Review Article

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How To Prescribe And Troubleshoot Continuous Renal Replacement Therapy: A Case-Based Review

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Abstract

Continuous RRT (CRRT) is the preferred dialysis modality for solute management, acid-base stability, and volume control in patients who are critically ill with 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 study, we provide a case-based review and recommendations of common scenarios and interventions encountered during the provision of CRRT to patients who are critically ill. Specific focus is 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 on the basis of step-wise decisions made during the care of this patient, according to the specific patient's needs and the logistics available at the corresponding institution.

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Introduction

AKI affects up to half of patients who are critically ill, admitted to intensive care units (ICU) (1,2). In patients with AKI and hemodynamic instability, continuous RRT (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 (1–3). Several factors contribute to these deleterious outcomes, including overall severity of acute illness, multiorgan failure, or the pathophysiologic effects of AKI itself (4,5).

CRRT is a lifesaving RRT modality for patients who are critically ill with AKI (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 patients who are critically ill has evolved and some standardization in practice has been achieved, such as the consensus on delivered effluent flow rates of 20–25 ml/kg per hour (7); however, several aspects of CRRT delivery are still not fully standardized, or do not have solid evidence-based foundations (8). Therefore, there is wide heterogeneity in clinical practice for the provision of CRRT and, for some patients, suboptimal care (6,9).

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

Patient Vignette

LC is a 68-year-old woman (weight before hospitalization 120 kg), with a 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. Then 2 weeks before 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 computed tomography scan with intravenous contrast before transfer that showed bilateral ground glass opacities.

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Nephrology was consulted 24 hours after ECMO cannulation for oliguric AKI.

At the time of consultation, she was intubated, mechanically ventilated, on veno-venous (VV) ECMO and systemic heparin. She was on an NE infusion, and treated with azithromycin, piperacillin-tazobactam, vancomycin, and oseltamivir. She had been anuric for the past 12 hours, despite a high-dose diuretic challenge. Admission sodium was 130 mEq/L and had been slowly drifting down over the hospital course. The patient at time of CRRT initiation had a 15 L positive fluid balance and >10% fluid overload from ICU admission. Her current weight at time of consultation was 135 kg (baseline 120 kg). See Table 1 for a summary of clinical data.

Scenario 1: Initial CRRT Prescription

LC is critically ill with multiorgan failure, including respiratory failure, shock, and anuric AKI. In addition, evolving fluid overload at a level consistently associated with mortality (>10%) (3,10–12) and biochemical abnormalities such as metabolic acidosis prompt CRRT initiation (13). For this patient, CRRT will be added in tandem to the ECMO

Table 1. Summary of patient's clinical data fluid overload from intensive care unit admission to outside hospital to continuous RRT initiation: +15 L >10% from before hospitalization (current weight 135 kg)

Parameter	Result
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	4600
ECMO sweep gas flow	5 L/min
ECMO FiO_2	100%
ECMO preoxy pressure	253 mm Hg
ECMO postoxy pressure	207 mm Hg
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
O_2 delivery device	Ventilator
Volume exchange	102 ml
Spontaneous rate	5 br/min
Peak airway pressure	34 cmH_20
Plateau pressure	29 cmH_20
FiO_2	100%
Pressure set	22 cmH_20
PEEP/CPAP set	12 cmH_20
PS level set	20 cmH_20
Labs at consultation	
Sodium (mEq/L)	119
Potassium (mEq/L)	5.4
Chloride (mEq/L)	96
Bicarbonate (mEq/L)	18
BUN (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 (U/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/mm^3) 15	
Hemoglobin (g/dl)	10.1
Hematocrit (%)	30%
Platelet (103 cells/mm^3)	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	NE

ECMO, extracorporeal membrane oxygenation; VV, veno-venous; SIMV, synchronized intermittent mechanical ventilation; PEEP, positive end expiratory pressure; CPAP, continuous positive airway pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time.

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 VV hemofiltration (CVVH, convective clearance) versus CVV hemodialysis (CVVHD, mostly diffusion) versus CVV hemodiafiltration (CVVHDF, diffusion and convection). Despite diffusion and convection being distinct dialysis physiologic 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 (14). 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 per hour). 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 20–25 ml/kg per hour for patients with AKI requiring CRRT on the basis of data from the Veterans Affairs / National Institutes of Health Acute Renal Failure Trial Network Study and Randomized Evaluation of Normal versus Augmented Level Replacement Therapy Study (7,15,16). 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 as a result of replacing filters, bags, tubing, or catheter-malfunction problems (17,18). 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 (6). When prescribing high-dose CRRT (>30 ml/kg per hour), 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 approximately 30 ml/kg per hour (4000 ml/h) accommodating for an expected 5%–10% downtime and the predilution factor.* Table 2 summarizes similar effluent doses under different CRRT modalities, including the adjustment for predilution if needed.
3. **What net ultrafiltration (UF)?** Due to objective data of fluid overload in our patient (*e.g.*, cumulative fluid balance, computed tomography of the chest, and respiratory status), tailored fluid removal is recommended to improve the patient's chance of survival and organ recovery. However, data on the rate of fluid removal are mostly observational and likely confounded by indication (19–21). Given the lack of clinical trials addressing this important aspect of the CRRT prescription, and the lack of fully validated methods of predicting and assessing fluid removal tolerance and need, significant heterogeneity in practice exists (22). Although the prescription of net UF is highly dynamic and commonly individualized, it is recommended not to exceed 1.5–2.0 ml/kg per hour of net UF as a general rule. *For our patient, LC, we will prescribe a net UF rate to achieve a goal of negative 50 ml/h until she is reassessed later in the treatment course.*
4. **What blood flow?** A minimum blood flow of 150 ml/min maximizes clearance for prefilter replacement fluid rates of up to 1500 ml/h and dialysis fluid rates of up to 3600 ml/h (23,24). *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 (25) at therapeutic levels prescribed for VV ECMO, therefore we will not use regional citrate anticoagulation (RCA) (26) at this time for CRRT.
6. **Summary of CRRT prescription** (Table 3). CVVHDF, blood flow rate 200 ml/min, dialysate fluid rate 2000 ml/h, preblood pump (prefilter replacement fluid) 1000 ml/h, postfilter replacement fluid 1000 ml/h, net UF goal of net negative 50 ml/h, solutions composition: sodium 140 mEq/L, potassium 4 mEq/L, chloride 113 mEq/L, calcium (Ca) 2.5 mEq/L, lactate 3 mEq/L, bicarbonate 32 mEq/L, glucose 110 mg/dl, osmolarity 300 mOsm/L.

