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Regional citrate anticoagulation for continuous renal replacement therapy without post-filter monitoring of ionized calcium

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ABSTRACT

Continuous renal replacement therapy (CRRT) modalities are usually preferred in hemodynamically unstable patients in the intensive care units (ICU) but perceived expense and complexity slows broad acceptance. Heparin remains a problematic choice for CRRT anticoagulation due to the risk of bleeding in ICU patients and concerns about heparin-induced thrombocytopenia. In this paper, we are describing our simplified regional citrate anticoagulation protocol, utilizing commercially available, premixed solutions exclusively and minimized laboratory monitoring. The protocol is employing Anticoagulant Citrate Dextrose-A (ACD-A) solution for citrate delivery, calcium-free dialysate or replacement fluids and separate calcium infusion, all commercially available in the United States. ACD-A is being infused pre-filter with an hourly rate of 1.5:1 to blood flow rate per minute without specific monitoring of post-filter ionized calcium concentration. Separate infusions of calcium-chloride, sodium phosphate and magnesium chloride are employed via triple lumen catheter to normalize peripheral ionized calcium, phosphate and magnesium concentrations, respectively. The protocol can be conveniently applied in both continuous veno-venous hemofiltration and hemodiafiltration regimens with several of the commercially available CRRT platforms. Built-in features of the protocol are the tendency alkalization and mild hypernatremia, which may be advantageous under select circumstances.

Implication for health policy/practice/research/medical education:
Establishing continuous renal replacement therapy (CRRT) in the intensive care units in a cost-effective manner remains a challenge. Regional citrate anticoagulation (RCA) during CRRT circumvents the risk of systemic anticoagulation, but represents yet another layer of complexity on an already intricate technology. Abandoning post-filter monitoring of ionized calcium during RCA offers improvement over existing approaches, including reduced complexity, potential for cost-saving and decreased potential for medical errors.

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Introduction

Providing safe and reliable renal replacement therapy in the intensive care setting remains a challenge. While continuous renal replacement therapy (CRRT) modalities are usually preferred in hemodynamically unstable patients, difficulties pertaining to the complexity of such therapy exist. Many aspects of CRRT delivery remain vigorously debated, including the timing and indications of initiation, dose and duration of therapy and the choice of anticoagulants (1-4). Preventing clot formation is key for successful delivery of renal replacement support (5). Heparin, the agent historically used for anticoagulation of the extracorporeal circuit, may also induce thrombocytopenia (6) or increase the risk of bleeding in patients already at high risk. Further, the suppression of the platelet count is frequently observed in the intensive care unit (ICU) setting due to a multitude of reasons, including drug effects, excessive uptake and the presence of acute critical illness itself (7-9). Thus, not surprisingly, the search has been on for some time seeking

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an alternative option of achieving regional anticoagulation in the extracorporeal circuit.

Materials and Methods

We conducted a literature search on three databases including PubMed, EMBASE, Scopus and Google Scholar. The search was performed using a combination of the following terms; continuous renal replacement therapy, hemofiltration, regional citrate anticoagulation, thrombocytopenia and intensive care unit. Further, the authors' clinically experience was considered, when writing this protocol paper.

Regional citrate anticoagulation

Regional citrate anticoagulation (RCA) is an attractive candidate to achieve this goal (10-13). However, RCA may potentially add substantially to the complexity of an already complicated technology, impeding acceptance and utilizing excessive resources (11,14). Delivering care in a uniform, safe and standardized setting with minimized need for laboratory testing appears to be the cornerstone of the implementation of RCA in the ICU setting. Simplifying the delivery of CRRT and offering uniform protocol may enhance acceptance by nursing staff and hospital administrators alike. In this paper, we would like to offer a description of a safe and effective standardized protocol with a potential to minimize errors.

