechanical ventilation with ECMO rescue.

For patients requiring both CRRT and ECMO, the CRRT machine may be connected directly to the ECMO circuit, or CRRT and ECMO may be performed independently (Figure 3). There are advantages and disadvantages to both options, but it is important to note that connecting CRRT with ECMO is not currently a U.S. Food and Drug Administration (FDA)-approved strategy. Combining CRRT with the ECMO circuit avoids additional catheter-associated complications, including risks associated with catheter insertion, infection, and mechanical complications.
However, combined CRRT and ECMO may result in abnormal pressures in the ECMO circuit (low-pressure alarms when the CRRT drainage or return access is placed before the blood pump, and high-pressure alarms when placed after the blood pump). High pressures in the CRRT circuit may result in treatment interruptions or stop the circuit. As a result, alarm adjustments may be necessary on some CRRT devices. Newer generation CRRT devices can be programmed to account for pressure changes when connecting to the ECMO circuit or automatically recognize an ECMO connection. There may be other complications related to combining CRRT with ECMO, including infection, clotting, air embolism, thromboembolism, flow limitations, and hemolysis. Whether connecting CRRT to the ECMO circuit ultimately reduces complications, as compared to providing each independently, is yet to be examined in a prospective manner.

Strategies for combining CRRT and ECMO have previously been described. An in-line hemofilter or CRRT circuit may be integrated into the ECMO circuit. The inlet limb (access port) of a hemofilter can be connected after the blood pump, and the outlet limb (return port) is typically connected prior to the membrane oxygenator. This approach is less costly compared to CRRT, but disadvantages include a lack of pressure alarms and poor control of net ultrafiltration. A stopcock or similar instrument to restrict blood flow can be added but may increase the risk of thrombosis or hemolysis. Alternatively, the CRRT and ECMO circuits can be joined together, thereby allowing for circuit pressure monitoring and better net ultrafiltration control. Depending on the ECMO device utilized, the inflow to the CRRT device can be placed before or after the blood pump, or in some cases between the blood pump and oxygenator when these components are separated. Blood from the CRRT device is typically returned to the ECMO circuit before the membrane oxygenator to reduce the risk of systemic emboli. Extracorporeal carbon dioxide removal can also be achieved by inserting a membrane oxygenator, rather than full ECMO support, into the CRRT circuit. This technique has been
used to permit protective lung ventilation in severe ARDS and to improve acidosis in hypercapnic respiratory failure.

For our patient, a Maquet Cardiohelp was used for ECMO support. In this device, the blood pump and membrane oxygenator are integrated. To combine CRRT with ECMO, the CRRT inlet line can be connected to an access port in the ECMO circuit after the membrane oxygenator. The CRRT outlet line is connected to an access port proximal to the blood pump / oxygenator. In addition to monitoring circuit pressures, several parameters should be followed when CRRT is connected with ECMO. Anticoagulation can prolong circuit life and can be monitored by activated clotting time (ACT), anti-Xa level, coagulation studies (partial thromboplastin time and prothrombin time), or thromboelastography (TEG). Plasma free hemoglobin levels can be monitored for hemolysis. Additional laboratory studies, including serum chemistries, complete blood count, platelet count, fibrinogen level, liver function profile, antithrombin level, and arterial blood gases are monitored to assess patient status and circuit performance. RCA can be used with or without systemic heparin when CRRT is combined with ECMO.

Scenario # 4: Considerations about dialysis catheters for CRRT

LC was successfully decannulated from veno-venous ECMO and her overall clinical status improved. However, she remains anuric without signs of kidney recovery at present. The nephrology team was called to determine best practices for CRRT dialysis access placement. It is critical to recognize that a functional vascular access is necessary for CRRT delivery, particularly because adequate blood flow is required to achieve CRRT goals. The latter is more relevant when prescribing convection (e.g., CVVH or CVVHDF) due to its effect on filtration fraction with post-filter mode and the relationship between blood flow and clearance when using pre-filter mode (6:1 blood flow rate to pre-filter replacement fluid ratio to maximize clearance). Furthermore, infection control maneuvers should be routinely employed to minimize catheter-related infections in patients on CRRT.
Theoretically, the optimal dialysis catheter should provide adequate blood flow (low resistance and low recirculation) during a long lifespan (~14 days for internal jugular catheters and ~7-10 days for femoral catheters) and with low rate of complications (infection, thrombosis, mechanical). Current KDIGO guidelines recommend: 1) use of a non-tunneled temporary dialysis catheter; 2) insertion of the catheter in the right internal jugular (RIJ) as first option, femoral site as second option, and left internal jugular (LIJ) as third option, and to avoid subclavian insertions; 3) use of a catheter with length of: 12-15 cm for RIJ, 15-20 cm for LIJ, and 19-24 cm for femoral sites, with a diameter of 11.5-14 F; and 4) location of the catheter tip in the mid-atrium with arterial lumen facing the mediastinum but not allowing the catheter tip to touch the atrium floor. A summary of characteristics, monitoring and complications of dialysis catheters for CRRT is provided in Table 6.