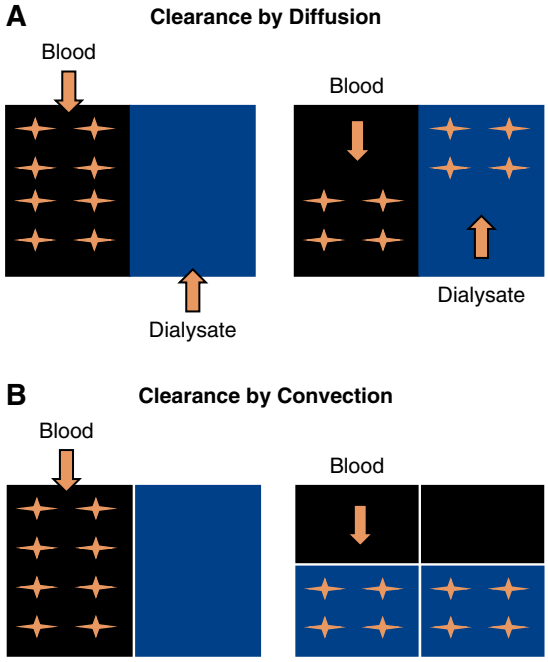

Figure 1. | Conceptual differentiation between diffusive and convective clearance with continuous RRT (CRRT). In diffusive clearance (A), solutes move across the hemodialyzer from a high concentration to a low concentration. Movement continues until equilibrium is reached. This method is good for small solutes. In convection clearance (B), movement of solutes is 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).

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 (27,28). Although serum sodium concentration increase with

Table 2. Simulation of effluent dosing under different continuous RRT modalities in our patient, assuming 100 ml/h of fluid removal rate is required to achieve a net ultrafiltration goal of net negative 50 ml/h as prescribed

Simulation of effluent dosing under different CRRT modalities
CVVHDF: total ultrafiltration rate (2000 ml/h)[a] + dialysate rate (2000 ml/h) + fluid removal rate (100 ml/h) = effluent dose of 30.4 ml/kg per h → 26.8 ml/kg per h after predilution adjustment (30.4×0.88)[b] assuming 50% of replacement fluid as prefilter (preblood pump =1000 ml/h) CVVH: total ultrafiltration rate (4000 ml/h)[a] + fluid removal rate (100 ml/h) = effluent dose of 30.4 ml/kg per h → 23.7 ml/kg per h after predilution adjustment (30.4×0.78)[b] assuming 50% of replacement fluid as prefilter (preblood pump =2000 ml/h) CVVHD: dialysate rate (4000 ml/h) + fluid removal rate (100 ml/h) = effluent dose of 30.4 ml/kg per h
Plasma flow rate (ml/h), blood flow rate (ml/min) ×60 (min/h) × (1-HCT); where HCT is the current hematocrit of the patient (HCT 30% for the case of our patient). CVVHDF, continuous veno-venous hemodiafiltration; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis. [a]Total ultrafiltration rate (ml/h) = preblood pump or prefilter replacement fluid rate + postfilter replacement fluid rate. [b]Dilution factor for predilution: Plasma flow rate (ml/h)/[Plasma flow rate (ml/h) + prefilter replacement fluid rate (ml/h)] = 0.88 for our patient (1000 ml/h prefilter replacement fluid in CVVHDF) and 0.78 (assuming 2000 ml/h of prefilter replacement fluid in CVVH).

CRRT is less rapid than hemodialysis, it can far exceed recommended correction limits (≤8 mEq/L) if factors affecting sodium change are ignored (29). Therefore, the CRRT prescription may need to be individualized on the basis of 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 (30). 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 nonisotonic fluid gains or losses (29,31). Bedside application of the single-pool, fixed-volume sodium kinetic model has been reported by several groups since it was first described by Yessayan *et al.* (29,32,33).

$$Na_{(t)} = Na_0 + \left(Na_{dial/RF} - Na_0\right) \times \left(1 - e^{\frac{-Dt}{V}}\right) \quad (1)$$

where $Na_{dial/RF}$ is the dialysate/replacement fluid sodium concentration, Na_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 (before hospitalization) and adding to this any estimated edema volume. In our case, the Na_0 is 119 mEq/L, $Na_{dial/RF}$ 140 mEq/L, D is roughly equal to the sum of dialysate and replacement fluid rates (4 L/h), and V is approximately 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 approximately 136 mEq/L, and thus will exceed the recommended limits of correction:

Table 3. Summary of initial continuous RRT prescription

Parameter	Prescription
Modality	CVVHDF
Filter type	HF1400 (per protocol)
Dose	30 ml/kg per h
Anticoagulation	Systemic heparin per ECMO protocol
Blood flow	200 ml/min
Preblood pump	4K/2.5Ca *140Na
Preblood pump rate	1000 ml/h
Dialysis fluid	4K/2.5Ca *140Na
Dialysis fluid rate	2000 ml/h
Replacement fluid (post)	4K/2.5Ca *140Na
Replacement fluid (post) rate	1000 ml/h
Net UF goal	Net negative 50 ml/h
Calcium chloride rate	None

ECMO, extracorporeal membrane oxygenation; UF, ultrafiltration; CVVHDF, continuous veno-venous hemodiafiltration.

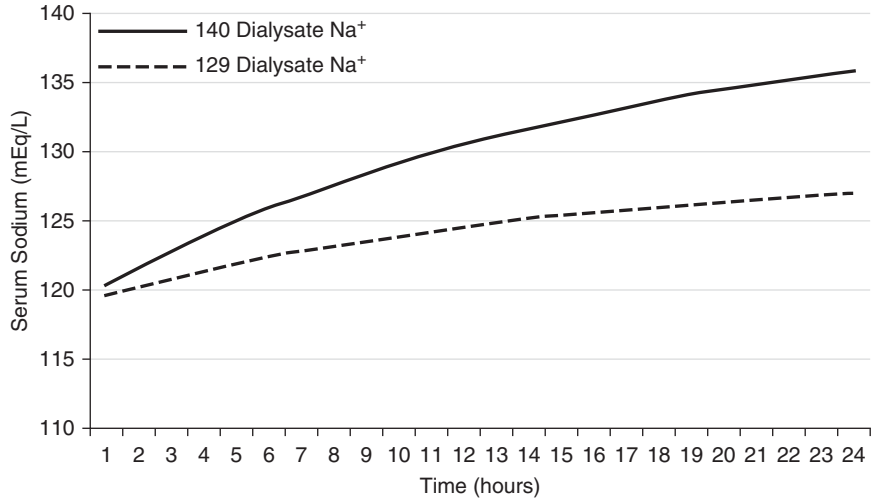

Figure 2. | Graphic simulation of serum sodium correction over 24 hours. Continuous RRT (CRRT) solutions were utilized with sodium concentration of 129 mEq/L (dotted line, the case of our patient) versus 140 mEq/L (solid line, standard CRRT solutions).

$$Na_{(t)} = 119 + (140 - 119) \times \left(1 - e^{\frac{-4 \times 24}{60}}\right) = 136 \text{ mEq/L} \quad (2)$$

(*2*) What strategies could be used to avoid serum sodium overcorrection and maintain 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 (31). 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 (31).