General concepts of regional citrate anticoagulation

For an adult weighing 70 kg, the total amount of dissolved calcium in the extracellular space is approximately 1000 mg at any given time. Under normal circumstances, total calcium concentration is approximately 2.5 mM/L (or 10 mg/dL), of which about 50% is ionized, 13 % is bound by small anions (lactate, citrate and phosphate) and the rest by negatively charged albumin molecules. This calcium amount is the approximate equivalent of ~4 amps of 10% calcium-chloride (6.8 mM of calcium per each 10 mL) or ~12 amps of 10% calcium gluconate (93 mg of calcium or 2.3 mM per each 10 mL). At physiologic P^H and ionic strength, ionized calcium is expected to decrease by 0.1 mM/L with each 0.5-0.6 mM/L (10 mg/dL) rise of plasma citrate. Assuming an initial ionized calcium concentration of 1.0-1.25 mM/L, ionized calcium is fully expected to be depleted once citrate concentration reaches about 5-6 mM/L (or 100 mg/dL). At this point, similarly to the blood exposed to anticoagulant ethylenediaminetetraacetic acid (EDTA), the coagulation cascade is rendered ineffective and blood clot formation impaired. Citrate exposure is known to confer less filter-induced complement activation, neutrophil degranulation and less endothelial activation than heparin during continuous hemofiltration (15). To deliver a cheap and easily available form of citrate supplementation, the Anticoagulant Citrate Dextrose-A (ACD-A) solution is an obvious choice. It contains an isotonic mixture of citric acid (0.8%), trisodium citrate (2.2%) and dextrose, resulting in a final citrate concentration of 3.0 % (or 112.9 mM/L). The normalization of systemic ionized calcium is achieved by simultaneous infusion of calcium-chloride and the endogenous metabolism of citrate, in the liver converting to bicarbonate in an approximate ratio of 1:3 and, simultaneously, releasing ionized calcium from the chelated form.

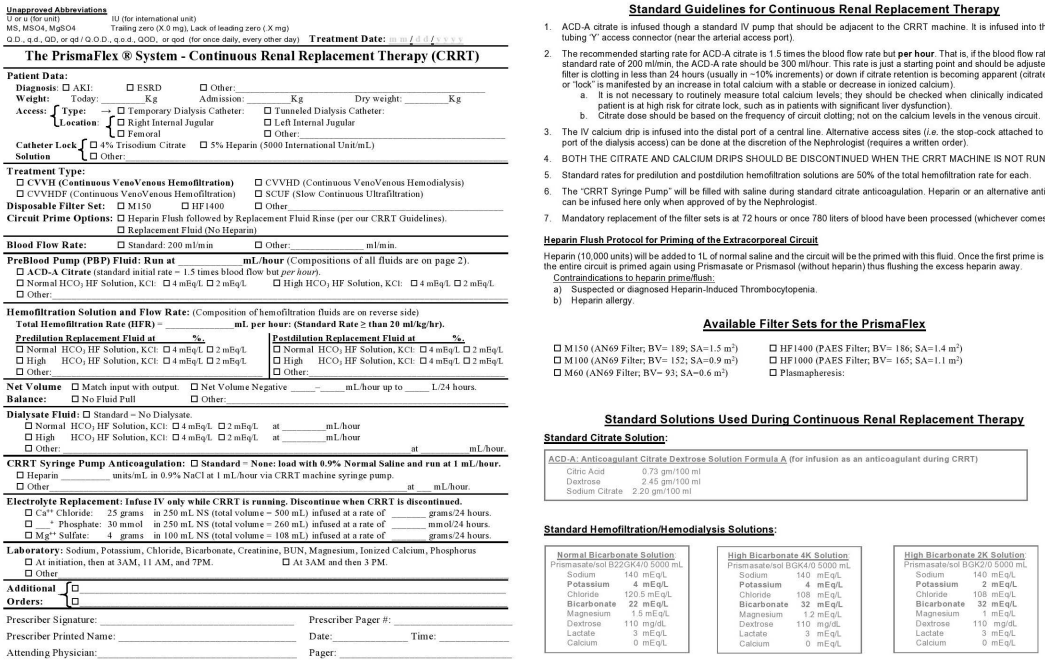
Goals of therapy

Successful implementation of CRRT should accommodate the following objectives;

- Utilization of physiologic or near-physiologic fluid solutions requiring little specific monitoring.
- Avoiding "customized" or pharmacy-made solutions, thus minimizing potential for medical errors.
- Avoiding systemic anticoagulants such as heparin in patients who are inherently at increased risk of bleeding.
- Minimizing clotting of extracorporeal circuit, thus avoiding frequent restarts and lost time with no ongoing renal replacement therapy.
- Avoiding the need for post-filter calcium monitoring, thus reducing the need for frequent testing and avoiding confusion resulting from markedly "abnormal" results of post-filter ionized calcium values.

