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# Management of dysnatremias with continuous renal replacement therapy

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## Abstract

Disorders of serum sodium concentration are common in critically ill patients who may have concomitant acute kidney injury, chronic kidney disease, or end-stage kidney disease. Many of these patients may require customized serum sodium level management with dialysis which, if not strictly controlled, can lead to significant complications. Thus, controlled correction of the serum sodium level is necessary to avoid the development of osmotic demyelination syndrome in hyponatremic patients and dialysis disequilibrium syndrome in hypernatremic patients. Continuous renal replacement therapy offers unique benefits through the ability to slowly and safely correct dysnatremias that can be tailored to specific patient needs and should be considered in select patients.

## 1 | INTRODUCTION

Sodium disorders can often complicate dialysis-requiring acute kidney injury, chronic kidney disease (CKD), or end-stage kidney disease.[1–3] When renal replacement therapy is performed in patients with dysnatremias (hyponatremia and hypernatremia), controlled correction of sodium disorders is necessary to decrease the risk of osmotic demyelination syndrome (hyponatremia) or dialysis disequilibrium syndrome and brain edema (hypernatremia). Various published treatment guidelines (2013 Expert Panel Recommendations, 2014 European Hyponatraemia Guideline Development Group) do not address these unique situations.

In some circumstances, the treatment of hyponatremia can be accomplished with simple modifications to existing therapies. For instance, when the serum sodium is only moderately decreased in chronic hyponatremia (i.e. ≥120 mEq/L), the patient's serum sodium could easily remain within guidelines for safe correction (i.e., no more than 6–8 mEq/L increase) by targeting Kt/V of 1.2 or less per treatment and lowering the dialysate sodium to its lowest limit of 130 mEq/L. Similarly, when the serum sodium is only moderately increased in chronic hypernatremia (i.e., ≤165 mEq/L), by targeting Kt/V of 1.2 or less per treatment and increasing dialysate sodium to its highest limit of 155 mEq/L, the extent of loss of sodium from the patient is limited and the serum sodium decrease is no more than 6–8 mEq/L. However, patients with more extreme dysnatremias ($[Na^+]$ <120 mEq/L or $[Na^+]$ >165 mEq/L) are best treated using continuous renal replacement therapy (CRRT) with the occasional need for hypotonic or hypertonic CRRT solutions or intravenous infusions. The use of CRRT has many advantages that increase the safety margin for the rate of correction of sodium disorders as will be discussed. These include the ability to adjust the rate and tonicity of dialysate fluid (DF) and replacement fluid (RF) which ultimately regulate the rate of systemic serum sodium level correction.[3–5] The calculations described assume provision of uninterrupted dialytic treatment, no profound non-isotonic sodium gains or losses and non-declining filter performance. For simplicity, we also assume the effluent is 100% saturated with small solutes with diffusive clearance. However, it is often not fully saturated because of dialysate shunting and access recirculation. Our general practice is not to exceed 8 mEq/L systemic sodium increase in hyponatremia and not to exceed 10 mEq/L systemic sodium decrease in hypernatremia in any 24-h period with the proposed mathematical approaches. Systemic sodium checks every 6 h should suffice with the proposed formulas while targeting the above limits of correction provided CRRT system settings are not changed and the prescribed urea clearance is about 25–30 ml/kg/h effluent flow (assuming ≥600 ml of total body water present per kilogram body weight, a reasonable estimate of sodium kinetic volume in fluid overloaded ICU patients). To avoid the impact

  

of declining sodium dialysance with partial filter clotting, we recommend the use of all convective CRRT (CVVH) when RCA is not used; and if diffusive CRRT is employed (CVVHD or CVVHDF), we suggest the use of RCA with citrate at least 4–5 mmol/L of blood flow to minimize clotting and increase the stability of the diffusive component of sodium dialysance over longer periods of time. Finally, we recommend maintaining the coordination between CRRT and non-isotonic infusions (e.g., dextrose water or 3% saline) administered to avoid rapid serum sodium correction during CRRT (i.e., when CRRT is interrupted, the non-isotonic infusions should be put on hold). A list of the equations we utilize to manage dysnatremias are available in the appendix.

## 2 | MANAGEMENT OF SEVERE HYPONATREMIA IN PATIENTS WITH KIDNEY FAILURE REQUIRING RENAL REPLACEMENT THERAPY

The management strategies described herein are not applicable to patients with severe acute hyponatremia, especially with acute or CKD, where infusion of hypertonic saline is recommended for symptomatic presentations. Since in many cases, the acuteness or chronicity (defined as >48 h) is not known, it is best to assume that the disorder is chronic and opt for slower correction of the serum sodium in order to avoid complications. Also, of note is that none of these various methods have been evaluated in randomized clinical trials and thus clinicians should use the approach that they are most comfortable with, and their choice may also be dictated by local resource constraints.