(*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 (29):

$$CRRT\ solution\ [Na^+] = \frac{desired\ \Delta\ serum\ [Na^+]}{\left(1 - e^{-\frac{D \times 24\ hr}{V}}\right)} + initial\ serum\ [Na^+] \quad (3)$$

For a desired change of 8 mEq/L at 24 hours, and an initial serum sodium of 119 mEq/L and sodium dialysance of 4 L/h, 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 (29). 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 (D5W) solution be administered to maintain the patient's serum sodium within a desired range of ≤8 mEq/L?

Infusing electrolyte-free water as a 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

Table 4. Effect of adding different volumes of sterile water to a 5 L dialysate/replacement fluid bag (NxStage PureFlow dialysate solutions RFP 401)

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

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a desired target level could be estimated using the following formula (31):

$$D5W\ \ rate = \frac{CRRT\ \ solution\ \ [Na^+] - target\ \ serum\ \ [Na^+]}{CRRT\ \ solution\ \ [Na^+]} \times desired\ \ clearance \quad (4)$$

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/h, the D5W infusion should be administered at a rate 0.314 L/h (314 ml/h) 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/h). *For 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 patient's most current 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 VV support. Less commonly, veno-arterial ECMO or a hybrid method of support may be utilized (34). Several studies have been performed over the last decade, examining ECMO for respiratory failure, with mixed results (35–40). Two prospective, multicenter trials of ECMO for severe respiratory failure or acute respiratory distress syndrome (Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure and the ECMO to Rescue Lung Injury in Severe Acute Respiratory Distress Syndrome) 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 with conventional mechanical ventilation with ECMO rescue (41,42).

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 US Food and Drug Administration–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

Table 5. Effect of exchanging different volumes of a 5 L dialysate/replacement fluid bag with sterile water (NxStage PureFlow dialysate solution RFP 401)

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

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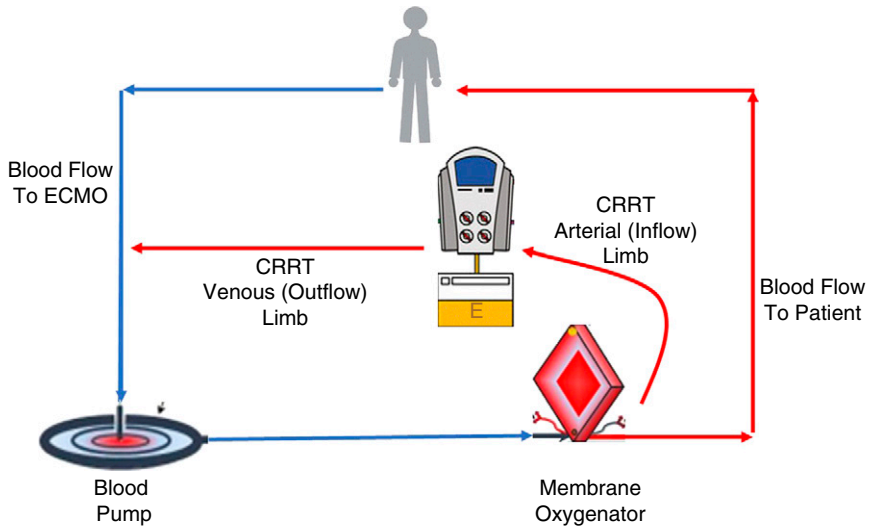

Figure 3. | **Continuous RRT (CRRT) and extracorporeal membrane oxygenation (ECMO) example.** Blood flows from the patient into the ECMO circuit toward the blood pump and membrane oxygenator. In this example, blood flows to the CRRT circuit from a site distal to the oxygenator. Blood returns from the CRRT device to the ECMO circuit at a position before the oxygenator. Other configurations that combine CRRT with ECMO are also possible.

blood pump) (43). High pressure 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 with providing each independently, is yet to be examined in a prospective manner.

Strategies for combining CRRT and ECMO have previously been described (44–48). 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 before the membrane oxygenator. This approach is less costly compared with CRRT, but disadvantages include a lack of pressure alarms and poor control of net UF. 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 UF 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 patients 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 (49,50). This technique has been used to permit protective lung ventilation in severe acute respiratory distress syndrome 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, anti-Xa level, coagulation studies (partial thromboplastin time and prothrombin time), or thromboelastography. 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 VV 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 the 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 postfilter mode and the relationship between blood flow and clearance when using prefilter mode (6:1 blood flow rate to

prefilter replacement fluid ratio to maximize clearance) (23,24). 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 (approximately 14 days for internal jugular catheters and approximately 7–10 days for femoral catheters) and with low rate of complications (infection, thrombosis, mechanical). Current Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend (*1*) use of a nontunneled temporary dialysis catheter; (*2*) insertion of the catheter in the right internal jugular (RIJ) as the first option, femoral site as the second option, and left internal jugular as a third option, and to avoid subclavian insertions (51); (*3*) use of a catheter with a length of 12–15 cm for RIJ, 15–20 cm for left internal jugular, and 19–24 cm for femoral sites, with a diameter of 11.5–14 F; and (*4*) location of the catheter tip in the midatrium with the arterial lumen facing the mediastinum, but not allowing the catheter tip to touch the atrium floor (7). 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 RCA 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 the 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. Microclotting 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, whereas 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 UF rate to plasma water flow rate and represents the fraction of plasma that is removed from the blood during hemofiltration. Maintaining a filtration fraction of <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 predilution 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 (7).

Table 6. Characteristics, monitoring and complications of dialysis catheters for continuous RRT (7,52,53)

Characteristic	Recommendation	Additional Considerations
Type	Nontunneled temporary catheter (*level of evidence 2D*)	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 nontunneled dialysis catheters
Catheter length	RIJ 12–15 cm, LIJ 15–20 cm, Fem 19–24 cm	
Catheter diameter	12–13 Fr	
Position	Catheter tip in the SVC (caval-atrial junction, <4 cm from RA) with arterial lumen facing the mediastinum	
Monitoring	Trigger for alarm	Action
Access pressure	>50–70 mm Hg pressure Δ from operating point	Evaluate for catheter malfunction (clots, kinks, malposition)
Return pressure	>50–70 mm Hg pressure Δ from operating point	Evaluate for catheter malfunction (clots, kinks, malposition)
Complications		
Acute complications (<1% to 2%)	Hemorrhage/hematoma, venous perforation, arterial puncture, pneumothorax, air embolism	
Subacute complications	Infection[a]: CR-BSI 1.6–5.5 episodes/1000 catheter d 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	

RIJ, right internal jugular; LIJ, left internal jugular; Fem, femoral; Fr, French; SVC, superior vena cava; RA, right atrium; Δ, change; CR-BSI, catheter related-blood stream infection.
[a]Extrapolated from data of tunneled hemodialysis catheters (54,55).