In 2008, the nephrology faculty of our medical center revised the existing protocols of continuous veno-venous hemofiltration (CVVHF) and hemodiafiltration (CVVHDF) regimens to deliver RCA in a uniform manner while minimizing cost, complexity and potential risk for the recipients of the therapy. We specifically desired the practice of abandoning post-filter monitoring of ionized calcium, highly inaccurate procedure during RCA. As we are a training institution regularly working with physician-in-training (nephrology fellows), it was important at that time to minimize handwritten orders to complement existing pre-printed order sets. Samples of our protocols are shown in Figures 1 and 2. These protocols can also easily be converted into electronic instruction formats in the current era.

As a rule, we routinely start with a blood flow of 200-250 mL/min for our adult patients. ACD-A solution (available from multiple manufacturers) is infused pre-filter at a rate of ×1.5 of the blood flow rate in mL/L (e.g. for a blood flow rate of 200 mL/min an ACD-A infusion rate of 300 mL/h will be applied). For replacement fluid or dialyzate fluid we are using calcium-free premixed solutions, close to physiologic concentrations (PrismaSate, PrismaSol; Gambro Renal Products Inc., Lakewood, CO), shown in Figures 1 and 2, second parts. The total effluent is calculated to achieve a net clearance of >20-25 mL/kg/h. In pure convective modality (CVVHF), we are routinely splitting the pre- and post-filter rate of the replacement fluid at 50:50 or 70:30 percent. A separate I.V. infusion will deliver calcium with calcium-chloride at an initial rate of 25 g/24 h (500 mL bag containing 25 g of calcium chloride



Unapproved Abbreviations
U or u (for unit) — IU (for international unit)
MS, MSO4, MgSO4 — Trailing zero (X.0 mg), Lack of leading zero (.X mg)
Q.D., q.d., QD, or qd / Q.O.D., q.o.d., QOD, or qod (for once daily, every other day) **Treatment Date:** m m / d d / y y y y

The PrismaFlex ® System - Continuous Renal Replacement Therapy (CRRT)

Patient Data:
Diagnosis: ☐ AKI: ☐ ESRD ☐ Other:
Weight: Today: _____Kg Admission: _____Kg Dry weight: _____Kg
Access: **Type:** → ☐ Temporary Dialysis Catheter: ☐ Tunneled Dialysis Catheter:
Location: ☐ Right Internal Jugular ☐ Left Internal Jugular ☐ Femoral ☐ Other:
Catheter Lock Solution ☐ 4% Trisodium Citrate ☐ 5% Heparin (5000 International Unit/mL) ☐ Other:

Treatment Type:
☐ **CVVH (Continuous VenoVenous Hemofiltration)** ☐ CVVHD (Continuous VenoVenous Hemodialysis)
☐ CVVHDF (Continuous VenoVenous Hemofiltration) ☐ SCUF (Slow Continuous Ultrafiltration)
Disposable Filter Set: ☐ M150 ☐ HF1400 ☐ Other
Circuit Prime Options: ☐ Heparin Flush followed by Replacement Fluid Rinse (per our CRRT Guidelines). ☐ Replacement Fluid (No Heparin)

Blood Flow Rate: ☐ Standard: 200 ml/min ☐ Other: _____ ml/min.

PreBlood Pump (PBP) Fluid: Run at _____mL/hour (Compositions of all fluids are on page 2).
☐ **ACD-A Citrate** (standard initial rate = 1.5 times blood flow but *per hour*).
☐ Normal HCO_3 HF Solution, KCl: ☐ 4 mEq/L ☐ 2 mEq/L ☐ High HCO_3 HF Solution, KCl: ☐ 4 mEq/L ☐ 2 mEq/L
☐ Other:

Hemofiltration Solution and Flow Rate: (Composition of hemofiltration fluids are on reverse side)
Total Hemofiltration Rate (HFR) = _____mL per hour: (Standard Rate ≥ than 20 ml/kg/hr).