As blood flow is susceptible to low refill rates, low stroke volume, circuit backflow, and catheter malposition or malfunction, distinct levels of high negative arterial (inflow) pressures or high positive venous (outflow) pressures are typically encountered during CRRT. Therefore, continuous monitoring of pressure parameters on flowsheets and early recognition of patterns suggesting catheter dysfunction are recommended, starting with the bedside ICU nurse and rounding ICU teams. If these alarms are not quickly recognized and interventions instituted (e.g., catheter change or repositioning), blood stagnation in the circuit occurs, resulting in clotting, circuit loss, and treatment interruptions.

Our patient, LC, underwent successful insertion of a RIJ dialysis catheter to continue CRRT.

Scenario # 5: Considerations about use of regional citrate anticoagulation for CRRT

Clotting of the hemofilter or CRRT circuit can markedly decrease the effectiveness of CRRT. Membrane clotting can be detected by closely monitoring the transmembrane pressure (TMP) and filter pressure drop. The TMP is the pressure exerted on the filter membrane and reflects the pressure difference between the fluid and blood compartments of the filter. During
treatment, membrane permeability decreases due to protein coating on the blood side and causes “clogging” of the filter, resulting in an increase in TMP. The filter pressure drop is the pressure reduction that occurs as blood flows through the filter. Micro-clotting in the hollow fibers causes the pressure drop to increase over time. A high TMP without as much of a concurrent rise in the filter pressure drop is more often due to clogging of the filter, while a high TMP along with a high filter pressure drop indicates clotting of the hemofilter. With filter clogging, the circuit can be salvaged by methods to decrease the filtration fraction or by adding anticoagulation; but with filter clotting, the hemofilter must be replaced.

The filtration fraction is the ratio of ultrafiltration rate to plasma water flow rate and represents the fraction of plasma which is removed from the blood during hemofiltration. Maintaining a filtration fraction less than 20 to 25% can prolong hemofilter patency. When blood flow, hematocrit, and total effluent flow rates are held constant, purely convective modes of therapy, such as CVVH, always have a higher filtration fraction compared with diffusive therapies (e.g., CVVHD). Hemofilter survival can be prolonged by using higher blood flow rates and pre-dilution replacement fluid to reduce the filtration fraction in convective CRRT. Despite these measures to improve filter survival, anticoagulation is often required for CRRT.

The KDIGO guidelines for CRRT anticoagulation recommend that RCA be preferentially used over heparin. Citrate is infused into the blood at the beginning of the extracorporeal circuit and provides anticoagulation by chelating ionized calcium (iCa²⁺). Optimal regional anticoagulation occurs when the iCa²⁺ concentration in the extracorporeal circuit is below 0.35 mmol/L, which corresponds to approximately 3 to 4 mmol of citrate per liter of blood. A portion of the calcium-citrate complex is lost across the hemofilter while the rest enters the systemic circulation where citrate is metabolized by the liver to bicarbonate and calcium is released into the circulation. Calcium is infused back to the patient to replace the calcium lost across the hemofilter.
LC’s initial CRRT prescription without anticoagulation results in clotting of the filter despite an appropriate dialysis access and filtration fraction <25%. We will therefore prescribe RCA. The decision of using citrate\textsuperscript{28} or other form of anticoagulation (systemic heparin\textsuperscript{27}) should be customized according to local expertise and available monitoring protocols. In a meta-analysis including 14 randomized controlled trials (1134 patients on CRRT), there was no difference in mortality when providing CRRT with RCA vs. systemic heparin. However, there was less risk of bleeding and prolonged filter life span (the latter specifically when using CVVH) with RCA vs. systemic heparin. There were also more episodes of hypocalcemia in the RCA group.\textsuperscript{58} Therefore, careful calcium monitoring (e.g., patient’s total calcium and ionized calcium) is mandatory when using CRRT with RCA.\textsuperscript{59}

Ensuring adequate citrate anticoagulation in the circuit can be done by either measuring the post-filter iCa\textsuperscript{++} and titrating the citrate rate to maintain the circuit iCa\textsuperscript{++} <0.35 mmol/L or fixing the citrate and blood flow rate to achieve a concentration of 3 to 4 mmol/L in the circuit without measurement of post-filter iCa\textsuperscript{++} levels. Table 7 lists the fixed citrate rate needed for various blood flow rates to maintain a citrate concentration of 3 mmol/L in the circuit using the most commonly used citrate solutions, 4% Trisodium Citrate (TSC) and 2.2% Anticoagulant Dextrose-A (ACD-A).