Citrate is infused into the blood at the beginning of the extracorporeal circuit and provides anticoagulation by chelating ionized Ca (iCa^{++}). Optimal regional anticoagulation occurs when the iCa^{++} concentration in the extracorporeal circuit is below 0.35 mmol/L, which corresponds to approximately 3–4 mmol of citrate per liter of blood. A portion of the Ca-citrate complex is lost across the hemofilter, whereas the rest enters the systemic circulation where citrate is metabolized by the liver to bicarbonate and Ca is released into the circulation. Ca is infused back to the patient to replace the Ca lost across the hemofilter (26,56–59).

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 (26) or other form of anticoagulation (systemic heparin [25]) 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 versus systemic heparin. However, there was less risk of bleeding and prolonged filter life span (the latter specifically when using CVVH) with RCA versus systemic heparin. There were also more episodes of hypocalcemia in the RCA group (60). Therefore, careful Ca monitoring (*e.g.*, patient's total Ca and iCa) is mandatory when using CRRT with RCA (61).

Ensuring adequate citrate anticoagulation in the circuit can be done by either measuring the postfilter iCa^{++} and titrating the citrate rate to maintain the circuit iCa^{++} <0.35 mmol/L, or fixing the citrate and blood flow rate to achieve a concentration of 3–4 mmol/L in the circuit without measurement of postfilter iCa^{++} 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 and 2.2% anticoagulant dextrose-A.

LC is not allergic to citrate and, despite evidence of coagulopathy, mild elevation in aspartate aminotransferase and alanine aminotransferase, 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 anticoagulant dextrose-A (3% combined trisodium citrate 2.2 g/100 ml and citric acid 0.73 g/100 ml; contains glucose 2.5%; total amount of citrate: 10–11 mmol/100 ml) at a rate of 250 ml/h (1.5 times blood flow of 170 ml/min, decreased from 200 ml/min) plus a continuous infusion of Ca chloride or equivalent (20 g of Ca chloride in 1 L of 0.9% sodium chloride or 10 g of Ca chloride in 0.5 L of 0.9% sodium chloride = 20 mg/ml or 0.136 mmol/ml of elemental Ca) at 25 ml/h to maintain the systemic iCa^{++} within normal range.*

Scenario 6: Recognizing Complications of RCA 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 Ca 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 (62).

Patients with severe shock liver and lactic acidosis may not be able to metabolize citrate (63,64). Citrate toxicity is characterized by low systemic serum iCa^{++} level, elevated serum total Ca level, total Ca to systemic iCa^{++} ratio >2.5, increasing anion gap acidosis, and escalating Ca 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. To minimize the systemic effects of citrate, we recommend a blood flow rate between 100 and 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 Ca to systemic iCa^{++} ratio remains <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 (65). 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 (<2 L/kg), low protein binding (<80%), and a MW smaller than the pore size of the CRRT filter (typically <20,000 days) will be removed through convection (66). Convective clearance has a positive linear relationship to replacement fluid rate. An UF rate of 2.5 L/h provides a creatinine clearance of

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

Blood Flow Rate (ml/min)	4% TSC (ml/h)	2.2% ACD-A (ml/h)
100	132	159
125	165	200
150	199	239
200	265	319

TSC, trisodium citrate; ACD-A, anticoagulant dextrose-A.

Table 8. Metabolic complications of citrate utilization with continuous RRT

Complication	Mechanism	Diagnosis	Management
Citrate excess	Metabolic conversion of citrate to bicarbonate resulting in excess buffer	Metabolic alkalosis Total Ca^{++}/iCa^{++} <2.5	Decrease blood flow rate 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 Decrease dialysate flow rate Increase buffer concentration in other CRRT solutions

Ca^{++}, calcium; iCa^{++}, ionized calcium; CRRT, continuous RRT.

40 ml/min (2500/60=40 ml/min); for every 0.5 L/h increase in convection, expect the clearance to increase by 10 ml/min (67). This provides an eGFR to use for medication dosing, recalling prefilter replacement fluids can reduce convective clearance up to 20% (65,68).

Diffusion-based modalities differ in solute removal because diffusion passively and preferentially removes drugs with a small MW (<500 days), such as beta-lactam antibiotics and antiepileptics. Clearance for larger molecules becomes inversely related to MW (65,69). 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 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 before CRRT initiation (10,70). Loading doses of hydrophilic antibiotics are paramount to optimize pharmacokinetic/pharmacodynamic parameters. Conversely, as euvolemia is achieved over the course of therapy, total body clearance will decrease. In addition, the convective and diffusive clearance of drugs decreases over the course of therapy (65,66). Taken together, there is high potential for medication accumulation to occur after 48 hours of CRRT, which has been observed in the literature (71,72).

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 >2 L/h of effluent dose (71,73). 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 predilution fluid reduces solute clearance. Therapeutic drug monitoring of all antimicrobials should occur when available. *For our patient, LC, the recommended initial doses of antibiotics include piperacillin-tazobactam 4.5 g 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 (approximately 14 mg/kg) every 24 hours, as our CRRT prescription provides an eGFR of 40–50 ml/min for vancomycin, accounting for the dilution factor, and diffusive clearance. Therapeutic drug monitoring should be done at a steady state. Also recommended is oseltamivir 75 mg twice daily and azithromycin 500 mg every 24 hours. 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.

Discussion

CRRT is a method of dialysis support commonly utilized in patients who are critically ill with AKI. However, several aspects of CRRT delivery are still not fully standardized and do not have solid evidence-based foundations. In this study, 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 RCA, and antibiotic dosing. This CRRT simulation highlights the importance of iterative assessment and adjustments of goals of therapy for patients on CRRT, and the need for effective communication among all multidisciplinary stakeholders involved in the care of this debilitated ICU population.

Disclosures

A. Tolwani reports a patent to 0.5% citrate solution issued, licensed, and with royalties paid. A. Tolwani, J.A. Neyra, and M. Thompson Bastin have provided consultations for Baxter Healthcare. All remaining authors have nothing to disclose.