### 2.1 | Diluting CRRT solutions based on kinetic principles

Commercially available calcium-containing CRRT solutions usually have a sodium concentration of 140 mEq/L and solutions with markedly lower amounts of sodium are not available. In institutions with adequate pharmacy support these solutions can be diluted with sterile water to achieve the desired sodium concentration. A stepwise change every 24 h to CRRT solutions with a higher sodium concentration than the patient's current serum sodium can be considered. The CRRT solution sodium concentration, CRRT[$Na^+$] needed to maintain the patient's serum sodium within the desired limits of correction can be estimated using the following kinetic formula[3]:

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

Desired Δ serum [$Na^+$] is equal to target serum sodium at 24 h—initial serum sodium, where *D* is the effective sodium dialysance. Sodium dialysance is equal to the sum of dialysate and RF rates when post-filter RF is used. When pre-filter RF is used, sodium dialysance is calculated by multiplying the RF plus dialysate flow rate by the pre-filter dilution factor for sodium. The dilution factor is equal to effective blood water flow for sodium divided by the sum of effective blood water flow of sodium and pre-filter RF rate. *V* is the total body water volume (in L) and can be determined using Watson's formula applied to the patient's estimated dry weight (EDW), or obtained from prior electronic health records data, and adding to this any measured ICU weight gain (current weight −EDW) as estimated 100% edema (water) volume. The advantage of this method is that by lowering the CRRT solution [$Na^+$] – initial serum [$Na^+$] difference, the overall clearance, K (≈*D*) can be increased as needed in conditions where immediate control of other solutes is necessary (e.g., hyperkalemia or acidemia) without faster correction of the dysnatremia.

The dilution can be achieved by injecting free water into the CRRT dialysate or RF bags or exchanging a specific volume of dialysate or replacement solution with an equivalent volume of water.[3] The exchange method keeps the CRRT fluid bag volume constant at 5 L. This method is useful when there is a concern for the commercial CRRT solution bag not having the extra space to accommodate the needed additional water volume (typically >1 L). The volume of sterile water to be added to a CRRT solution bag to achieve a desired sodium concentration can be estimated by the equation:

$$\text{Volume to add} = \frac{\text{CRRT } V \times \left(\text{initial CRRT}\left[Na^+\right] - \text{desired CRRT}\left[Na^+\right]\right)}{\text{desired CRRT}[Na^+]}, \quad (2)$$

where CRRT *V* is the CRRT solution volume. As an example, if you want to dilute the sodium in a 5 L CRRT fluid bag from 140 to 120 mEq/L, you would need to add 833 ml. Alternatively, the volume to be exchanged with sterile water can be calculated using the following formula:

$$\text{Volume to exchange} = \text{CRRT } V - \frac{\text{desired CRRT}\left[Na^+\right] \times \text{CRRT}V}{\text{initial CRRT}[Na^+]}. \quad (3)$$

As an example, to dilute the sodium in a 5 L bag from 140 to 120 mEq/L, 714 ml of CRRT fluid will need to be exchanged with 714 ml of free water. The effect of sterile water added or exchanged on CRRT fluid sodium and other electrolyte concentrations is demonstrated in Tables 1 and 2. The tables use NxStage PureFlow® dialysate solution RFP 401 as an example.

### 2.2 | Administering hypotonic fluid via a separate infusion line

Infusing 5% dextrose water (D5W) solution intravenously into the patient or into the return blood line of the CRRT circuit is another approach to keep the systemic sodium within desired limits of correction.[6] Standard hemodialysis provides high sodium dialysance (~about 250 ml/min = 15L/h or more) and would require extremely large volumes of D5W infusion even with the lowest dialysate sodium setting of 130 mEq/L to prevent a rapid rise in a patient's serum

**TABLE 1** Effect of adding different volumes of water to 5-Liter 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 |
| 500 | 127.27 | 3.64 | 30.91 | 2.73 | 0.91 | 102.73 |
| 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 |

Not all commercial CRRT bags may be able to accommodate additional volume.

**TABLE 2** Effect of exchanging different volumes of a 5-L 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 |
| 500 | 126.00 | 3.60 | 28.80 | 2.70 | 0.90 | 101.70 |
| 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 |

sodium. Therefore, D5W infusion in tandem with standard hemodialysis is unsuitable and not recommended for use in most cases of severe hyponatremia.