LC is not allergic to citrate and despite evidence of coagulopathy, mild elevation in AST and ALT, and thrombocytopenia; we will prescribe citrate as we can carefully monitor the RCA protocol in the ICU. For our patient, LC, we will prescribe citrate in the form of ACD-A (3% combined trisodium citrate 2.2g/100mL and citric acid 0.73g/100mL; contains glucose 2.5%; total amount of citrate: 10-11 mmol/100mL) at a rate of 250 ml/hr (1.5 times blood flow of 170 ml/min –decreased from 200 ml/min) plus a continuous infusion of calcium chloride or equivalent (20 g of calcium chloride in 1 liter of 0.9% sodium chloride or 10 g of calcium chloride
in 0.5 liter of 0.9% sodium chloride =20 mg/mL or 0.136 mmol/ml of elemental calcium) at 25 ml/hr to maintain the systemic \( iCa^{++} \) within normal range.

Scenario # 6: Recognizing complications of regional citrate anticoagulation during CRRT

LC initially does well with RCA with no further clotting issues. However, her clinical condition deteriorates with new sepsis, and she develops worsening hypotension with a lactic acid level of 10 mmol/L. She now has an increasing anion gap, a decreasing serum bicarbonate concentration, and requires an escalating calcium infusion to maintain \( iCa^{++} \) in a normal range. Because of the concern for citrate accumulation, RCA is stopped. Common metabolic signs of citrate accumulation/toxicity are described in Table 8.\(^60\)

Patients with severe shock liver and lactic acidosis may not be able to metabolize citrate.\(^61,62\) Citrate toxicity is characterized by low systemic serum \( iCa^{++} \) level, elevated serum total calcium level, total calcium to systemic \( iCa^{++} \) ratio >2.5, increasing anion gap acidosis, and escalating calcium infusion requirements. Citrate accumulation can be managed by decreasing the blood flow and corresponding citrate infusion rate, increasing the effluent rate, decreasing the target citrate concentration in the hemofilter, or changing to an alternate form of anticoagulation. In order to minimize the systemic effects of citrate, we recommend a blood flow rate between 100 to 180 ml/min.

Besides citrate accumulation, metabolic acidosis can also result if the amount of citrate delivered is insufficient to adequately buffer the acidosis. In this situation, there is no evidence of citrate accumulation and the total calcium to systemic \( iCa^{++} \) ratio remains less than 2.5. This can be corrected by increasing the blood flow, thereby requiring an obligatory increase in the citrate rate to achieve the target \( iCa^{++} \) in the filter, or by decreasing the effluent rate, resulting in less citrate lost across the hemofilter. Both methods result in the delivery of more citrate to the patient, and therefore, more bicarbonate generation when citrate is metabolized.
**Scenario # 7: Considerations about antibiotic dosing during CRRT**

Medications with primary renal elimination (>25%) will likely be removed through CRRT. Volume of distribution (Vd), protein binding and molecular weight (MW) are the three most important physiochemical determinants of removal by CRRT. A drug with a low Vd (<2L/kg), low protein binding (<80%) and a MW smaller than the pore size of the CRRT filter (typically <20,000 daltons) will be removed through convection. Convective clearance has a positive linear relationship to replacement fluid rate. An ultrafiltration rate of 2.5L/hr provides a creatinine clearance of 40ml/min (2500/60 = 40ml/min); for every 0.5L/hr increase in convection, expect the clearance to increase by 10ml/min. This provides an estimated GFR to use for medication dosing, recalling pre-filter replacement fluids can reduce convective clearance up to 20%.

Diffusion based modalities differ in solute removal as diffusion passively and preferentially removes drugs with a small MW (<500 daltons), such as beta-lactam antibiotics and antiepileptics. Clearance for larger molecules becomes inversely related to MW. Thus for middle-sized molecules such as vancomycin or daptomycin, the diffusive clearance will be lower than an equivalent dose of convective clearance.