Predilution Replacement Fluid at _____%.
☐ Normal HCO_3 HF Solution, KCl: ☐ 4 mEq/L ☐ 2 mEq/L
☐ High HCO_3 HF Solution, KCl: ☐ 4 mEq/L ☐ 2 mEq/L
☐ Other:

Postdilution Replacement Fluid at _____%.
☐ Normal HCO_3 HF Solution, KCl: ☐ 4 mEq/L ☐ 2 mEq/L
☐ High HCO_3 HF Solution, KCl: ☐ 4 mEq/L ☐ 2 mEq/L
☐ Other:

Net Volume Balance: ☐ Match input with output. ☐ Net Volume Negative _____–_____mL/hour up to _____ L/24 hours. ☐ No Fluid Pull ☐ Other:

Dialysate Fluid: ☐ Standard = No Dialysate.
☐ Normal HCO_3 HF Solution, KCl: ☐ 4 mEq/L ☐ 2 mEq/L at _____mL/hour
☐ High HCO_3 HF Solution, KCl: ☐ 4 mEq/L ☐ 2 mEq/L at _____mL/hour
☐ Other: at _____mL/hour.

CRRT Syringe Pump Anticoagulation: ☐ Standard = None: load with 0.9% Normal Saline and run at 1 mL/hour.
☐ Heparin _____ units/mL in 0.9% NaCl at 1 mL/hour via CRRT machine syringe pump.
☐ Other at ___mL/hour.

Electrolyte Replacement: Infuse IV only while CRRT is running. Discontinue when CRRT is discontinued.
☐ Ca^{++} Chloride: 25 grams in 250 mL NS (total volume = 500 mL) infused at a rate of _____ grams/24 hours.
☐ $^{++}$ Phosphate: 30 mmol in 250 mL NS (total volume = 260 mL) infused at a rate of _____ mmol/24 hours.
☐ Mg^{++} Sulfate: 4 grams in 100 mL NS (total volume = 108 mL) infused at a rate of _____ grams/24 hours.

Laboratory: Sodium, Potassium, Chloride, Bicarbonate, Creatinine, BUN, Magnesium, Ionized Calcium, Phosphorus
☐ At initiation, then at 3AM, 11 AM, and 7PM. ☐ At 3AM and then 3 PM.
☐ Other

Additional Orders: ☐ ☐

Prescriber Signature: _____ Prescriber Pager #: _____
Prescriber Printed Name: _____ Date: _____ Time: _____
Attending Physician: _____ Pager: _____

Standard Guidelines for Continuous Renal Replacement Therapy

1. ACD-A citrate is infused though a standard IV pump that should be adjacent to the CRRT machine. It is infused into the dialysis tubing 'Y' access connector (near the arterial access port).
2. The recommended starting rate for ACD-A citrate is 1.5 times the blood flow rate but **per hour**. That is, if the blood flow rate is at the standard rate of 200 ml/min, the ACD-A rate should be 300 ml/hour. This rate is just a starting point and should be adjusted up if the filter is clotting in less than 24 hours (usually in ~10% increments) or down if citrate retention is becoming apparent (citrate retention or "lock" is manifested by an increase in total calcium with a stable or decrease in ionized calcium).
   a. It is not necessary to routinely measure total calcium levels; they should be checked when clinically indicated (i.e. if the patient is at high risk for citrate lock, such as in patients with significant liver dysfunction).
   b. Citrate dose should be based on the frequency of circuit clotting; not on the calcium levels in the venous circuit.
3. The IV calcium drip is infused into the distal port of a central line. Alternative access sites (*i.e.* the stop-cock attached to the return port of the dialysis access) can be done at the discretion of the Nephrologist (requires a written order).
4. BOTH THE CITRATE AND CALCIUM DRIPS SHOULD BE DISCONTINUED WHEN THE CRRT MACHINE IS NOT RUNNING.
5. Standard rates for predilution and postdilution hemofiltration solutions are 50% of the total hemofiltration rate for each.
6. The "CRRT Syringe Pump" will be filled with saline during standard citrate anticoagulation. Heparin or an alternative anticoagulant can be infused here only when approved of by the Nephrologist.
7. Mandatory replacement of the filter sets is at 72 hours or once 780 liters of blood have been processed (whichever comes first).

Heparin Flush Protocol for Priming of the Extracorporeal Circuit

Heparin (10,000 units) will be added to 1L of normal saline and the circuit will be the primed with this fluid. Once the first prime is complete, the entire circuit is primed again using Prismasate or Prismasol (without heparin) thus flushing the excess heparin away.
Contraindications to heparin prime/flush:
a) Suspected or diagnosed Heparin-Induced Thrombocytopenia.
b) Heparin allergy.