The approach of infusing D5W water in conjunction with CRRT offers the advantage of managing severe hyponatremia at the bedside in institutions without adequate pharmacy support to dilute CRRT fluid bags. The method could be adopted for both post-dilution CVVH and CVVHDF or counter-current CVVHD using standard CRRT fluids. The D5W infusion rate to keep the patient's sodium concentration at a target level can be roughly estimated from Equation (4) when predilution RF is not used and the effluent is 100% saturated with small solutes. As mentioned above, the effluent is often not fully saturated with diffusive clearance. Therefore, the D5W rate required to keep serum sodium at target may be about 10% less than suggested by this formula:

$$\text{D5W rate} = \frac{\text{CRRT}\left[Na^+\right] - \text{target serum}\left[Na^+\right]}{\text{target serum}\left[Na^+\right]} \times \left(Q_D + Q_{RF}\right), \quad (4)$$

where $Q_D$ is the DF rate and $Q_{RF}$ is the RF rate. For example, a patient with an initial serum sodium of 105 mEq/L, who is initiated on continuous venovenous hemodialysis with dialysate flow rate ~2000 ml/h, dialysate sodium 140 mEq/L, about 435 ml/h of D5W (infused intravenously into the patient or into the return blood line of the CRRT circuit) will be needed to keep target sodium concentration less than or equal to ~115 mEq/L in the next 24 h. The net ultrafiltration setting is typically increased by the rate of the D5W infusion = 435 mL/h to maintain net fluid balance. Of note, the initial D5W rate may be started at 90% of that suggested by Equation (4) (i.e., ~390 ml/h in the example) to account for not fully saturated effluent and is then adjusted every 6–8 h if needed to stay within the desired limits of correction. For patients receiving CRRT with hypertonic, concentrated citrate anticoagulation at a rate of $Q_{citrate}$ and without predilution $Q_{RF}$, the additional D5W rate required to mitigate non-isotonic sodium gain post-filter that would accrue from the high sodium concentration in the citrate infusions can be roughly estimated from this formula:

$$\text{D5W rate to mitigate ACDA sodium gain} = \frac{Q_{Cit} \times \left(\text{Citrate}\left[Na^+\right] - \text{CRRT}\left[Na^+\right]\right) \times \left(1 - \frac{Q_{Eff}}{Q_{Cit}+Q_{Be}}\right)}{\text{target serum}\left[Na^+\right]}, \quad (5)$$

where $Q_{Eff}$ is the effluent rate and is about equal to the sum of DF flow ($Q_D$), replacement fluid ($Q_{RF}$) flow, and ultrafiltration rate (including citrate flow rate ($Q_{Cit}$); $Q_{Be}$ is the effective circuit blood water flow for sodium, and is about 0.9 × $Q_B$; citrate [$Na^+$] is the sodium concentration of the citrate solution (acid citrate dextrose A [ACDA] solution [$Na^+$] = 224 mEq/L). In the same example above, a patient receiving CVVHD with ACDA at a rate of 200 ml/h (0.2 L/h), blood flow ($Q_B$) of 150 ml/min (=9 L/h), and $Q_{Eff}$ of 2635 ml/h (=$Q_D$ + $Q_{UF}$ (where $Q_{UF}$ includes the D5W rate calculated above and $Q_{Cit}$)), the D5W rate has to be increased by additional 0.1 L/h (~100 ml/h) based on Equation (5).

Frequent laboratory confirmation is still advised. Variables that affect sodium change may change over time (i.e., sodium gain/loss from non-isotonic fluid gains or losses) and readjustment of the D5W infusion rate may be necessary. Safety concerns (besides the obviously very high hourly glucose load) with this technique include

the theoretical risk of worsening hyponatremia if the effective sodium dialysance is significantly decreased compared to predicted due to progressive filter clotting or marked access recirculation or if CRRT is interrupted while dextrose water continues to infuse. Alternatively, systemic sodium may increase beyond desired limits if the D5W infusion is stopped for several hours while the CRRT continues. Thus, vigilance to ensure proper functioning and coordination of the CRRT and non-isotonic infusions is critical.

## 2.3 | Regulating sodium dialysance to achieve a desired systemic sodium trend by applying kinetic principles

Changes in serum sodium are faster with hemodialysis when compared to CRRT due to the higher blood and dialysate flow rates. Intermittent hemodialysis (IHD) machines, which generate dialysate online, cannot be set for $Q_D$ below 100 ml/min due to the technical limitations of how concentrate mixing and fresh dialysate warming is implemented. Furthermore, low$Q_B$ cannot be set arbitrarily below 100 ml/min on most machines, and low $Q_B$ settings even if possible are limited by the risk of clotting (unless regional citrate anticoagulation [RCA] is used). The overall impact of $Q_B$ and $Q_D$ settings restrictions is limiting to our ability to decrease the sodium dialysance to levels afforded by CRRT. Furthermore, most machines do not allow dialysate sodium to be set below 130 mEq/L due to the risk of inducing brain edema during high-efficiency IHD with accidentally <130 sodium dialysate and will force the fresh dialysate into bypass with a low conductivity alarm. Theoretically, the dialysis machine's alarm system could be manipulated and calibrated to allow the use of fresh dialysate sodium <130 mEq/L. However, this would be at the expense of a treatment session with nonfunctional conductivity monitoring system and would pose an unwarranted and significant safety risk with online dialysate generation.