Because total body clearance (CLTB) is a factor of both clearance and Vd, volume status assessment is vital, at CRRT initiation and throughout therapy. One should recognize that many patients are volume overloaded prior to CRRT initiation. Loading doses of hydrophilic antibiotics are paramount to optimize pharmacokinetic/pharmacodynamic parameters. Conversely, as euvolemia is achieved over the course of therapy, CLTB will decrease. In addition, the convective and diffusive clearance of drugs decreases over the course of therapy. Taken together, there is high potential for medication accumulation to occur after 48 hours of CRRT, which has been observed in the literature.

Beta lactam medications (piperacillin-tazobactam) should be dosed aggressively (full, unadjusted doses) with prolonged or continuous infusions for at least the first 72 hours of
therapy for any patient on CRRT with >2L/hr of effluent dose.\textsuperscript{69,71} Vancomycin should be dosed according to the estimated clearance provided by the CRRT effluent dose, recalling convective clearance is more effective for larger molecules than diffusive clearance, and pre-dilution fluid reduces solute clearance. Therapeutic drug monitoring (TDM) of all antimicrobials should occur when available. For our patient, LC, the recommended initial doses of antibiotics include: piperacillin-tazobactam 4.5 grams every 6 hours, infused over 3 hours; vancomycin loading dose of 25 mg/kg (3250 mg) to account for increased Vd due to body habitus, volume overload and critical illness, followed by 1750 mg (~14mg/kg) every 24h, as our CRRT prescription provides an eGFR of 40-50ml/min for vancomycin, accounting for dilution factor, and diffusive clearance. TDM should be done at steady-state. Also recommended is oseltamivir 75mg twice daily and azithromycin 500mg every 24h. Azithromycin has primary hepatic clearance and no renal dosage recommendations, thus can be given at full unadjusted doses, per indication. Specific considerations and rationale of medication dosing are provided in Table 9.

Conclusions

CRRT is a method of dialysis support commonly utilized in critically ill patients with AKI. However, several aspects of CRRT delivery are still not fully standardized and do not have solid evidence-based foundations. In this manuscript, we discussed the stepwise decision making process made for the care of a specific patient according to specific clinical needs and the logistics available at the corresponding institution. We provided a framework for evidence and considerations in relation to initial prescription, CRRT dosing, and adjustments related to severe hyponatremia management, concomitant ECMO support, dialysis catheter placement, use of regional citrate anticoagulation and antibiotic dosing. This CRRT simulation highlights the importance of iterative assessment and adjustments of goals of therapy for patients on CRRT, as well as the need for effective communication among all multidisciplinary stakeholders involved in the care of this debilitated ICU population.
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Healthcare. A. Tolwani reports a patent to 0.5% CITRATE SOLUTION issued, licensed, and
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Author Contributions
J. Neyra: Conceptualization; Supervision; Writing - original draft
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M. Thompson Bastin: Conceptualization; Writing - original draft
K. Wille: Conceptualization; Writing - original draft
A. Tolwani: Conceptualization; Methodology; Supervision; Writing - original draft
References


**Table 1: Summary of patient’s clinical data**

Fluid overload from ICU admission to OSH to CRRT initiation: +15 liters >10% from prior to hospitalization (current weight 135 kg)

No known drug allergies

**ECMO Assessment:** VV-ECMO  
**ECMO type:** Maquet Cardiohelp  
**Clots on oxygenator:** Not present  
**Quality of oxygenator:** Good

**ECMO Total Flow:** 6.21  
**RPM:** 4,600  
**ECMO Sweep Gas Flow:** 5 L/min  
**ECMO FiO₂:** 100 %  
**ECMO Pre-oxy Pressure:** 253 mmHg  
**ECMO Post-oxy Pressure:** 207 mmHg  
**ECMO Delta Pressure:** 46

**Ventilator Settings:**  
**Minute Ventilation** 1.02 L/min  
**Vent Rate Set** 10 br/min  
**I: E Ratio** 1:2.00  
**Vent Mode** SIMV  
**O2 Delivery Device** Ventilator  
**Volume Exchange** 102 mL  
**Spontaneous Rate** 5 br/min  
**Peak Airway Pressure** 34 cmH₂O  
**Plateau Pressure** 29 cmH₂O  
**FiO₂** 100 %  
**Pressure Set** 22 cmH₂O  
**PEEP/CPAP Set** 12 cmH₂O  
**PS Level Set** 20 cmH₂O

