Sodium-Based Osmotherapy in Continuous Renal Replacement Therapy: a Mathematical Approach

Jerry Yee, Naushaba Mohiuddin, Tudor Gradinariu, Junior Uduman, and Stanley Frinak

Abstract
Cerebral edema, in a variety of circumstances, may be accompanied by states of hyponatremia. The threat of brain injury from hypotonic stress-induced astrocyte demyelination is more common when vulnerable patients with hyponatremia who have end stage liver disease, traumatic brain injury, heart failure, or other conditions undergo overly rapid correction of hyponatremia. These scenarios, in the context of declining urinary output from CKD and/or AKI, may require controlled elevations of plasma tonicity vis-à-vis increases of the plasma sodium concentration. We offer a strategic solution to this problem via sodium-based osmotherapy applied through a conventional continuous RRT modality: predilution continuous venovenous hemofiltration.

Introduction
Generally, sodium-based osmotherapy (SBO) is tonicity therapy with the aim of reducing cerebral edema during states of hypotonic hyponatremia. Depending on the circumstance, plasma tonicity may be increased or decreased. Because the sodium concentration ([Na]) in the plasma at any time (t), PNa(t), and accompanying anions constitute the bulk of plasma tonicity, SBO is predicated on gradual alteration of PNa in contrast to the relatively rapid PNa increases imposed by steep dialysate-to-plasma [Na] gradients associated with conventional hemodialysis. Generally, osmotherapy is carried out when there is severe hyponatremia, oligo-anuria, and inability to excrete sufficient electrolyte-free water to maintain isotonicity (1–3). Thus, SBO has played a role in patients with end stage liver disease and advanced heart failure.

Osmotic demyelination syndrome may transpire in patients who are hyponatremic with end stage liver disease after abrupt PNa elevations during orthotopic liver transplantation (4,5). Correspondingly, presurgical elevation of PNa among individuals prone to osmotic demyelination may be prophylactic. Less commonly, supranormal PNa elevations have been imposed during traumatic brain injury or intracerebral hemorrhage to reduce brain swelling (6,7).

To rectify severe plasma hypotonicity, a relatively hypertonic/hypernatric solution is administered in a controlled fashion during continuous renal replacement therapy (CRRT), and PNa is increased at rates consistent with consensus guidelines (8). Controlled PNa elevations can be achieved by hemodialysis, but special device- and protocol-specific modifications are required to avoid dialysis disequilibrium syndrome (9). Sustained low-efficiency dialysis or slow continuous ultrafiltration with simultaneous infusion of a solution relatively hypernatric to PNa is also feasible (10). In terms of CRRT, SBO has been conducted with continuous venovenous hemofiltration (CVVH) (11,12), continuous venovenous hemodialysis (13), or continuous venovenous hemodiafiltration (14).

General Principles of SBO
SBO can be implemented as a stepwise approach based on established biophysical principles governing sodium transit via predilution CVVH. The following urea- and sodium-based kinetic methodology involves six steps: (1) establishing a time-dependent [Na] gradient [VNa(0)] between the plasma and a replacement fluid (RF) based on a sodium concentration adjustment ratio (NaAR) (Figure 1), (2) estimation of total body water (TBW), (3) determination of sodium ion dialysance (DNa) that approximates the urea hemofilter transfer rate, (4) on-treatment prediction of PNa(t), (5) determination of sodium balance, and (6) troubleshooting.

Predilition CVVH
RF is infused postblood pump and prehemofilter at a specified rate (QRF) into the plasma flow (Qp) to raise (or lower) PNa from its pretreatment level, NaPre or PNa(0), to its post-treatment level, NaPost or PNa(t) (Figure 1). Employing a fixed-volume model where TBW volume is constant and analogizing to established urea kinetic principles, the rate change of PNa can be computed over a specified time interval (15,16). Thus, sodium advected from the RF gradually increases NaPre to NaPost with their difference equaling ΔNa (Equation 1).

To produce an [Na] gradient, a stock RF (RF1) of nominal [Na] NaRF1 is adjusted to NaRF2, thereby establishing VNa(0), the maximal [Na] gradient at time 0 (Equation 2). ΔNa is also the product of VNa(0) and NaAR, and NaAR is the ratio of ΔNa to VNa(0) (Equation 3).

1Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, Michigan; and 2St. Clair Specialty Physicians, Roseville, Michigan

Correspondence: Dr. Jerry Yee, Division of Nephrology and Hypertension, Henry Ford Hospital, 2799 West Grand Boulevard, CFP-514, Detroit, MI 48202. Email: jyee1@hfhs.org
Sodium Kinetic Principles

The NaAR is a function of treatment time (t), TBW (V, Watson volume), and DNa. The NaAR is similar to the urea reduction ratio (URR, Equation 4), with equivalence of DNa to the urea clearance constant, KUrea (Equation 4, A and B).

\[ \Delta Na = Na_{\text{post}} - Na_{\text{pre}} \]  
\[ VNa(0) = Na_{RF2} - Na_{\text{pre}} \]  
\[ \text{NaAR} = \Delta Na / VNa(0) = (Na_{\text{post}} - Na_{\text{pre}}) / (Na_{RF2} - Na_{\text{pre}}) \]  
\[ \text{Equation 3} \]

Replacement Fluids

To generate VNa(0), the sodium-adjusted RF [Na], NaRF2, is often simply assigned an [Na] that is 6–10 mM greater than NaPre. However, NaRF2 can be more rationally determined from intrinsic parameters of predilution CVVH (Tables 1 and 2). First, by predetermining a target NaPost, ΔNa is defined. Second, estimation of NaAR from URR (Equations 3 and 4) and rearrangement of Equation 3 yields NaRF2 as Equation 5.

\[ \text{NaRF2} = Na_{\text{pre}} + \left( \Delta Na / \text{NaAR} \right) \]  
\[ \text{Equation 5} \]

In summary, urea kinetics function to approximate NaAR. These principles are illustrated by the following example.

**Case 1.** A 42-year-old man, 178 cm and 90 kg, is anuric with stage 3 AKI. He has no peripheral edema. Laboratory data: NaPre 116 mM; BUN(0), 80 mg/dl; hematocrit, 0.25. The target BUN and PNa after 24 hours of CVVH are 48 mg/dl and 124 mM, respectively. First, NaAR approximating URR is calculated, with \( BUN_{\text{Dialysate}} \) as “zero.”
\[
\text{NaAR} \approx \text{URR} = \left( \frac{\text{BUN}(0) - \text{BUN}(1440))}{\text{BUN}(0)} \right) = (80 - 48)\text{mg/dl}/80\text{mg/dl} = 0.4
\]

Second, after NaAR is determined, \( \Delta \text{Na} \), \( \nabla \text{Na}(0) \), and NaRF2 are calculated.

\[
\Delta \text{Na} = \text{NaPost} - \text{NaPre} = 124 \text{mM} - 116 \text{mM} = 8 \text{mM} \\
\nabla \text{Na}(0) = \Delta \text{Na}/\text{NaAR} = 8 \text{mM}/0.4 = 20 \text{mM} \\
\text{NaRF2} = \text{NaPre} + (\Delta \text{Na}/\text{NaAR}) = 116 \text{mM} + 8 \text{mM}/0.4 \\
= 116 \text{mM} + 20 \text{mM} = 136 \text{mM} \\
\text{NB: } \nabla \text{Na}(0) = \text{NaRF2} - \text{NaPre} = 136 \text{mM} - 116 \text{mM} = 20 \text{mM}
\]

The time dependencies of NaPost, NaAR, and \( \Delta \text{Na} \) during prolonged SBO are tabulated in Table 3. Figure 2 demonstrates the effect of increasing \( \nabla \text{Na}(0) \) on \( \text{PNa} \) at \( \text{NaAR} \) of 0.4 over 1440 minutes of treatment. The random assignment of a 6–10 mM \( \nabla \text{Na}(0) \) would have suboptimally elevated \( \text{PNa} \) underscoring this approach of using NaAR to determine NaRF2. Note the relatively low NaAR complements the large \( \nabla \text{Na}(0) \). Importantly, a low URR of 0.4 provides a therapeutic advantage by mitigating the risk of inducing cerebral edema by lowering overall urea flux.