Available Filter Sets for the PrismaFlex

☐ M150 (AN69 Filter; BV= 189; SA=1.5 m^2) ☐ HF1400 (PAES Filter; BV= 186; SA=1.4 m^2)
☐ M100 (AN69 Filter; BV= 152; SA=0.9 m^2) ☐ HF1000 (PAES Filter; BV= 165; SA=1.1 m^2)
☐ M60 (AN69 Filter; BV= 93; SA=0.6 m^2) ☐ Plasmapheresis:

Standard Solutions Used During Continuous Renal Replacement Therapy

Standard Citrate Solution:

ACD-A: Anticoagulant Citrate Dextrose Solution Formula A (for infusion as an anticoagulant during CRRT)

Citric Acid	0.73 gm/100 ml
Dextrose	2.45 gm/100 ml
Sodium Citrate	2.20 gm/100 ml

Standard Hemofiltration/Hemodialysis Solutions:

Normal Bicarbonate Solution: Prismasate/sol B22GK4/0 5000 mL

Sodium	140 mEq/L
Potassium	**4 mEq/L**
Chloride	120.5 mEq/L
Bicarbonate	**22 mEq/L**
Magnesium	1.5 mEq/L
Dextrose	110 mg/dL
Lactate	3 mEq/L
Calcium	0 mEq/L

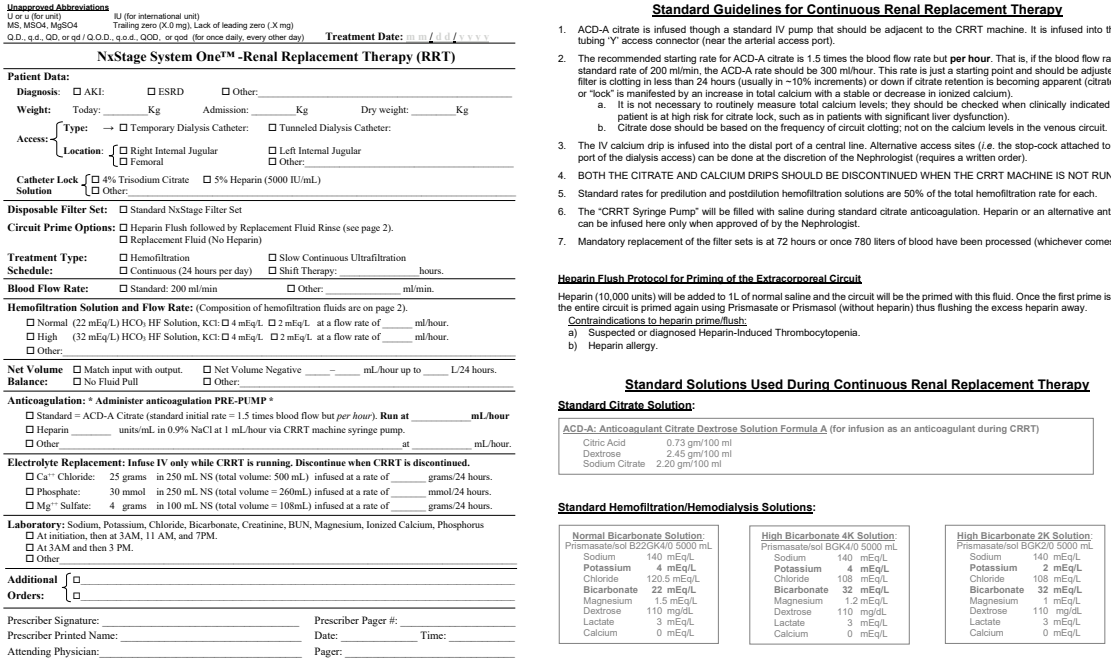
High Bicarbonate 4K Solution: Prismasate/sol BGK4/0 5000 mL

Sodium	140 mEq/L
Potassium	**4 mEq/L**
Chloride	108 mEq/L
Bicarbonate	**32 mEq/L**
Magnesium	1.2 mEq/L
Dextrose	110 mg/dL
Lactate	3 mEq/L
Calcium	0 mEq/L

High Bicarbonate 2K Solution: Prismasate/sol BGK2/0 5000 mL

Sodium	140 mEq/L
Potassium	**2 mEq/L**
Chloride	108 mEq/L
Bicarbonate	**32 mEq/L**
Magnesium	1 mEq/L
Dextrose	110 mg/dL
Lactate	3 mEq/L
Calcium	0 mEq/L

Figure 1. Adult Prismaflex CVVHD/HDF protocol.