Despite the lower sodium dialysance afforded by CRRT, thoughtful adjustment of CRRT dose may still be necessary to keep the patient's serum sodium within desired limits. A single-pool fixed-volume sodium kinetic equation may be used in a manner similar to urea kinetic analysis for the quantification of sodium dialysance needed to keep the systemic sodium level change within desired limits and to predict the serum sodium trend with any prescribed CRRT dose.[3,7,8] This is because sodium and urea have similar dialyzer solute transfer characteristics as both are non-protein bound small solutes with similar *apparent* effective blood water flow and *apparent* volume of distribution of total body water.[9]

Sodium kinetic modeling will require quantitative measurement and/or estimation of variables involved in the transfer of sodium ions across the dialyzer or the filter such as estimating the dialysance of sodium, and apparent volume of distribution (total body water) and sodium generation rate (non-isotonic sodium and potassium gain or loss from the body) when non-negligible.[10] Methods to account for the Gibbs–Donnan effect across the dialyzer on steady-state systemic sodium have been described but the enhanced small degree of accuracy with these methods is negligible and adds needless complexity. Serum sodium level at any time, $[Na^+](t)$ during CRRT treatments may be estimated by the following equation[3,7]:

$$\left[Na^+\right](t) = \left[Na^+\right]_i + \left(CRRT\left[Na^+\right] - \left[Na^+\right]_i\right) \times \left(1 - e^{\frac{-Dt}{V}}\right) + \frac{G}{D}\left(1 - e^{\frac{-Dt}{V}}\right), \quad (6)$$

where $\left[Na^+\right]_i$ is the initial serum sodium, G is the net non-isotonic sodium balance (in mEq/h) resulting from sodium gains post-filter (e.g., sodium gain from ACDA) and sodium losses (e.g., ultrafiltration of fluids infused as dextrose water to maintain even fluid balance).

When non-isotonic gains or losses are negligible, Equation (6) may be reduced to:

$$\left[Na^+\right](t) = \left[Na^+\right]_i + \left(CRRT\left[Na^+\right] - \left[Na^+\right]_i\right) \times \left(1 - e^{\frac{-Dt}{V}}\right). \quad (7)$$

Equation (7) demonstrates that CRRT with modest $Q_D$ and post-filter $Q_{RF}$ rates (i.e., sodium dialysance = D in the equation above) may remarkably exceed the recommended limits of correction in some patients with severe hyponatremia. The rise in sodium will be more excessive the greater the difference between the CRRT fluid sodium and the initial sodium level of patient, the greater the D or the lower the total body water volume, *V*. For example, an 80-kg woman with initial sodium of 105 mEq/L, 36 L of total body water, undergoing CRRT (without citrate anticoagulation) at a dialysate flow rate of 2 L/h using commercial CRRT fluid with sodium 140 mEq/L will have her serum sodium increase to 130 mEq/L in 24 h after CRRT initiation.

$$\left[Na^+\right](t) = 105 + (140 - 105) \times \left(1 - e^{\frac{-2x24}{36}}\right) = 130\,\text{mEq/L}.$$

Equation (7) also highlights the risk of a marked increase in serum sodium during a conventional hemodialysis session particularly in patients with low total body water. For example, in a patient (starting serum sodium of 105 mEq/L) with 25 L of total body water, a 3-h hemodialysis with a blood flow of 300 ml/min, dialysate flow of 600 ml/min, and dialysate sodium of 130 mEq/L will provide a sodium dialysance of about 250 ml/min or 15 L/h and will raise the serum sodium to 125 mEq/L in 3 h.

$$\left[Na^+\right](t) = 105 + (130 - 105) \times \left(1 - e^{\frac{-15x3}{25}}\right) = 125\,\text{mEq/L}.$$

By rearranging Equation (7), the required *D* (L/h) needed for a desired sodium change at any elapsed time (*t*) or for every 24-h period could be estimated:

$$D = -\frac{V}{t\,(\text{h})} \times \ln\left(1 - \frac{\left[Na^+\right](t) - \left[Na^+\right]_i}{CRRT\left[Na^+\right] - \left[Na^+\right]_i}\right). \quad (8)$$

For example, an 80-kg woman with initial sodium of 105 mEq/L, 36 L of body water, undergoing CRRT (without citrate anticoagulation) using commercial DF/RF with sodium 140 mEq/L will require the sodium dialysance (~DF+RF flow rate in L/h) to be adjusted to