**Replacement Fluid Manipulation**

In predilution CVVH SBO, the NaRF1 is frequently lowered from a nominal level of 130 or 140 mM. For Case 1, NaRF1 can be adjusted to an NaRF2 of 136 mM by several methods (Figure 3) (11,12): method 1, diluting RF1 (NaRF1 140 mM) with 147 ml sterile water; method 2, exchanging 143 ml of RF1 (NaRF1 140 mM) for sterile water; and method 3, addition of 7.8 ml of 4 M saline (23.4%) to 5 L of RF1 solution (NaRF1 130 mM).

**Effective Replacement Fluid Sodium Concentrations**

If institutional policy prohibits RF manipulations, an effective RF [Na] (Eff-NaRF) equal to the desired NaRF2 must be generated via flow-rate adjustments of an unadjusted RF1 and a separate solution (H; Figure 3, method 4) (14,17–19). Peripheral infusion of 5% dextrose in water (D5W) or sterile water by central vein may be used as “0” mM [Na] solutions (20).

**Step 2: Estimating TBW as Watson Volume**

Watson Volume

NaAR is a function of time, \( D_{\text{Na}} \), and TBW (V, Watson volume). Hence, accurate determination of V is critical. Consequently, the Watson volume, representing TBW as urea space, is used in subsequent calculations because it is a

### Table 1. Sodium-based osmotherapy parameters

| Row | Parameter | Definition | Units |
|-----|-----------|------------|-------|
| 1   | \( \Delta \text{Na} \) | Post-treatment [Na] minus pretreatment [Na] | mmol/l, mM |
| 2   | \( \nabla \text{Na}(0) \) | [Na] gradient at time (t)=0 | mmol/l, mM |
| 3   | \[\text{Na}\] | Sodium concentration | mmol/l, mM |
| 4   | \( \Sigma \text{Na} \) | Sodium balance | mmol |
| 5   | \( D_{\text{Na}} \) | Dialysance of sodium ion | ml/min |
| 6   | Eff-NaRF | Effective replacement fluid [Na] from combined infusions of NaRF1 and NaF | mmol/l, mM |
| 7   | NaAR | Sodium concentration adjustment ratio | Dimensionless |
| 8   | \( \text{NaF} \) | [Na] of a defined hypo-, iso-, hypertonic solution H | mmol/l, mM |
| 9   | \( \text{NaPre} \) | Pretreatment \( \text{PNa} \), i.e., \( \text{PNa}(0) \) | mmol/l, mM |
| 10  | \( \text{NaPost} \) | End treatment \( \text{PNa} \) | mmol/l, mM |
| 11  | \( \text{NaRF1} \) | RF1 [Na], unadjusted replacement fluid | mmol/l, mM |
| 12  | \( \text{NaRF2} \) | RF2 [Na], sodium-adjusted replacement fluid | mmol/l, mM |
| 13  | \( \text{PNa}(t) \) | Plasma [Na] at time (t) | mmol/l, mM |
| 14  | \( Q_{\text{H}} \) | Solution H flow rate | ml/min |
| 15  | \( Q_{\text{R}} \) | Respective blood and plasma fluid flow rates | ml/min |
| 16  | \( Q_{\text{EFF}} \) | Replacement fluid flow rate | ml/min |
| 17  | \( Q_{\text{UF}} \) | Net ultrafiltration flow rate | ml/min |
| 18  | \( Q_{\text{EFF}} \) | Combined flow rate of \( Q_{\text{RF1}} \) and \( Q_{\text{H}} \) | ml/min |
| 19  | RF1 | Replacement fluid 1 | — |
| 20  | RF2 | Replacement fluid 2 | — |
| 21  | \( t \) | Time | min |
| 22  | URR | Urea reduction ratio | Dimensionless |
| 23  | V | Total body water, i.e., Watson volume | ml, L |
| 24  | \( V_{\text{AM}} \) | Volume of added hypertonic saline | ml, L |
| 25  | \( V_{\text{RF1}} \) | Volume of RF1 | ml, L |
| 26  | \( V_{\text{RF2}} \) | Volume of RF2 | ml, L |
| 27  | \( V_{\text{W}} \) | Volume of added sterile water | ml, L |