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U or u (for unit) — IU (for international unit)
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Q.D., q.d., QD, or qd / Q.O.D., q.o.d., QOD, or qod (for once daily, every other day) **Treatment Date:** m m / d d / y y y y

NxStage System One™ -Renal Replacement Therapy (RRT)

Patient Data:
Diagnosis: ☐ AKI: ☐ ESRD ☐ Other:
Weight: Today: _____Kg Admission: _____Kg Dry weight: _____Kg
Access: **Type:** → ☐ Temporary Dialysis Catheter: ☐ Tunneled Dialysis Catheter:
Location: ☐ Right Internal Jugular ☐ Left Internal Jugular ☐ Femoral ☐ Other:
Catheter Lock Solution ☐ 4% Trisodium Citrate ☐ 5% Heparin (5000 IU/mL) ☐ Other:

Disposable Filter Set: ☐ Standard NxStage Filter Set
Circuit Prime Options: ☐ Heparin Flush followed by Replacement Fluid Rinse (see page 2). ☐ Replacement Fluid (No Heparin)
Treatment Type: ☐ Hemofiltration ☐ Slow Continuous Ultrafiltration
Schedule: ☐ Continuous (24 hours per day) ☐ Shift Therapy: _____hours.
Blood Flow Rate: ☐ Standard: 200 ml/min ☐ Other: _____ ml/min.

Hemofiltration Solution and Flow Rate: (Composition of hemofiltration fluids are on page 2).
☐ Normal (22 mEq/L) HCO_3 HF Solution, KCl: ☐ 4 mEq/L ☐ 2 mEq/L at a flow rate of _____ ml/hour.
☐ High (32 mEq/L) HCO_3 HF Solution, KCl: ☐ 4 mEq/L ☐ 2 mEq/L at a flow rate of _____ ml/hour.
☐ Other:

Net Volume Balance: ☐ Match input with output. ☐ Net Volume Negative _____–_____ mL/hour up to _____ L/24 hours. ☐ No Fluid Pull ☐ Other:

Anticoagulation: * Administer anticoagulation PRE-PUMP *
☐ Standard = ACD-A Citrate (standard initial rate = 1.5 times blood flow but *per hour*). **Run at _____mL/hour**
☐ Heparin _____ units/mL in 0.9% NaCl at 1 mL/hour via CRRT machine syringe pump.
☐ Other at _____ mL/hour.

Electrolyte Replacement: Infuse IV only while CRRT is running. Discontinue when CRRT is discontinued.
☐ Ca^{++} Chloride: 25 grams in 250 mL NS (total volume: 500 mL) infused at a rate of _____ grams/24 hours.
☐ Phosphate: 30 mmol in 250 mL NS (total volume = 260mL) infused at a rate of _____ mmol/24 hours.
☐ Mg^{++} Sulfate: 4 grams in 100 mL NS (total volume = 108mL) infused at a rate of _____ grams/24 hours.

Laboratory: Sodium, Potassium, Chloride, Bicarbonate, Creatinine, BUN, Magnesium, Ionized Calcium, Phosphorus
☐ At initiation, then at 3AM, 11 AM, and 7PM.
☐ At 3AM and then 3 PM.
☐ Other

Additional Orders: ☐ ☐

Prescriber Signature: _____ Prescriber Pager #: _____
Prescriber Printed Name: _____ Date: _____ Time: _____
Attending Physician: _____ Pager: _____