**Labs at Consultation:**  
**Sodium (mEq/L)** 119  
**Potassium (mEq/L)** 5.4  
**Chloride (mEq/L)** 96  
**Bicarbonate (mEq/L)** 18  
**Blood urea nitrogen (mg/dL)** 64  
**Creatinine (mg/dL)** 3.0  
**Calcium (mg/dL)** 9.9  
**Albumin (g/dL)** 3.1  
**Lactate (mMol/L)** 2.5  
**AST/ALT (Units/L)** 78 / 53 (nl: 12-39 / 7-52)  
**PT/INR/PTT (s)** 33/3.14/48  
**Arterial blood gas** 7.36/38/20/50  
**White blood cell (103 cells/mm³)** 15  
**Hemoglobin (g/dL)** 10.1  
**Hematocrit (%)** 30%  
**Platelet (103 cells/mm³)** 61  
**Total Bilirubin (mg/dL)** 2.5 (nl: 0.3-1.4)  
**Plasma haptoglobin (mg/dL)** 110  
**LDH (U/L)** 987  
**Urine microscopy** Multiple granular casts  
**Vasopressor requirement** Norepinephrine
Table 2: Simulation of effluent dosing under different CRRT modalities in our patient assuming 100 ml/hr of fluid removal rate is required to achieve a net ultrafiltration goal of net negative 50 ml/hr as prescribed

<table>
<thead>
<tr>
<th>CRRT Modality</th>
<th>Ultrafiltration Rate</th>
<th>Dialysate Rate</th>
<th>Fluid Removal Rate</th>
<th>Effluent Dose</th>
<th>Pre-Dilution Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVVHDF</td>
<td>2000 ml/hr + 2000 ml/hr + 100 ml/hr</td>
<td>30.4 ml/kg/hr</td>
<td>30.4 ml/kg/hr</td>
<td>26.8 ml/kg/hr</td>
<td>(30.4 \times 0.88)</td>
</tr>
<tr>
<td>CVVH</td>
<td>4000 ml/hr + 100 ml/hr</td>
<td>30.4 ml/kg/hr</td>
<td>30.4 ml/kg/hr</td>
<td>23.7 ml/kg/hr</td>
<td>(30.4 \times 0.78)</td>
</tr>
<tr>
<td>CVVHD</td>
<td>4000 ml/hr + 100 ml/hr</td>
<td>30.4 ml/kg/hr</td>
<td>30.4 ml/kg/hr</td>
<td>30.4 ml/kg/hr</td>
<td>30.4 ml/kg/hr</td>
</tr>
</tbody>
</table>

\*Total ultrafiltration rate (ml/hr) = pre-blood pump or pre-filter replacement fluid rate + post-filter replacement fluid rate

\#Dilution factor for pre-dilution: Plasma flow rate (ml/hr) / [Plasma flow rate (ml/hr) + pre-filter replacement fluid rate (ml/hr)] = 0.88 for our patient (1000 ml/hr pre-filter replacement fluid in CVVHDF) and 0.78 (assuming 2000 ml/hr of pre-filter replacement fluid in CVVH)

Plasma flow rate (ml/hr) = blood flow rate (ml/min) x 60 (min/hr) x (1-HCT); where HCT is the current hematocrit of the patient (HCT 30% for the case of our patient)
### Table 3: Summary of initial CRRT prescription

<table>
<thead>
<tr>
<th>Modality</th>
<th>CVVHDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filter type</td>
<td>HF1400 (per protocol)</td>
</tr>
<tr>
<td>Dose</td>
<td>30 ml/kg/hr</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Systemic heparin per ECMO protocol</td>
</tr>
<tr>
<td>Blood flow</td>
<td>200 ml/min</td>
</tr>
<tr>
<td>Pre-blood pump</td>
<td>4K/2.5Ca *140Na</td>
</tr>
<tr>
<td>Pre-blood pump rate</td>
<td>1000 ml/hr</td>
</tr>
<tr>
<td>Dialysis fluid</td>
<td>4K/2.5Ca *140Na</td>
</tr>
<tr>
<td>Dialysis fluid rate</td>
<td>2000 ml/hr</td>
</tr>
<tr>
<td>Replacement fluid (post)</td>
<td>4K/2.5Ca *140Na</td>
</tr>
<tr>
<td>Replacement fluid (post)</td>
<td>1000 ml/hr</td>
</tr>
<tr>
<td>Net UF goal</td>
<td>Net negative 50 ml/hr</td>
</tr>
<tr>
<td>Calcium chloride rate</td>
<td>none</td>
</tr>
</tbody>
</table>
Table 4. Effect of adding different volumes of sterile water to a 5 L dialysate/replacement fluid bag (NxStage PureFlow dialysate solutions RFP 401)