0.56 L/h or 560 ml/h to keep the desired increase is serum sodium no more than 8 mEq/L in 24 h:

$$D = -\frac{36}{24} \times \ln\left(1 - \frac{8}{25}\right) = 0.56\,\text{L/h or } 560\,\text{ml/h}.$$

In the second 24 h, the physician could reevaluate the *D* required depending on the achieved final sodium concentration and substitute that as the initial sodium for the second interval. While the low delivered sodium dialysance of 560 ml/h avoids overcorrection of serum sodium in this patient with the prescription parameters outlined above, it compromises the clearance of other solutes (CRRT effluent dose of ~8 ml/kg/h). This approach should be avoided in those with concomitant significant abnormalities of other solutes (e.g., severe acidosis, hyperkalemia). For the majority of patients lowering the CRRT fluid sodium level or administering hypotonic fluid in a separate infusion line is the preferred approach while maintaining a delivered effluent dose of at least 20–25 ml/kg/h.

For patients on CRRT with regional citrate anticoagulation, the added sodium from the high sodium concentration citrate solution may not always be negligible and can be accounted for by Equation (6) described above[7,10]:

$$\left[Na^+\right](t) = \left[Na^+\right]_i + \left(\text{CRRT}\left[Na^+\right] - \left[Na^+\right]_i\right) \times \left(1 - e^{\frac{-Dt}{V}}\right) + \frac{G}{D}\left(1 - e^{\frac{-Dt}{V}}\right), \quad (6)$$

where *G* (mEq/hr) is the non-isotonic sodium gain per hour post-filter from citrate infusion and is determined by the $Q_{Eff}$ rate relative to effective sodium water flow rate. *G* is roughly equal to:

$$G\left(\frac{\text{mEq}}{\text{h}}\right) = Q_{\text{citrate}} \times \left(\text{citrate}\left[Na^+\right] - \text{CRRT}\left[Na^+\right]\right) \times \left(1 - \frac{Q_{Eff}}{Q_{Cit} + Q_{Be}}\right). \quad (9)$$

Equation (6) highlights that even regional citrate anticoagulation CRRT prescriptions with a relatively low $Q_{Cit}/Q_{Be}$ ratio and the use of less hypertonic, USP ACD-A citrate can considerably increase the patient's serum sodium level beyond the CRRT fluid sodium concentration, particularly if the $Q_{Eff}/(Q_{Cit} + Q_{Be})$ ratio is low. When treating a patient with hyponatremia, the clinician should be cognizant of the net sodium gain through the citrate infusion, especially if a more hypernatremic 4% sodium citrate solution is used (Na 420 mEq/L) and mitigate its effect when warranted either by concomitant hypotonic infusion as described above or minimizing sodium gain post-filter by increasing the $Q_{Eff}$ rate relative to circuit blood effective water flow rate for sodium. For example, a CRRT prescription with dialysate flow 2000 ml/h (2 L/h), blood flow 200 ml/min (12 L/h), and ACDA 300 ml/h (0.3 L/h) will increase the steady-state sodium to 150 mEq/L. The same dialysate flow rate of 2000 ml/h (2 L/h) but with blood flow ($Q_B$) of 100 ml/h (6 L/h), ACDA 200 ml/h (0.2 L/h) will increase the steady-state sodium to only 145 mEq/L while providing a higher $Q_{Cit}/Q_B$ ratio.

## 3 | MANAGEMENT OF SEVERE HYPERNATREMIA IN PATIENTS REQUIRING RENAL REPLACEMENT THERAPY

The recommendation for slow correction of serum sodium (defined as ≤0.5 mEq/L per hour or ≤12 mEq/L in 24 h) in patients with severe hypernatremia has been recently questioned in the absence of robust data showing increased neurologic injury. Indeed, one recent retrospective chart review did not identify greater neurologic injury or mortality in patients hospitalized with hypernatremia.[11] The authors advise caution in extending the results to all hypernatremic patients and particularly to those requiring conventional hemodialysis for solute control. First, sodium correction rates with conventional hemodialysis may far exceed correction rates provided with hypotonic fluids. Second, in addition to a rapid lowering of high serum sodium, rapid dialytic removal of urea and other uremic solutes might induce dialysis disequilibrium or exacerbate brain edema particularly in patients with brain injury.[12,13] Indeed, "osmotherapy" with hypertonic saline is considered the mainstay of therapy for brain swelling.[14]

Patients with kidney failure and chronic, extreme hypernatremia ($[Na^+]$ >165 mEq/L) are therefore best treated with CRRT. The rate of correction can be regulated by a variety of methodologies including the use of hypertonic CRRT solutions or separate hypertonic infusions or adjustment of sodium dialysance. The methodology used may depend on physician comfort with the technique, local renal replacement therapy practices. and institutional resources.