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Table 9. Summary of dosing recommendations during continuous RRT for common antimicrobials utilized in patients who are critically ill

CRRT Dose	Estimated clearance	Vancomycin	Cefepime	Piperacillin-Tazobactam	Meropenem	Amikacin	Acyclovir	Oseltamivir
References	Churchwell and Mueller (65)	Churchwell and Mueller (65) Lexicomp	Moriyama *et al.* (73) Seyler *et al.* (71) Chaijamorn *et al.* (77) Shaw and Mueller (79) Lexicomp	Moriyama *et al.* (73) Seyler *et al.* (71) Lexicomp	Moriyama (*et al.*73) Seyler *et al.* (71) Lexicomp	D'Arcy *et al.* (74) Lam and Bauer (76) Taccone *et al.* (78) Roger *et al.* (80) Lexicomp	Churchwell and Mueller (65) Lexicomp	Flannery Thompson Bastin (75) Lexicomp
Replacement 1 L/h prefilter 1 L/h postfilter	2000 ml/h + 2000 ml/h+ 200 ml/h =70 ml/min	25 mg/kg loading dose (3250 mg)	2 g loading dose	4.5 g loading dose	2 g loading dose	Approximately 25 mg/kg (adjusted BW of 90 kg)	10 mg/kg (IBW 68 kg) loading dose	75 mg q 12h
Dialysate 2 L/h UF 200 ml/h		(14 mg/kg actual BW) 1750 mg q24h	2 g q8h extended or continuous infusion	4.5 g q6h extended or continuous infusion	1–2 g q8h extended infusion	2250 mg q48h	680 mg 680 mg q8h 10 mg/kg (IBW) q8h (encephalitis dosing)	
Physiochemical properties	Always assess for residual UOP during therapy, and take into consideration set downtime	MW: 1485 d PB: 55% V_d: 0.7 L/kg	MW: 480 d PB: 20% V_d:0.28 L/kg	MW: 500 d PB: 30% V_d: 0.24 L/kg	MW: 383 d PB: 2% V_d: 0.2 L.kg	MW: 585 d PB: 11% V_d: 0.25 L/kg	MW: 225 d PB: 33% V_d: 0.8 L/kg	MW: 312 d PB: 3% V_d: 0.37 L/kg
Maintenance dose on the basis of		40–50 ml/min eGFR	70 ml/min	70 ml/min	70 ml/min	70ml/min	70 ml/min	70 ml/min
Caveats		Convective clearance > diffusive clearance. Can use population PK estimated for dosing interval, once determined from CRRT Rx. TDM at steady state.	Total clearance of 70 ml/min requires full unadjusted dose, consider dose reduction after 48–72 h on the basis of cultures, indication etc.			TDM after first dose.	Will require adjustments if eGFR <50 ml/min.	Excellent absorption even in shock/CRRT/ECMO. Supratherapeutic levels achieved with normal dosing.

BW, body weight; IBW, ideal body weight; MW, mol wt; PB, protein binding; V_d, volume of distribution; UOP, urine output; TDM, therapeutic drug monitoring; CRRT, continuous RRT; ECMO, extracorporeal membrane oxygenation; Rx, prescription.

Author Contributions

A. Tolwani was responsible for the methodology; A. Tolwani and J.A. Neyra were responsible for the supervision; and all authors were responsible for the conceptualization and wrote the original draft.