Variables and abbreviations used in text and equations.
Table 2. Sodium-based osmotherapy equations

| Row | Description                                      | Equation |
|-----|--------------------------------------------------|----------|
| 1   | Dialysance of sodium ion                         | $D_{\text{Na}} = -(V/t) \times LN(1 - \text{NaAR})$ |
|     |                                                  | $D_{\text{Na}} = Q_{p} \times [(Q_{\text{UF}} + Q_{\text{RF}})/(Q_{p} + Q_{\text{RF}})]$ |
| 2   | Method 1 calculation of added water volume       | $V_{\text{RF}} = V_{\text{RF1}} \times (\text{Na}_{\text{RF1}} - \text{Na}_{\text{RF2}})/\text{Na}_{\text{RF1}}$ |
| 3   | Method 2 calculation of water exchange volume    | $V_{\text{W}} = V_{\text{RF1}} \times [(\text{Na}_{\text{RF1}} - \text{Na}_{\text{RF2}})/\text{Na}_{\text{RF1}}]$ |
| 4   | Method 3 volume calculation of added 4 M hypertonic saline volume (23.4%) | $V_{AM} = V_{\text{RF1}} \times (\text{Na}_{\text{RF2}} - \text{Na}_{\text{RF1}})/(\text{Na}_{\text{AM}} - \text{Na}_{\text{RF2}})$ |
| 5   | Method 4 calculation of solution H fluid flow rate | $Q_{H} = Q_{\text{ER}} \times (\text{Na}_{\text{RF1}} - \text{Eff-Na}_{\text{RF2}})/\text{Na}_{\text{RF1}}$ |
| 6   | Method 4 replacement fluid 1 (RF1) flow rate     | $Q_{\text{RF1}} = Q_{\text{ER}} \times \text{(Eff-Na}_{\text{RF1}} - \text{Na}_{\text{RF1}})/\text{Na}_{\text{RF1}}$ |
| 7   | Plasma flow rate calculation                     | $Q_{p} = Q_{b} \times (1 - \text{hematocrit})$ |
| 8   | Sodium concentration at treatment time (t)       | $P_{\text{Na}}(t) = P_{\text{Na}}(0) + V_{\text{Na}}(0) \times (1 - e^{D_{\text{Na}}(t)/V})$; $P_{\text{Na}}(0) = \text{Na}_{\text{pre}}$ |
| 9   | Replacement fluid flow rate                       | $Q_{\text{RF}} = Q_{p} \times (D_{\text{Na}} - Q_{\text{RF}})/(Q_{p} - D_{\text{Na}}); Q_{\text{RF}} = 0$ |
| 10  | Sodium balance at time (t)                       | $\Delta \text{Na}(t) = P_{\text{Na}}(t) \times (V - Q_{\text{UF}}\times t - (\text{Na}_{\text{pre}} \times V))$ |
| 11  | Sodium concentration adjustment ratio            | $\Delta \text{Na} = V_{\text{Na}}(0)/\text{Na}_{\text{AR}}$ |
| 12  | Sodium concentration gradient, initial           | $V_{\text{Na}}(0) = V_{\text{NaRF2}} - \text{Na}_{\text{pre}} + \Delta \text{Na}/(1 - e^{D_{\text{Na}}(t)/V})$ |
| 13  | Sodium concentration of RF2                     | $V_{\text{RF2}} = \text{Na}_{\text{pre}} + \Delta \text{Na}/(1 - e^{D_{\text{Na}}(t)/V})$ |
| 14  | Time at which specified $P_{\text{Na}}$ occurs (t) | $t_{x} = -(V/D_{\text{Na}}) \times LN[(\text{Na}_{\text{RF2}} - \text{Na}_{\text{RF1}})/\text{Na}_{\text{RF2}}]$ |
| 15  | Ultrafiltration rate to achieve net zero sodium balance at time (t) | $Q_{\text{UF}}(t) = (\text{Na}_{\text{post}} + V)/[\text{Na}_{\text{pre}} \times V)]/(\text{Na}_{\text{post}} - t)$ |
| 16  | Urea reduction ratio                             | $U_{\text{RR}} = 1 - e^{-C_{\text{UF}}(t)/V}$ |
| 17  | Watson volume                                    | $V_{\text{Watson}} = 2.447 - 0.09156 \times (\text{age, yr})$ |
| 18  |                                                  | $+0.1074 \times (\text{height, cm}) + 0.3362 \times (\text{weight, kg})$ |

See Table 1 for definitions of variables.