### 3.1 | Spiking of the dialysate/replacement fluid $[Na^+]$ in CRRT

The sodium concentration of standard CRRT solutions can be increased to the desired value by adding hypertonic saline. A stepwise switch to fluid bags with 10 mEq/L lower sodium than patient's current serum sodium can be considered every 24 h. Using this approach, overly rapid correction may be avoided. Alternatively, the exact concentration of the CRRT solution to keep the patient's sodium change within a desired limit over a certain time can be estimated using Equation (1) mentioned above. CRRT solutions can be spiked with 23.4% hypertonic saline (4 mEq of sodium per each ml of solution). The mEq of sodium to be added to a CRRT bag can be calculated by the following equation:

$$\text{mEq}\,Na^+ = \text{CRRT}\left[Na^+\right]_{\text{desired}} \times \text{CRRT}V_f - \text{CRRT}\left[Na^+\right]_{\text{initial}} \times \text{CRRT}V_i, \quad (10)$$

where CRRT $V_f$ is the CRRT solution final volume and CRRT $V_i$ is the solution's initial volume. Since the 23.4% hypertonic saline volume is negligible, the CRRT solution's final volume is nearly equal to its initial volume and Equation (11) will be reduced to:

$$\text{mEq}\,Na^+ = \text{CRRT}\,V \times \left(\text{CRRT}\left[Na^+\right]_{\text{desired}} - \text{CRRT}\left[Na^+\right]_{\text{initial}}\right), \quad (11)$$

For example, to increase the sodium concentration of a 5-L CRRT solution from 140 to 170 mEq/L, 150 mEq Na or 150/4 = 37.5 ml of 23.4% (=4 mEq/ml) hypertonic saline will be required.

## 3.2 | Administering a hypertonic infusion in a separate infusion line

Infusing 3% saline intravenously into the patient or into the return line of the CRRT blood circuit is another approach to mitigate hypernatremia in a controlled fashion during CRRT when using standard 140 mEq/L CRRT solutions. The ultrafiltration rate is adjusted to account for the volume of 3% saline infused. Safety risks include worsening hypernatremia if CRRT is stopped while the infusion continues or if the 3% saline is given in a central vein while the effective sodium dialysance is significantly decreased compared to predicted due to progressive filter clotting or marked access recirculation. There could also be rapid correction of hypernatremia if the 3% saline infusion is interrupted for hours (e.g., if the 3% saline solution bag runs out without being replaced in a timely fashion while the CRRT continues).

The estimated infusion rate of 3% saline when using a specific CRRT [$Na^+$] sodium level can be approximated by this formula:

$$3\,\%\,\text{saline infusion rate} = \frac{\text{target serum } [Na+] - \text{CRRT } [Na+]}{513 - \text{target serum } [Na+]} \times (Q_D + Q_{RF}). \tag{12}$$

For example, a patient with an initial sodium 180 mEq/L with target sodium concentration of no lower than 170 mEq/L who is initiated on CVVHD at dialysate flow rate of 2000 ml/h with CRRT fluid [Na +]= 140 mEq/L will require 3% saline infused at rate of ~175 ml/h. The net ultrafiltration setting should be increased by the rate of 3% saline infusion (i.e., ~175 ml/h) for isovolemic ultrafiltration.

For patients on citrate anticoagulation, the sodium load form ACDA will contribute to non-isotonic sodium gain post-filter and the rate of 3% to keep serum sodium at target would be lower.

$$3\,\%\,\text{saline infusion rate} = \frac{\text{target serum } [Na+] - \text{CRRT } [Na+] - \frac{G}{Q_D + Q_{RF}}}{513 - \text{target } [Na+]} \times (Q_D + Q_{RF}), \tag{13}$$

where $G$ (mEq/h) is the non-isotonic sodium gain per hour post-filter from the hypertonic citrate infusion and is determined by $Q_{Cit}$, citrate[Na+], and the $Q_{Eff}/Q_{Be}$ ratio as described in Equation (10). For example, the same patient with an initial sodium 180 mEq/L with target sodium concentration of no lower than 170 mEq/L who is initiated on CVVHD at blood flow 150 ml/min (9 L/h), ACDA 225 ml/h (0.225 L/h), dialysate flow rate of 2000 ml/h will require 3% saline infused at rate of ~155 ml/h. The net ultrafiltration setting is increased by the rate of 3% saline infusion (i.e., 155 ml/h).