Standard Guidelines for Continuous Renal Replacement Therapy

1. ACD-A citrate is infused though a standard IV pump that should be adjacent to the CRRT machine. It is infused into the dialysis tubing 'Y' access connector (near the arterial access port).
2. The recommended starting rate for ACD-A citrate is 1.5 times the blood flow rate but **per hour**. That is, if the blood flow rate is at the standard rate of 200 ml/min, the ACD-A rate should be 300 ml/hour. This rate is just a starting point and should be adjusted up if the filter is clotting in less than 24 hours (usually in ~10% increments) or down if citrate retention is becoming apparent (citrate retention or "lock" is manifested by an increase in total calcium with a stable or decrease in ionized calcium).
   a. It is not necessary to routinely measure total calcium levels; they should be checked when clinically indicated (i.e. if the patient is at high risk for citrate lock, such as in patients with significant liver dysfunction).
   b. Citrate dose should be based on the frequency of circuit clotting; not on the calcium levels in the venous circuit.
3. The IV calcium drip is infused into the distal port of a central line. Alternative access sites (*i.e.* the stop-cock attached to the return port of the dialysis access) can be done at the discretion of the Nephrologist (requires a written order).
4. BOTH THE CITRATE AND CALCIUM DRIPS SHOULD BE DISCONTINUED WHEN THE CRRT MACHINE IS NOT RUNNING.
5. Standard rates for predilution and postdilution hemofiltration solutions are 50% of the total hemofiltration rate for each.
6. The "CRRT Syringe Pump" will be filled with saline during standard citrate anticoagulation. Heparin or an alternative anticoagulant can be infused here only when approved of by the Nephrologist.
7. Mandatory replacement of the filter sets is at 72 hours or once 780 liters of blood have been processed (whichever comes first).

Heparin Flush Protocol for Priming of the Extracorporeal Circuit

Heparin (10,000 units) will be added to 1L of normal saline and the circuit will be the primed with this fluid. Once the first prime is complete, the entire circuit is primed again using Prismasate or Prismasol (without heparin) thus flushing the excess heparin away.
Contraindications to heparin prime/flush:
a) Suspected or diagnosed Heparin-Induced Thrombocytopenia.
b) Heparin allergy.

Standard Solutions Used During Continuous Renal Replacement Therapy

Standard Citrate Solution:

ACD-A: Anticoagulant Citrate Dextrose Solution Formula A (for infusion as an anticoagulant during CRRT)

Citric Acid	0.73 gm/100 ml
Dextrose	2.45 gm/100 ml
Sodium Citrate	2.20 gm/100 ml

Standard Hemofiltration/Hemodialysis Solutions:

Normal Bicarbonate Solution: Prismasate/sol B22GK4/0 5000 mL

Sodium	140 mEq/L
Potassium	**4 mEq/L**
Chloride	120.5 mEq/L
Bicarbonate	**22 mEq/L**
Magnesium	1.5 mEq/L
Dextrose	110 mg/dL
Lactate	3 mEq/L
Calcium	0 mEq/L

High Bicarbonate 4K Solution: Prismasate/sol BGK4/0 5000 mL

Sodium	140 mEq/L
Potassium	**4 mEq/L**
Chloride	108 mEq/L
Bicarbonate	**32 mEq/L**
Magnesium	1.2 mEq/L
Dextrose	110 mg/dL
Lactate	3 mEq/L
Calcium	0 mEq/L

High Bicarbonate 2K Solution: Prismasate/sol BGK2/0 5000 mL

Sodium	140 mEq/L
Potassium	**2 mEq/L**
Chloride	108 mEq/L
Bicarbonate	**32 mEq/L**
Magnesium	1 mEq/L
Dextrose	110 mg/dL
Lactate	3 mEq/L
Calcium	0 mEq/L

Figure 2. Adult NxStage protocol.

solution with 250 mL of normal saline [manufactured at a compounding pharmacy]). Following the initial 24-48 hours, most patients will need separate infusions of phosphorus (e.g. sodium-phosphate of 30-45 mM/24 h) and magnesium (magnesium chloride of 2-4 gm/24 h). Ionized calcium is not being monitored on the return limb, to minimize expense and avoid potential confusion with regard to very low values (minimizing potential for false alarms and medical errors). For serum ionized calcium, we are targeting normal values (1.25 mM/L) but with a bias to keep it in a high-normal range (1.10-1.30 mM/L) for critically ill patients. Target range for phosphorus is between 3.5-4.5 mg/dL and 1.5-2 mg/dL for magnesium. As ACD-A is both a source of bicarbonate

and hypertonic (sodium 225 mEq/L), built-in features of the protocol are the tendencies for metabolic alkalosis and mild hypernatremia, may be advantageous under select circumstances (e.g., brain edema). However, should serum bicarbonate rise to an undesirable degree (e.g., >28 mM/L), the blood flow rate can be reduced to 150 mL/min, with consequential reduction of ACD-A flow rate to 220-230 mL/h and decreased net citrate delivery.