Step 3: Dialysance of Sodium Ion

**Sodium Ion Dialysance**

Dialysance of sodium ion ($D_{\text{Na}}$) comprises three flow rates: plasma ($Q_{p}$), RF ($Q_{\text{RF}}$), and net ultrafiltration ($Q_{\text{UF}}$) (22). $Q_{p}$ has the greatest influence on $D_{\text{Na}}$ by virtue of its greater magnitude. $D_{\text{Na}}$ is also the product of $Q_{p}$ and the filtration fraction as follows.

$$D_{\text{Na}} = Q_{p} \times [(Q_{\text{UF}} + Q_{\text{RF}})/(Q_{p} + Q_{\text{RF}})] \quad (\text{Equation 6})$$

We recommend a blood flow ($Q_{b}$) of 250–300 ml/min to promote clearance and prevent filter clotting (23). As shown, at a $Q_{b}$ of 300 ml/min and hematocrit (Hct) of 0.25, $Q_{p}$ is 225 ml/min (Equation 7).

$$Q_{p} = Q_{b} \times (1 - \text{Hct}) = 300 \text{ ml/min} \times (1 - 0.25) = 225 \text{ ml/min} \quad (\text{Equation 7})$$

**Application**

In Case 1, NaAR at 1440 minutes equals 0.4. Thus, $D_{\text{Na}}$ is resolved by specifying V and t and rearranging Equation 6 as Equation 8.

$$D_{\text{Na}} = -(V/t) \times LN(1 - \text{NaAR}) = -(48,000 \text{ ml/min}/1440 \text{ min}) \times LN(1 - 0.4)$$

$$= -33.3 \text{ ml/min} \times -0.51 = 17.0 \text{ ml/min} \quad (\text{Equation 8})$$

With $D_{\text{Na}}$ known, $Q_{\text{RF}}$ is determined by rearranging Equation 6 as Equation 9.

$$Q_{\text{RF}} = Q_{p} \times (D_{\text{Na}} - Q_{\text{UF}})/(Q_{p} - D_{\text{Na}}); Q_{\text{UF}} = 0$$

$$= (225 \text{ ml/min} \times 17 \text{ ml/min})/(225 \text{ ml/min} - 17 \text{ ml/min})$$

$$= 18.4 \text{ ml/min}/1.1 \text{ L/h}$$

In summary, steps 1–3 determine an NaAR of 0.4 and a VNa(0) of 20 mM that yield a $D_{\text{Na}}$ of 8 mM. Similar results are obtained by increasing $D_{\text{Na}}$ (i.e., greater NaAR) and proportionally decreasing VNa(0). For example, if NaAR is 0.6, VNa(0) becomes 13.3 mM and NaRF2 becomes 129.3.
Also, the NaRF2 that produces a specified ΔNa at time \( t \) is calculated from Equations 4B and 5 (Equation 10).

\[
NaRF2 = NaPre + \left[ ΔNa \left( 1 - e^{-DNa/t/V} \right) \right]
\]  
(Equation 10)

Step 4: Plasma Sodium Concentration during Osmotherapy

Targeting the Plasma Sodium Concentration

Because \( DNa \) and TBW are constants within the constraints of a fixed-volume model, \( PNa(0) \) can be projected over a specified treatment interval \( t \) (Equation 11).

\[
PNa(t) = NaPre + \left[ (NaRF2 - NaPre) \times (1 - e^{-DNa/t/V}) \right]
\]  
(Equation 11)

This concept is depicted in Figure 4 where time- and volume-dependencies of \( PNa(t) \) are displayed for a man and woman of equal height and weight. The time \( (tX) \) when a specified \( PNa(tX) \) occurs is ascertained by substituting \( tX \) into Equation 11 and solving for it.