References

1. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, Honoré PM, Joannes-Boyau O, Joannidis M, Korhonen AM, Lavrentieva A, Mehta RL, Palevsky P, Roessler E, Ronco C, Uchino S, Vazquez JA, Vidal Andrade E, Webb S, Kellum JA: Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med* 41: 1411–1423, 2015 https://doi.org/10.1007/s00134-015-3934-7
2. Bouchard J, Acharya A, Cerda J, Maccariello ER, Madarasu RC, Tolwani AJ, Liang X, Fu P, Liu ZH, Mehta RL: A prospective international multicenter study of AKI in the intensive care unit. *Clin J Am Soc Nephrol* 10: 1324–1331, 2015 https://doi.org/10.2215/CJN.04360514
3. Woodward CW, Lambert J, Ortiz-Soriano V, Li Y, Ruiz-Conejo M, Bissell BD, Kelly A, Adams P, Yessayan L, Morris PE, Neyra JA: Fluid overload associates with major adverse kidney events in critically ill patients with acute kidney injury requiring continuous renal replacement therapy. *Crit Care Med* 47: e753–e760, 2019 https://doi.org/10.1097/CCM.0000000000003862
4. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C; Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators: Acute renal failure in critically ill patients: A multinational, multicenter study. *JAMA* 294: 813–818, 2005 https://doi.org/10.1001/jama.294.7.813
5. de Mendonça A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, Takala J, Sprung C, Cantraine F: Acute renal failure in the ICU: Risk factors and outcome evaluated by the SOFA score. *Intensive Care Med* 26: 915–921, 2000 https://doi.org/10.1007/s001340051281
6. Neyra JA, Goldstein SL: Optimizing renal replacement therapy deliverables through multidisciplinary work in the intensive care unit. *Clin Nephrol* 90: 1–5, 2018 https://doi.org/10.5414/CN109447
7. Kidney Disease: Improving Global Outcomes: Acute Kidney Injury (AKI). Available at: https://kdigo.org/guidelines/acute-kidney-injury. Accessed August 1, 2020
8. Bagshaw SM, Darmon M, Ostermann M, Finkelstein FO, Wald R, Tolwani AJ, Goldstein SL, Gattas DJ, Uchino S, Hoste EA, Gaudry S: Current state of the art for renal replacement therapy in critically ill patients with acute kidney injury. *Intensive Care Med* 43: 841–854, 2017 https://doi.org/10.1007/s00134-017-4762-8
9. Rewa OG, Villeneuve PM, Lachance P, Eurich DT, Stelfox HT, Gibney RTN, Hartling L, Featherstone R, Bagshaw SM: Quality indicators of continuous renal replacement therapy (CRRT) care in critically ill patients: A systematic review. *Intensive Care Med* 43: 750–763, 2017 https://doi.org/10.1007/s00134-016-4579-x
10. Neyra JA, Li X, Canepa-Escaro F, Adams-Huet B, Toto RD, Yee J, Hedayati SS; Acute Kidney Injury in Critical Illness Study Group: Cumulative fluid balance and mortality in septic patients with or without acute kidney injury and chronic kidney disease. *Crit Care Med* 44: 1891–1900, 2016 https://doi.org/10.1097/CCM.0000000000001835
11. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL; Program to Improve Care in Acute Renal Disease (PICARD) Study Group: Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 76: 422–427, 2009 https://doi.org/10.1038/ki.2009.159
12. Goldstein SL, Currier H, Graf Cd, Cosio CC, Brewer ED, Sachdeva R: Outcome in children receiving continuous venovenous hemofiltration. *Pediatrics* 107: 1309–1312, 2001 https://doi.org/10.1542/peds.107.6.1309
13. Tolwani A: Continuous renal-replacement therapy for acute kidney injury. *N Engl J Med* 367: 2505–2514, 2012 https://doi.org/10.1056/NEJMct1206045
14. Cerdá J, Ronco C: Modalities of continuous renal replacement therapy: Technical and clinical considerations. *Semin Dial* 22: 114–122, 2009 https://doi.org/10.1111/j.1525-139X.2008.00549.x
15. Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, Finkel K, Kellum JA, Paganini E, Schein RM, Smith MW, Swanson KM, Thompson BT, Vijayan A, Watnick S, Star RA, Peduzzi P; VA/NIH Acute Renal Failure Trial Network: Intensity of renal support in critically ill patients with acute kidney injury [published correction appears in *N Engl J Med* 361: 2391, 2009]. *N Engl J Med* 359: 7–20, 2008 https://doi.org/10.1056/NEJMoa0802639
16. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S; RENAL Replacement Therapy Study Investigators: Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 361: 1627–1638, 2009 https://doi.org/10.1056/NEJMoa0902413
17. Venkataraman R, Kellum JA, Palevsky P: Dosing patterns for continuous renal replacement therapy at a large academic medical center in the United States. *J Crit Care* 17: 246–250, 2002 https://doi.org/10.1053/jcrc.2002.36757
18. Claure-Del Granado R, Macedo E, Chertow GM, Soroko S, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL: Effluent volume in continuous renal replacement therapy overestimates the delivered dose of dialysis [published correction appears in *Clin J Am Soc Nephrol* 6: 1802, 2011]. *Clin J Am Soc Nephrol* 6: 467–475, 2011 https://doi.org/10.2215/CJN.02500310
19. Murugan R, Balakumar V, Kerti SJ, Priyanka P, Chang CH, Clermont G, Bellomo R, Palevsky PM, Kellum JA: Net ultrafiltration intensity and mortality in critically ill patients with fluid overload. *Crit Care* 22: 223, 2018 https://doi.org/10.1186/s13054-018-2163-1
20. Murugan R, Kerti SJ, Chang CH, Gallagher M, Clermont G, Palevsky PM, Kellum JA, Bellomo R: Association of net ultrafiltration rate with mortality among critically ill adults with acute kidney injury receiving continuous venovenous hemodiafiltration: A secondary analysis of the randomized evaluation of normal vs augmented level (RENAL) of renal replacement therapy trial. *JAMA Netw Open* 2: e195418, 2019 https://doi.org/10.1001/jamanetworkopen.2019.5418
21. Naorungroj T, Neto AS, Zwakman-Hessels L, Yanase F, Eastwood G, Murugan R, Kellum JA, Bellomo R: Early net ultrafiltration rate and mortality in critically ill patients receiving continuous renal replacement therapy [published online ahead of print April 7, 2020]. *Nephrol Dial Transplant* https://doi.org/10.1093/ndt/gfaa032
22. Murugan R, Ostermann M, Peng Z, Kitamura K, Fujitani S, Romagnoli S, Di Lullo L, Srisawat N, Todi S, Ramakrishnan N, Hoste E, Puttarajappa CM, Bagshaw SM, Weisbord S, Palevsky PM, Kellum JA, Bellomo R, Ronco C: Net ultrafiltration prescription and practice among critically ill patients receiving renal replacement therapy: A multinational survey of critical care practitioners. *Crit Care Med* 48: e87–e97, 2020 https://doi.org/10.1097/CCM.0000000000004092
23. Leypoldt JK, Kamerath CD, Gilson JF, Friederichs G: Dialyzer clearances and mass transfer-area coefficients for small solutes at low dialysate flow rates. *ASAIO J* 52: 404–409, 2006 https://doi.org/10.1097/01.mat.0000227687.88929.08
24. Relton S, Greenberg A, Palevsky PM: Dialysate and blood flow dependence of diffusive solute clearance during CVVHD. *ASAIO J* 38: M691–M696, 1992 https://doi.org/10.1097/00002480-199207000-00127
25. Karakala N, Tolwani A: We use heparin as the anticoagulant for CRRT. *Semin Dial* 29: 272–274, 2016 https://doi.org/10.1111/sdi.12503
26. Tolwani AJ, Prendergast MB, Speer RR, Stofan BS, Wille KM: A practical citrate anticoagulation continuous venovenous hemodiafiltration protocol for metabolic control and high solute clearance. *Clin J Am Soc Nephrol* 1: 79–87, 2006 https://doi.org/10.2215/CJN.00040505
27. Huang WY, Weng WC, Peng TI, Ro LS, Yang CW, Chen KH: Central pontine and extrapontine myelinolysis after rapid correction of hyponatremia by hemodialysis in a uremic patient. *Ren*