<table>
<thead>
<tr>
<th>Volume added (ml)</th>
<th>Sodium final (mEq/L)</th>
<th>Potassium final (mEq/L)</th>
<th>Bicarbonate final (mEq/L)</th>
<th>Calcium final (mEq/L)</th>
<th>Magnesium final (mEq/L)</th>
<th>Chloride final (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>140.00</td>
<td>4.00</td>
<td>34.00</td>
<td>3.00</td>
<td>1.00</td>
<td>113.00</td>
</tr>
<tr>
<td>250</td>
<td>133.33</td>
<td>3.81</td>
<td>32.38</td>
<td>2.86</td>
<td>0.95</td>
<td>107.62</td>
</tr>
<tr>
<td>429</td>
<td>128.94</td>
<td>3.68</td>
<td>31.31</td>
<td>2.76</td>
<td>0.92</td>
<td>104.07</td>
</tr>
<tr>
<td>500</td>
<td>127.27</td>
<td>3.64</td>
<td>30.91</td>
<td>2.73</td>
<td>0.91</td>
<td>102.73</td>
</tr>
<tr>
<td>713</td>
<td>122.53</td>
<td>3.50</td>
<td>29.76</td>
<td>2.63</td>
<td>0.88</td>
<td>98.90</td>
</tr>
<tr>
<td>750</td>
<td>121.74</td>
<td>3.48</td>
<td>29.57</td>
<td>2.61</td>
<td>0.87</td>
<td>98.26</td>
</tr>
<tr>
<td>1000</td>
<td>116.67</td>
<td>3.33</td>
<td>28.33</td>
<td>2.50</td>
<td>0.83</td>
<td>94.17</td>
</tr>
<tr>
<td>1250</td>
<td>112.00</td>
<td>3.20</td>
<td>27.20</td>
<td>2.40</td>
<td>0.80</td>
<td>90.40</td>
</tr>
</tbody>
</table>

This table was published in American Journal of Kidney Disease, Vol 64, Yessayan et al, Treatment of severe hyponatremia in patients with kidney failure: role of continuous venovenous hemofiltration with low-sodium replacement fluid, 305-310, Copyright Elsevier (2014).
Table 5. Effect of exchanging different volumes of a 5 L dialysate/replacement fluid bag with sterile water (NxStage PureFlow dialysate solution RFP 401)

<table>
<thead>
<tr>
<th>Volume replaced (ml)</th>
<th>Sodium final (mEq/L)</th>
<th>Potassium final (mEq/L)</th>
<th>Bicarbonate final (mEq/L)</th>
<th>Calcium final (mEq/L)</th>
<th>Magnesium final (mEq/L)</th>
<th>Chloride final (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>140.00</td>
<td>4.00</td>
<td>32.00</td>
<td>3.00</td>
<td>1.00</td>
<td>113.00</td>
</tr>
<tr>
<td>250</td>
<td>133.00</td>
<td>3.80</td>
<td>30.40</td>
<td>2.85</td>
<td>0.95</td>
<td>107.35</td>
</tr>
<tr>
<td>429</td>
<td>127.99</td>
<td>3.66</td>
<td>29.25</td>
<td>2.74</td>
<td>0.91</td>
<td>103.30</td>
</tr>
<tr>
<td>500</td>
<td>126.00</td>
<td>3.60</td>
<td>28.80</td>
<td>2.70</td>
<td>0.90</td>
<td>101.70</td>
</tr>
<tr>
<td>713</td>
<td>120.04</td>
<td>3.43</td>
<td>27.44</td>
<td>2.57</td>
<td>0.86</td>
<td>96.89</td>
</tr>
<tr>
<td>750</td>
<td>119.00</td>
<td>3.40</td>
<td>27.20</td>
<td>2.55</td>
<td>0.85</td>
<td>96.05</td>
</tr>
<tr>
<td>1000</td>
<td>112.00</td>
<td>3.20</td>
<td>25.60</td>
<td>2.40</td>
<td>0.80</td>
<td>90.40</td>
</tr>
<tr>
<td>1250</td>
<td>105.00</td>
<td>3.00</td>
<td>24.00</td>
<td>2.25</td>
<td>0.75</td>
<td>84.75</td>
</tr>
</tbody>
</table>