For premature filter clotting, at each restart we increase ACD-A rate by 10% (30 mL/h). For hypocalcemia with low ionized calcium, we increase the calcium infusion rate by 10%-20%. For "citrate lock" (elevated total calcium with low or normal ionized calcium) we decrease citrate rate by 10%. Should further clotting take place, in the absence of contraindication, we may add fixed low-dose (500-750 units/hour) or aPTT-adjusted I.V. heparin into the circuit. On the other hand, expense is prohibitive for direct thrombin inhibitor argatroban, except in very unusual cases (16). While it is technically possible to add additional potassium to the pre-mixed solution, we generally avoid such practice. In the anecdotal experience of the authors, filter survival usually reached 48-72 hours under these circumstances for most (~70%) of the patients.

Additional issues of implementation

Large volume hemofiltration or dialysate rates (>2-3 L/h) frequently result in hypothermia in the ICU. The use of blood warmers is therefore routinely needed for the extracorporeal circuits with occasional measures of additional passive warming (heating blanket, additional covering of neck-head area). Thyroid dysfunction should always be on the differential for unexplained hypothermia despite these measures (17). For hemodialysis access we are preferentially using double dialysis catheters placed into the internal jugular vein. Patients also need a triple-lumen catheter placed into a central vein for infusion of calcium, phosphate and magnesium. Only in rare circumstances do we permit the omission of triple-lumen catheter placement and the infusion of calcium via the return limb (attending physician's signature required) for those with critical electrolyte abnormalities and central access difficulties, where even a few hours delay would cause harm. Avoiding post-filter ionized calcium monitoring reduced the expense and potential for misunderstanding, reporting on the extremely low, non-physiologic ionized calcium concentrations. Similar abandonment of routine post-filter monitoring has been reported since by others (18) and the accuracy of measured post-filter ionized calcium has been called into question by others, as well (19,20). We routinely place safety locks on the dialysis catheter-to-extracorporeal connection (e.g., HemaClip Bloodline Connector Clip for Hemodialysis, Fresenius Medical Care North America, Waltham, MA) to prevent accidental disconnection (Figure 3). The back page of the protocol serves also as a quick, hands-on reference guide for physicians to review available solutions for renal replacement therapy. Protocols from Figures 1 and 2 are further adaptable for the individual user's institutions.

Figure 3. Blood line connector safety clip in place.

In our experience, nursing acceptance is critical for successful implementation. Education, including lectures and seminars given to nursing staff, hands-on training session and the development of a cadre of highly trained "super-users" for each ICU is critical. Maintaining training and outcome monitoring is essential and part of ensuring quality of care. Hospital administrations need to be on board, along with the hospital pharmacy program, to recognize the cost effectiveness and full potential of our protocol.

Conclusion

Abandoning post-filter monitoring of ionized calcium during RCA offers improvement over existing approaches, including simplification of management and reducing the burden of complexity, hence decreasing the potential for medical errors. Our paper described sample protocols of RCA-assisted CRRT and briefly reviewed practical points of implementation. We kept the language of this paper deliberately simple, hence it would be easy to read and understand by non-nephrology physicians, nurses and dialysis technicians alike.

Acknowledgements

Drs. Fülöp and Zsom are former faculty members of the University of Mississippi Medical Center, Department of Medicine, as well as former Medical Directors of Dialysis at the University of Mississippi Medical Center. Dr. Fülöp is currently affiliated with the Medical University of South Carolina and the Ralph H. Johnson VA Medical Center in Charleston, SC, USA. Dr. Sohail Abdul Salim is a recent graduate of Department of Medicine Nephrology Fellowship at the University of Mississippi Medical Center (Class of 2017); he is currently affiliated with Central Nephrology, Jackson, MS. We sincerely appreciated the assistance of Mr. Attila Lénárt-Muszka during editing and grammar review.

Authors' contribution

Primary draft by TF. Editing the final manuscript by SAS

and LZ. All authors read and signed the final manuscript.

Conflicts of interest

Dr. Zsom is an employee of Fresenius Medical Care (FMC) Hungary and Dr Fülöp is a former employee of FMC Hungary. However, the views and opinions expressed herewith do not reflect the official opinion of the Fresenius Medical Care Hungary.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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