Fail 29: 635–638, 2007 https://doi.org/10.1080/08860220701392314
28. Peces R, Ablanedo P, Alvarez J: Central pontine and extrapontine myelinolysis following correction of severe hyponatremia. *Nephron* 49: 160–163, 1988 https://doi.org/10.1159/000185044
29. Yessayan L, Yee J, Frinak S, Szamosfalvi B: Treatment of severe hyponatremia in patients with kidney failure: Role of continuous venovenous hemofiltration with low-sodium replacement fluid. *Am J Kidney Dis* 64: 305–310, 2014 https://doi.org/10.1053/j.ajkd.2014.01.451
30. Pozzoni P, DI Filippo S, Pontoriero G, Locatelli F: Effectiveness of sodium and conductivity kinetic models in predicting end-dialysis plasma water sodium concentration: Preliminary results of a single-center experience. *Hemodial Int* 11: 169–177, 2007 https://doi.org/10.1111/j.1542-4758.2007.00165.x
31. Yessayan L, Yee J, Frinak S, Szamosfalvi B: Continuous renal replacement therapy for the management of acid-base and electrolyte imbalances in acute kidney injury. *Adv Chronic Kidney Dis* 23: 203–210, 2016 https://doi.org/10.1053/j.ackd.2016.02.005
32. Paquette F, Goupil R, Madore F, Troyanov S, Bouchard J: Continuous venovenous hemofiltration using customized replacement fluid for acute kidney injury with severe hypernatremia. *Clin Kidney J* 9: 540–542, 2016 https://doi.org/10.1093/ckj/sfw036
33. Neyra JA, Ortiz-Soriano VM, Ali D, Morris PE, Johnston CM: A multidisciplinary approach for the management of severe hyponatremia in patients requiring continuous renal replacement therapy. *Kidney Int Rep* 4: 59–66, 2018 https://doi.org/10.1016/j.ekir.2018.09.001
34. Brasseur A, Scolletta S, Lorusso R, Taccone FS: Hybrid extracorporeal membrane oxygenation. *J Thorac Dis* 10[Suppl 5]: S707–S715, 2018 https://doi.org/10.21037/jtd.2018.03.84
35. Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, Forrest P, Gattas D, Granger E, Herkes R, Jackson A, McGuinness S, Nair P, Pellegrino V, Pettilä V, Plunkett B, Pye R, Torzillo P, Webb S, Wilson M, Ziegenfuss M; Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators: Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 302: 1888–1895, 2009
36. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, Sadique MZ, Sekhon JS, McAuley DF, Firmin RK, Harvey C, Cordingley JJ, Price S, Vuylsteke A, Jenkins DP, Noble DW, Bloomfield R, Walsh TS, Perkins GD, Menon D, Taylor BL, Rowan KM: Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA* 306: 1659–1668, 2011 https://doi.org/10.1001/jama.2011.1471
37. Patroniti N, Zangrillo A, Pappalardo F, Peris A, Cianchi G, Braschi A, Iotti GA, Arcadipane A, Panarello G, Ranieri VM, Terragni P, Antonelli M, Gattinoni L, Oleari F, Pesenti A: The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: Preparation for severe respiratory emergency outbreaks. *Intensive Care Med* 37: 1447–1457, 2011 https://doi.org/10.1007/s00134-011-2301-6
38. Pham T, Combes A, Rozé H, Chevret S, Mercat A, Roch A, Mourvillier B, Ara-Somohano C, Bastien O, Zogheib E, Clavel M, Constan A, Marie Richard JC, Brun-Buisson C, Brochard L; REVA Research Network: Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: A cohort study and propensity-matched analysis. *Am J Respir Crit Care Med* 187: 276–285, 2013 https://doi.org/10.1164/rccm.201205-0815OC
39. Schmidt M, Zogheib E, Rozé H, Repesse X, Lebreton G, Luyt CE, Trouillet JL, Bréchot N, Nieszkowska A, Dupont H, Ouattara A, Leprince P, Chastre J, Combes A: The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *Intensive Care Med* 39: 1704–1713, 2013 https://doi.org/10.1007/s00134-013-3037-2
40. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, Scheinkestel C, Cooper DJ, Brodie D, Pellegrino V, Combes A, Pilcher D: Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. *Am J Respir Crit Care Med* 189: 1374–1382, 2014 https://doi.org/10.1164/rccm.201311-2023OC
41. Peek GJ, Clemens F, Elbourne D, Firmin R, Hardy P, Hibbert C, Killer H, Mugford M, Thalanany M, Tiruvoipati R, Truesdale A, Wilson A: CESAR: Conventional ventilatory support vs extracorporeal membrane oxygenation for severe adult respiratory failure. *BMC Health Serv Res* 6: 163, 2006 https://doi.org/10.1186/1472-6963-6-163
42. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, Da Silva D, Zafrani L, Tirot P, Veber B, Maury E, Levy B, Cohen Y, Richard C, Kalfon P, Bouadma L, Mehdaoui H, Beduneau G, Lebreton G, Brochard L, Ferguson ND, Fan E, Slutsky AS, Brodie D, Mercat A; EOLIA Trial Group, REVA, and ECMONet: Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 378: 1965–1975, 2018 https://doi.org/10.1056/NEJMoa1800385
43. de Tymowski C, Augustin P, Houissa H, Allou N, Montravers P, Delzongle A, Pellenc Q, Desmard M: CRRT connected to ECMO: Managing high pressures. *ASAIO J* 63: 48–52, 2017 https://doi.org/10.1097/MAT.0000000000000441
44. Santiago MJ, Sánchez A, López-Herce J, Pérez R, del Castillo J, Urbano J, Carrillo A: The use of continuous renal replacement therapy in series with extracorporeal membrane oxygenation. *Kidney Int* 76: 1289–1292, 2009 https://doi.org/10.1038/ki.2009.383
45. Askenazi DJ, Selewski DT, Paden ML, Cooper DS, Bridges BC, Zappitelli M, Fleming GM: Renal replacement therapy in critically ill patients receiving extracorporeal membrane oxygenation. *Clin J Am Soc Nephrol* 7: 1328–1336, 2012 https://doi.org/10.2215/CJN.12731211
46. Villa G, Katz N, Ronco C: Extracorporeal membrane oxygenation and the kidney. *Cardiorenal Med* 6: 50–60, 2015 https://doi.org/10.1159/000439444
47. Ostermann M, Connor M Jr, Kashani K: Continuous renal replacement therapy during extracorporeal membrane oxygenation: Why, when and how? *Curr Opin Crit Care* 24: 493–503, 2018 https://doi.org/10.1097/MCC.0000000000000559
48. Kashani K, Ostermann M: Optimizing renal replacement therapy for patients who need extracorporeal membrane oxygenation: Cross-talk between two organ support machines. *BMC Nephrol* 20: 404, 2019 https://doi.org/10.1186/s12882-019-1602-9
49. Terragni PP, Birocco A, Faggiano C, Ranieri VM: Extracorporeal CO_2 removal. *Contrib Nephrol* 165: 185–196, 2010 https://doi.org/10.1159/000313758
50. Nentwich J, Wichmann D, Kluge S, Lindau S, Mutlak H, John S: Low-flow CO_2 removal in combination with renal replacement therapy effectively reduces ventilation requirements in hypercapnic patients: A pilot study. *Ann Intensive Care* 9: 3, 2019 https://doi.org/10.1186/s13613-019-0480-4
51. Parienti JJ, Mégarbane B, Fischer MO, Lautrette A, Gazui N, Marin N, Hanouz JL, Ramakers M, Daubin C, Mira JP, Charbonneau P, du Cheyron D; Cathedia Study Group: Catheter dysfunction and dialysis performance according to vascular access among 736 critically ill adults requiring renal replacement therapy: A randomized controlled study. *Crit Care Med* 38: 1118–1125, 2010 https://doi.org/10.1097/CCM.0b013e3181d454b3
52. Bhutta ST, Culp WC: Evaluation and management of central venous access complications. *Tech Vasc Interv Radiol* 14: 217–224, 2011 https://doi.org/10.1053/j.tvir.2011.05.003
53. Bream PR Jr: Update on insertion and complications of central venous catheters for hemodialysis. *Semin Intervent Radiol* 33: 31–38, 2016 https://doi.org/10.1055/s-0036-1572547
54. Beathard GA, Urbanes A: Infection associated with tunneled hemodialysis catheters. *Semin Dial* 21: 528–538, 2008 https://doi.org/10.1111/j.1525-139X.2008.00497.x
55. Miller DL, O'Grady NP: Guidelines for the prevention of intravascular catheter-related infections: Recommendations relevant to interventional radiology. *J Vasc Interv Radiol* 14: 133–136, 2003 https://doi.org/10.1016/S1051-0443(07)60120-1
56. Tolwani A, Wille KM: Advances in continuous renal replacement therapy: Citrate anticoagulation update. *Blood Purif* 34: 88–93, 2012 https://doi.org/10.1159/000342378