## 3.3 | Controlling sodium change with CRRT in hypernatremia by applying kinetic principles

Using the principles of sodium kinetics discussed under the section of hyponatremia, the serum sodium at any time during CRRT is predictable by Equation (7), allowing for regulating correction rates by adjusting the sodium dialysance. For example, an 80-kg woman with initial sodium of 170 mEq/L, 36 L of body water, undergoing countercurrent and/or post-dilution $Q_{RF}$ CRRT (without citrate anticoagulation and without significant predilution $Q_{RF}$) using a commercial CRRT solution with sodium 140 mEq/L and $Q_D + Q_{RF}$= at 2000 (L/h) will have serum sodium of about 148 mEq/L at 24 h using Equation (7).

$$[Na^+](t) = 170 + (140 - 170) \times \left(1 - e^{\frac{-2 \times 24}{36}}\right). \tag{7}$$

A correction rate of 22 mEq/L of this magnitude is undesirable particularly in patients with preexisting uremia undergoing their first dialysis or in patients with preexisting brain edema. By plugging in different dialysance rates (at increments of 0.5 L/h), and estimating the achieved serum sodium at 24 h with each particular dialysance and prescription, the most ideal sodium dialysance needed to stay within the desired range can be identified. For example, clearance rates of 1500 and 1000 ml/h will lower the serum sodium by 19 and 15 mEq/L. A rate of 750 ml/h will lower it by about 12 mEq/L.

In those receiving RCA, the serum sodium at 24 h can also be calculated using Equation (6) and sodium gain (G) from RCA is calculated using Equation (9). For example, in the same patient with initial sodium of 170 mEq/L, 36 L of body water, undergoing CRRT using CRRT solution with sodium 140 mEq/L, ACDA 225 ml/h (0.225 L/h), blood flow 150 ml/min (9 L/h), serum sodium will decrease by 17 mEq/L to ~153 mEq/L when DF/RF flow rate at 2000 ml/h (2 L/h), and by ~13 to 157 mEq/L if DF/RF flow rate is at 1500 ml/h (1.5L/h).

$$\begin{aligned}
[Na^+](t) &= 170 + (140-170) \times \left(1-e^{\frac{-2 \times 24}{36}}\right) + \frac{14}{2} \times \left(1-e^{\frac{-2 \times 24}{36}}\right) \\
[Na^+](t) &= 170 + (-30) \times (0.74) + \frac{14}{2} \times (0.74) \\
[Na^+](t) &= 170 - 22 + 5 = 153\ \text{mEq/L}
\end{aligned} \tag{6}$$

## 4 | SUMMARY

In conclusion, all renal replacement modalities could be potentially harmful when used in a patient with severe dysnatremia. Controlled, predictable correction of all dysnatremias is possible with CRRT. Embracing an analytical approach to the understanding of sodium fluxes during CRRT allows for a more regulated correction of dysnatremias. However, frequent laboratory testing is still advised (i.e., patients who experience profound net non-isotonic sodium gains or losses) and our approach may require readjustment based on laboratory measurements.

## CONFLICT OF INTEREST

Lenar Yessayan: none. Balazs Szamosfalvi: none. Mitchell Rosner: Consulting fees: Baxter.

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## APPENDIX

- CRRT solution sodium concentration needed to maintain the patient's serum sodium at 24 h within the desired limits of correction with a prescribed sodium dialysance (*D*):

$$\text{CKRT}\left[\text{Na}^+\right] = \frac{\text{desired}\Delta\text{serum}\left[\text{Na}^+\right]}{\left(1-\text{e}^{-\frac{D\times 24\ \text{h}}{V}}\right)} + \text{initial serum}\left[\text{Na}^+\right], \quad (1)$$

where desired Δ serum [$Na^+$] is equal to target serum sodium at 24 h− initial serum sodium. The formula may be used in cases of hypo- and hypernatremia.

- Volume of sterile water to be added to dilute CRRT solution bag to a desired CRRT [$Na^+$]:

$$\text{Volume to add} = \frac{\text{CKRT } V \times \left(\text{ initial CKRT}\left[\text{Na}^+\right] - \text{desired CKRT}\left[\text{Na}^+\right]\right)}{\text{desired CKRT}[\text{Na}^+]}. \quad (2)$$

- Volume of CRRT fluid to be exchanged with sterile water to dilute CRRT solution bag to a desired CRRT [$Na^+$]:

$$\text{Volume to exchange} = \text{CKRT } V - \frac{\text{desired CKRT}\left[\text{Na}^+\right] \times \text{CKRT } V}{\text{initial CKRT}[\text{Na}^+]}. \quad (3)$$

- Dextrose water infusion rate post-filter or peripherally required to keep serum sodium at target when CRRT is prescribed with no RCA:

$$\text{D5W rate} = \frac{\text{CKRT}\left[\text{Na}^+\right] - \text{target serum}\left[\text{Na}^+\right]}{\text{target serum}\left[\text{Na}^+\right]} \times \left(Q_D + Q_{RF}\right). \quad (4)$$