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Table 6: Characteristics, monitoring and complications of dialysis catheters for CRRT \(^{7,79,80}\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recommendation</th>
<th>Additional considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Non-tunneled temporary catheter (level of evidence 2D)</td>
<td>Avoid subclavian catheters, use ultrasound guidance for insertion; obtain chest x-rays before use (IJ or subclavian); no need for topical antibiotics or antibiotic locks for non-tunneled dialysis catheters</td>
</tr>
<tr>
<td>Catheter length</td>
<td>RIJ 12-15 cm, LIJ 15-20 cm, Fem 19-24 cm</td>
<td></td>
</tr>
<tr>
<td>Catheter diameter</td>
<td>12-13 Fr</td>
<td></td>
</tr>
<tr>
<td>Position</td>
<td>Catheter tip in the SVC (caval-atrial junction, &lt;4 cm from RA) with arterial lumen facing the mediastinum</td>
<td></td>
</tr>
</tbody>
</table>

**Monitoring**

<table>
<thead>
<tr>
<th>Trigger for alarm</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access Pressure</td>
<td>&gt; 50-70 mmHg pressure ∆ from operating point</td>
</tr>
<tr>
<td>Return Pressure</td>
<td>&gt; 50-70 mmHg pressure ∆ from operating point</td>
</tr>
</tbody>
</table>

**Complications**

| Acute complications (< 1-2%) | Hemorrhage/hematoma, venous perforation, arterial puncture, pneumothorax, air embolism |
| Subacute complications | Infection*: CR-BSI 1.6 to 5.5 episodes/1,000 catheter days or exit site infection, Catheter malfunction: fibrin sheath formation, thrombus within catheter, catheter kinks, catheter fracture or disconnection, catheter malposition or migration, catheter tip adherent to vessel wall |

*extrapolated from data of tunneled hemodialysis catheters \(^{81,82}\)

RIJ =right internal jugular; LIJ =left internal jugular; Fem =femoral; Fr =French; SVC =superior vena cava; RA =right atrium; ∆ =change; CR-BSI =catheter related-blood stream infection
**Table 7:** Dose of common formulations of citrate for fixed blood flow rate: amount of citrate delivered to achieve blood citrate concentration of 3 mmol/L in the circuit

<table>
<thead>
<tr>
<th>Blood Flow Rate (mL/min)</th>
<th>4% TSC (mL/hr)</th>
<th>2.2% ACD-A (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>132</td>
<td>159</td>
</tr>
<tr>
<td>125</td>
<td>165</td>
<td>200</td>
</tr>
<tr>
<td>150</td>
<td>199</td>
<td>239</td>
</tr>
<tr>
<td>200</td>
<td>265</td>
<td>319</td>
</tr>
</tbody>
</table>

Abbreviations: Trisodium Citrate, TSC; Anticoagulant Dextrose-A, ACD-A
| Citrate Excess | Metabolic conversion of citrate to bicarbonate resulting in excess buffer | -Metabolic Alkalosis  
-Total Ca++/iCa++ <2.5 | -Decrease blood flow rate, or  
-Increase dialysate flow rate, or  
-Decrease buffer concentration in other CRRT solutions |
|---------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Citrate Toxicity | Decreased metabolic conversion of citrate resulting in accumulation of citrate-calcium complexes in blood | -Anion Gap Metabolic Acidosis  
-Total Ca++/iCa++ >2.5  
-Escalating Ca++ infusion rate | -Decrease blood flow rate, or  
-Increase dialysate flow rate, or  
-Discontinue citrate |
| Citrate Deficit | Metabolic conversion of citrate to bicarbonate resulting in insufficient buffer | -Metabolic Acidosis  
-Total Ca++/iCa++ <2.5 | -Increase blood flow rate, or  
-Decrease dialysate flow rate, or  
-Increase buffer concentration in other CRRT solutions |

Abbreviations: Ca++, calcium; iCa++, ionized calcium; CRRT, continuous renal replacement therapy
### Table 9: Summary of dosing recommendations during CRRT for common antimicrobials utilized in critically ill patients