57. Morabito S, Pistolesi V, Tritapepe L, Fiaccadori E: Regional citrate anticoagulation for RRTs in critically ill patients with AKI. *Clin J Am Soc Nephrol* 9: 2173–2188, 2014 https://doi.org/10.2215/CJN.01280214
58. Davenport A, Tolwani A: Citrate anticoagulation for continuous renal replacement therapy (CRRT) in patients with acute kidney injury admitted to the intensive care unit. *NDT Plus* 2: 439–447, 2009
59. Calatzis A, Toepfer M, Schramm W, Spannagl M, Schiffl H: Citrate anticoagulation for extracorporeal circuits: Effects on whole blood coagulation activation and clot formation. *Nephron* 89: 233–236, 2001 https://doi.org/10.1159/000046075
60. Liu C, Mao Z, Kang H, Hu J, Zhou F: Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: A meta-analysis with trial sequential analysis of randomized controlled trials. *Crit Care* 20: 144, 2016 https://doi.org/10.1186/s13054-016-1299-0
61. Meier-Kriesche HU, Gitomer J, Finkel K, DuBose T: Increased total to ionized calcium ratio during continuous venovenous hemodialysis with regional citrate anticoagulation. *Crit Care Med* 29: 748–752, 2001 https://doi.org/10.1097/00003246-200104000-00010
62. Schneider AG, Journois D, Rimmelé T: Complications of regional citrate anticoagulation: Accumulation or overload? *Crit Care* 21: 281, 2017 https://doi.org/10.1186/s13054-017-1880-1
63. Apsner R, Schwarzenhofer M, Derfler K, Zauner C, Ratheiser K, Kranz A: Impairment of citrate metabolism in acute hepatic failure. *Wien Klin Wochenschr* 109: 123–127, 1997
64. Kramer L, Bauer E, Joukhadar C, Strobl W, Gendo A, Madl C, Gangl A: Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients. *Crit Care Med* 31: 2450–2455, 2003 https://doi.org/10.1097/01.CCM.0000084871.76568.E6
65. Churchwell MD, Mueller BA: Drug dosing during continuous renal replacement therapy. *Semin Dial* 22: 185–188, 2009 https://doi.org/10.1111/j.1525-139X.2008.00541.x
66. Pistolesi V, Morabito S, Di Mario F, Regolisti G, Cantarelli C, Fiaccadori E: A guide to understanding antimicrobial drug dosing in critically ill patients on renal replacement therapy. *Antimicrob Agents Chemother* 63: e00583-19, 2019 https://doi.org/10.1128/AAC.00583-19
67. Troyanov S, Cardinal J, Geadah D, Parent D, Courteau S, Caron S, Leblanc M: Solute clearances during continuous venovenous haemofiltration at various ultrafiltration flow rates using Multiflow-100 and HF1000 filters. *Nephrol Dial Transplant* 18: 961–966, 2003 https://doi.org/10.1093/ndt/gfg055
68. Brunet S, Leblanc M, Geadah D, Parent D, Courteau S, Cardinal J: Diffusive and convective solute clearances during continuous renal replacement therapy at various dialysate and ultrafiltration flow rates. *Am J Kidney Dis* 34: 486–492, 1999 https://doi.org/10.1016/S0272-6386(99)70076-4
69. Smetana KS, Cook AM, Bastin ML, Oyler DR: Antiepileptic dosing for critically ill adult patients receiving renal replacement therapy. *J Crit Care* 36: 116–124, 2016 https://doi.org/10.1016/j.jcrc.2016.06.023
70. Kim IY, Kim JH, Lee DW, Lee SB, Rhee H, Seong EY, Kwak IS, Song SH: Fluid overload and survival in critically ill patients with acute kidney injury receiving continuous renal replacement therapy. *PLoS One* 12: e0172137, 2017 https://doi.org/10.1371/journal.pone.0172137
71. Seyler L, Cotton F, Taccone FS, De Backer D, Macours P, Vincent JL, Jacobs F: Recommended β-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. *Crit Care* 15: R137, 2011 https://doi.org/10.1186/cc10257
72. Beumier M, Casu GS, Hites M, Seyler L, Cotton F, Vincent JL, Jacobs F, Taccone FS: β-lactam antibiotic concentrations during continuous renal replacement therapy. *Crit Care* 18: R105, 2014 https://doi.org/10.1186/cc13886
73. Moriyama B, Henning SA, Neuhauser MM, Danner RL, Walsh TJ: Continuous-infusion beta-lactam antibiotics during continuous venovenous hemofiltration for the treatment of resistant gram-negative bacteria. *Ann Pharmacother* 43: 1324–1337, 2009 https://doi.org/10.1345/aph.1L638
74. D'Arcy DM, Casey E, Gowing CM, Donnelly MB, Corrigan OI: An open prospective study of amikacin pharmacokinetics in critically ill patients during treatment with continuous venovenous haemodiafiltration. *BMC Pharmacol Toxicol* 13: 14, 2012 https://doi.org/10.1186/2050-6511-13-14
75. Flannery AH, Thompson Bastin ML: Oseltamivir dosing in critically ill patients with severe influenza. *Ann Pharmacother* 48: 1011–1018, 2014 https://doi.org/10.1177/1060028014535362
76. Lam SW, Bauer SR: Amikacin pharmacokinetics during continuous veno-venous hemodialysis. *Infect Dis Ther* 2: 217–226, 2013 https://doi.org/10.1007/s40121-013-0012-8
77. Chaijamorn W, Charoensareerat T, Srisawat N, Pattharachayakul S, Boonpeng A: Cefepime dosing regimens in critically ill patients receiving continuous renal replacement therapy: A Monte Carlo simulation study. *J Intensive Care* 6: 61, 2018 https://doi.org/10.1186/s40560-018-0330-8
78. Taccone FS, de Backer D, Laterre PF, Spapen H, Dugernier T, Delattre I, Wallemacq P, Vincent JL, Jacobs F: Pharmacokinetics of a loading dose of amikacin in septic patients undergoing continuous renal replacement therapy. *Int J Antimicrob Agents* 37: 531–535, 2011 https://doi.org/10.1016/j.ijantimicag.2011.01.026
79. Shaw AR, Mueller BA: Antibiotic dosing in continuous renal replacement therapy. *Adv Chronic Kidney Dis* 24: 219–227, 2017 https://doi.org/10.1053/j.ackd.2017.05.004
80. Roger C, Wallis SC, Muller L, Saissi G, Lipman J, Lefrant JY, Roberts JA: Influence of renal replacement modalities on amikacin population pharmacokinetics in critically ill patients on continuous renal replacement therapy. *Antimicrob Agents Chemother* 60: 4901–4909, 2016 https://doi.org/10.1128/AAC.00828-16

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