\[
tX = \frac{-V/DNa \times LN[(NaRF2 - PNa(tX))/(NaRF2 - NaPre)]}{V/DNa}
\]  
(Equation 12)

Step 5: Sodium Balance during Osmotherapy

In a fixed-volume model of SBO, sodium accrual is inevitable as \( PNa \) increases. If patient vulnerability to volume overload is present, net ultrafiltration is advised. Consequently, real-time net sodium balance (\( ΣNa \)) monitoring is critical and computed by Equation 13.

\[
ΣNa(t) = PNa(t) \times (V - QUF \times t) - (NaPre \times V)
\]

\[
ΣNa(t) = PNa(t) \times (V - QUF \times t) - (PNa(0) \times V)
\]  
(Equation 13)

In Case 1, \( ΣNa(1440) \) is +384 mmol if \( QUF = 0 \) but -62.4 mmol if \( QUF \) is 0.15 L/h or 3.6 L per day.

---

**Table 3. Time-dependencies of plasma sodium concentration and sodium concentration adjustment ratio during sodium-based osmotherapy**

| Time (t, min) | \( PNa(0) \) (mM) | NaAR | \( ΔNa(t) \) (mM) | \( PNa(t) \) (mM) |
|--------------|-------------------|------|------------------|------------------|
| 0            | 116.0             | 0.0  | 0.0 (0.0)        | 116.0 (116.0)    |
| 360          | 116.0             | 0.12 | 2.4 (2.9)        | 118.4 (118.9)    |
| 720          | 116.0             | 0.23 | 4.5 (5.4)        | 120.5 (121.4)    |
| 1080         | 116.0             | 0.32 | 6.4 (7.5)        | 122.4 (123.5)    |
| 1440         | 116.0             | 0.40 | 8.0 (9.3)        | 124.0 (125.3)    |
| 2880         | 116.0             | 0.64 | 12.8 (14.3)      | 128.8 (130.3)    |
| 4320         | 116.0             | 0.78 | 15.7 (16.9)      | 131.7 (132.9)    |

Predilution continuous venovenous hemofiltration is carried out on a hypothetical 42-year-old, 178-cm, 90-kg man with \( PNa(0) \) 116 mM and Watson volume 48.0 L for times shown. The replacement fluid is adjusted from a nominal [Na] of 140 mM to 136 mM to achieve a 20 mM [Na] gradient. Values in parentheses are those of a 42-year-old woman with a Watson volume of 39.1 L, treated with the same parameters. \( PNa \), plasma sodium concentration; NaAR, sodium concentration adjustment ratio; \( ΔNa(t) \), \( PNa(t) \) minus \( PNa(0) \); \( PNa(t) \), \( PNa \) at time \( t \); [Na], sodium concentration; \( PNa(0) \), \( PNa \) at time \( t = 0 \).

---

**Figure 2.** Plasma sodium concentration increases are time- and sodium concentration gradient-dependent. Data are modeled from a hypothetical 42-year-old, 178-cm, 90-kg man with Watson volume 48.0 L (see text, Case 1). Plasma sodium concentration (\( PNa \)) is 116 mM before predilution continuous venovenous hemofiltration is carried out at four different [Na] gradients. NaAR equals 0.4 after 1440 minutes of sodium-based osmotherapy. At end treatment, \( PNa \) increases in direct proportion to \( VNa(0) \). \( VNa(0) \), [Na] gradient between plasma and replacement fluid at time (0).
\[ \text{QUF} = \frac{V_{RF2} - V_{RF1}}{V_{RF1}} \]

\[ \text{Na} = \text{Na}_{RF1} - \text{Na}_{RF2} \]

\[ \text{Na}_{RF1} \times \text{V}_{RF1} = \frac{\text{P}_{Na} (t) \times V - (\text{Na}_{Pre} \times V)}{\text{Q}_{UF}} = 0 \text{ ml/min} \]

\[ \text{Na}(1440) = (124 \text{ mM} \times 48.0 \text{ L}) - (116 \text{ mM} \times 48.0 \text{ L}) = 38 \text{ mmol} \]

\[ \text{Na}(1440) = 124 \text{ mM} \times (48.0 \text{ L} - 0.15 \text{ L/h} \times 24 \text{ h}) - (116 \text{ mM} \times 48.0 \text{ L}) = -62.4 \text{ mmol} \]