<table>
<thead>
<tr>
<th>CRRT Dose</th>
<th>Estimated clearance</th>
<th>Vancomycin</th>
<th>Cefepime</th>
<th>Piperacillin-tazobactam</th>
<th>Meropenem</th>
<th>Amikacin</th>
<th>Acyclovir</th>
<th>Oseltamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td></td>
<td>Churchwell⁶³</td>
<td>Moriyama⁷¹, Seyler⁷⁹, Chaijamorn⁷², Shaw³</td>
<td>Moriyama⁷¹, Seyler⁷⁹, Lexicomp</td>
<td>Moriyama⁷¹, Seyler⁷⁹, Lexicomp</td>
<td>D’Arcy⁴⁴, Lam⁷⁵, Taccone⁷⁶, Roger⁷⁷</td>
<td>Churchwell⁶³, Flannery⁷⁸</td>
<td></td>
</tr>
<tr>
<td>Replacement</td>
<td>1L/hr prefilter</td>
<td>2000ml/hr + 2000ml/hr = 4000ml/hr</td>
<td>25mg/kg loading dose (3,250 mg) (14mg/kg actual BW) 1750mg Q24h</td>
<td>2 gram loading dose</td>
<td>4.5 gram loading dose</td>
<td>2 gram loading dose</td>
<td>~25 mg/kg (adjusted BW of 90kg) 2250 mg q48h</td>
<td>10mg/kg (IBW 68kg) loading dose 680mg 680mg q8h 10mg/kg (IBW) q8h (encephalitis dosing)</td>
</tr>
<tr>
<td></td>
<td>1L/hr post-filter</td>
<td>70ml/min</td>
<td>2 gram q8h extended or continuous infusion</td>
<td>4.5gram q6h extended or continuous infusion</td>
<td>1-2 gram q8h extended infusion</td>
<td>10mg/kg (IBW) q8h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysate</td>
<td>2L/hr</td>
<td>2500 ml/hr + 2000ml/hr = 4500ml/hr</td>
<td>70ml/min</td>
<td>70ml/min</td>
<td>70ml/min</td>
<td>70ml/min</td>
<td>70ml/min</td>
<td></td>
</tr>
<tr>
<td>UF 200ml/hr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiochemical properties</td>
<td></td>
<td>MW: 1485d PB: 55% ( V_d: 0.7L/kg )</td>
<td>MW: 480d PB: 20% ( V_d: 0.28L/kg )</td>
<td>MW: 500d PB: 30% ( V_d: 0.24L/kg )</td>
<td>MW: 383d PB: 2% ( V_d: 0.2L/kg )</td>
<td>MW: 585d PB: 11% ( V_d: 0.25L/kg )</td>
<td>MW: 225d PB: 33% ( V_d: 0.8L/kg )</td>
<td>MW: 312d PB: 3% ( V_d: 0.37L/kg )</td>
</tr>
<tr>
<td>Maintenance dose based on</td>
<td>40-50 ml/min eGFR</td>
<td>70ml/min</td>
<td>70 ml/min</td>
<td>70ml/min</td>
<td>70ml/min</td>
<td>70ml/min</td>
<td>70ml/min</td>
<td></td>
</tr>
<tr>
<td>Caveats</td>
<td>Always assess for residual UOP during therapy, and take into consideration set downtime</td>
<td>Convective clearance &gt; diffusive clearance. Can use population PK estimated for dosing interval, once determined from CRRT RX. TDM at steady state.</td>
<td>Total clearance of 70ml/min requires full unadjusted dose, consider dose reduction after 48-72h based on cultures, indication etc.</td>
<td>TDM after first dose.</td>
<td>Will require adjustments if eGFR &lt;50ml/min.</td>
<td>Excellent absorption even in shock/CRRT/ECMO. Supratherapeutic levels achieved with normal dosing.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure Legend

Figure 1. Conceptual differentiation between diffusive (panel A) and convective (panel B) clearance with CRRT.

Figure 2. Graphic simulation of serum sodium correction over 24 hours utilizing CRRT solutions with sodium concentration of 129 mEq/L (dotted line, the case of our patient) versus 140 mEq/L (solid line, standard CRRT solutions).

Figure 3. CRRT and ECMO example. Blood flows from the patient into the ECMO circuit toward the blood pump and membrane oxygenator. In this example, blood flows to the CRRT circuit from a site distal to the oxygenator. Blood returns from the CRRT device to the ECMO circuit at a position prior to the oxygenator. Other configurations that combine CRRT with ECMO are also possible.
Panel A  Clearance by Diffusion

- Movement of solutes across the hemodialyzer from a high concentration to a low concentration
- Movement continues until equilibrium is reached
- Good for small solutes
Clearance by Convection

- Movement of solutes associated with fluid movement (solute drag)
- Movement is depended on the rate of fluid movement (total ultrafiltration rate)
- No gradient is needed, middle-sized solutes are pushed out along with the fluid (replacement fluid is needed)