- Dextrose water infusion required (in addition to calculated in Equation 4 above) to mitigate an increase in serum sodium concentration due to RCA use:

$$\text{D5W rate to mitigate RCA} = \frac{Q_{Cit} \times \left(\text{Citrate}\left[\text{Na}^+\right] - \text{CKRT}\left[\text{Na}^+\right]\right) \times \left(1-\frac{Q_{Eff}}{Q_{Cit}+Q_{Be}}\right)}{\text{target serum}\left[\text{Na}^+\right]}. \quad (5)$$

- Serum sodium level at time = *t* from CRRT treatment initiation accounting for the effect of non-isotonic sodium gains or losses:

$$\left[\text{Na}^+\right](t) = \left[\text{Na}^+\right]_i + \left(\text{CKRT}\left[\text{Na}^+\right] - \left[\text{Na}^+\right]_i\right) \times \left(1-\text{e}^{\frac{-Dt}{V}}\right) + \frac{G}{D}\left(1-\text{e}^{\frac{-Dt}{V}}\right). \quad (6)$$

where $[Na^+]i$ is the initial serum sodium concentration and $[Na^+]t$ is serum sodium concentration at time = $t$ from CRRT initiation.

The formula may be used in cases of hypo- and hypernatremia.

- Serum sodium level at time = $t$ from CRRT treatment initiation when non-isotonic gains or losses are negligible:

$$\left[Na^+\right](t) = \left[Na^+\right]_i + \left(CKRT\left[Na^+\right] - \left[Na^+\right]_i\right) \times \left(1 - e^{\frac{-Dt}{V}}\right). \quad (7)$$

The formula may be used in cases of hypo- and hypernatremia.

- Sodium dialysance ($D$) in L/h needed for a desired serum sodium change at 24 h:

$$D = -\frac{V}{24} \times \ln\left(1 - \frac{\left[Na^+\right](t) - \left[Na^+\right]_i}{CKRT\left[Na^+\right] - \left[Na^+\right]_i}\right). \quad (8)$$

The formula may be used in cases of hypo- and hypernatremia.

- The rate of non-isotonic sodium gains (mEq/h) post-filter from citrate infusion:

$$G\left(\frac{mEq}{h}\right) = Q_{citrate} \times \left(citrate\left[Na^+\right] - CKRT\left[Na^+\right]\right) \times \left(1 - \frac{Q_{Eff}}{Q_{Cit} + Q_{Be}}\right). \quad (9)$$

- The amount of sodium (mEqs) to be added to a CRRT bag to achieve a desired hypertonic CRRT $[Na^+]$:

$$mEq\,Na^+ = CKRT\left[Na^+\right]_{desired} \times CKRTV_f - CKRT\left[Na^+\right]_{initial} \times CKRTV_i. \quad (10)$$

- The amount of sodium (mEqs) to be added to a CRRT bag to achieve a desired hypertonic CRRT $[Na^+]$ when using 23.4% hypertonic saline:

$$mEq\,Na^+ = CKRT\,V \times \left(CKRT\left[Na^+\right]_{desired} - CKRT\left[Na^+\right]_{initial}\right). \quad (11)$$

- Infusion rate of 3% saline to keep serum sodium at target level when using a specific CRRT$[Na^+]$ (i.e., to avoid rapid correction of serum sodium with CRRT in a patient with hypernatremia):

$$3\%\text{saline infusion rate} = \frac{\text{target serum}\left[Na^+\right] - CKRT\left[Na^+\right]}{513 - \text{target serum}\left[Na^+\right]} \times \left(Q_D + Q_{RF}\right). \quad (12)$$

- Infusion rate of 3% saline for patients on citrate anticoagulation to keep serum sodium at target level when using a specific CRRT$[Na^+]$. The sodium load from ACDA will contribute to non-isotonic sodium gain post-filter and the rate of 3% to keep serum sodium at target would be lower than that calculated in Equation (12).

$$3\%\text{saline infusion rate} = \frac{\text{target serum}\left[Na^+\right] - CKRT\left[Na^+\right] - \frac{G}{Q_D + Q_{RF}}}{513 - \text{target serum}\left[Na^+\right]} \times \left(Q_D + Q_{RF}\right). \quad (13)$$

Abbreviations: Δ, delta; CRRT, continuous kidney replacement therapy; $[Na^+]$, sodium concentration; $D$, sodium dialysance; $V$, total body water; D5W, 5% dextrose water, $Q_D$, dialysate flow rate; $Q_{RF}$, replacement fluid rate; $Q_{Eff}$, effluent flow rate; $Q_{Cit}$, citrate solution flow rate; citrate $[Na^+]$, sodium concentration of the citrate solution; $Q_{Be}$, effective circuit blood water flow for sodium, and is about $0.9 \times Q_B$ where $Q_B$ is the circuit blood flow; $G$, rate of net non-isotonic sodium gains or losses (mmol/h); CRRT $V_f$, CRRT solution final volume; CRRT $V_i$, CRRT solution initial volume; CRRT $V$, CRRT solution volume.