The Q_{UF} that “zeros” the sodium load at time (t) is calculated as 3.1 L per 24 hours by Equation 14.

\[ \text{Q}_{UF}(t) = \frac{[(\text{Na}_{Post} \times V) - (\text{Na}_{Pre} \times V)]}{(\text{Na}_{Post} \times t)} = \frac{(V \times \Delta \text{Na})}{(\text{Na}_{Post} \times t)} \]

\[ \text{Q}_{UF}(t) = \frac{(V \times \Delta \text{Na})}{(\text{Na}_{Post} \times t)} = (48 \text{ L} \times 8 \text{ mM})/(124 \text{ mM} \times 1440 \text{ min}) = 0.00215 \text{ L/min} = 3.1 \text{ L per 24 hours} \]

For patients vulnerable to volume excess/overload, \( \Sigma \text{Na} \) should be modeled a priori, and we demonstrate this concept as follows.

\[ \text{Na}_{RF2} \times \text{V}_{RF2} = \text{V}_{RF1} \times (\text{Na}_{RF1} - \text{Na}_{RF2})/\text{Na}_{RF1} \]

Figure 3. | Replacement fluid sodium concentration adjustment. Method 1: Sterile water is added to replacement fluid 1 (RF1) of volume \( V_{RF1} \) and sodium concentration \( \text{Na}_{RF1} \) to produce replacement fluid 2 (RF2) of volume \( V_{RF2} \) and sodium concentration \( \text{Na}_{RF2} \). Method 2: A volume from RF1 (\( V_w \)) is exchanged with sterile water to produce \( \text{Na}_{RF2} \). Method 3: A volume of 4 M sodium chloride solution (\( V_{AM} \)) is added to RF1 to produce RF2 volume \( V_{RF2} \) and \( \text{Na}_{RF2} \). Method 4: Solution H is infused post blood pump and pre hemofilter at flow rate \( Q_H \) in parallel with RF1 at flow rate \( \text{Q}_{RF1} \) to produce a blended solution with an effective [Na] (Eff-\( \text{Na}_{RF} \)) at flow rate \( \text{Q}_{Eff} \). H, solution of defined [Na]; Eff-\( \text{Na}_{RF} \), effective-[Na] of RF1 and solution H; \( \text{Na}_{RF1} \), solution H [Na]; \( \text{Q}_{RF1} \), additive flow rate of \( \text{Q}_{RF1} \) and \( \text{Q}_{H} \); \( \text{Q}_{H} \), solution H flow rate; \( \text{Q}_{RF1} \), RF1 flow rate; \( \text{Q}_{RF2} \), RF2 flow rate; \( V_{RF1} \), 4 M saline volume; \( V_{AM} \), water volume added to RF1; \( V_{RF1} \), RF1 exchange volume.

\[ \Sigma \text{Na}(t) = (\text{P}_{Na}(t) \times V) - (\text{Na}_{Pre} \times V); \text{Q}_{UF} = 0 \text{ ml/min} \]

\[ \Sigma \text{Na}(1440) = (124 \text{ mM} \times 48.0 \text{ L}) - (116 \text{ mM} \times 48.0 \text{ L}) = 38 \text{ mmol} \]

\[ \Sigma \text{Na}(t) = (\text{P}_{Na}(t) \times V - \text{Q}_{UF} \times t) - (\text{Na}_{Pre} \times V) \]

\[ \Sigma \text{Na}(1440) = 124 \text{ mM} \times (48.0 \text{ L} - 0.15 \text{ L/h} \times 24 \text{ h}) - (116 \text{ mM} \times 48.0 \text{ L}) = -62.4 \text{ mmol} \]

\[ \Sigma \text{Na}(t) = (\text{P}_{Na}(t) \times V - \text{Q}_{UF} \times t) - (\text{Na}_{Pre} \times V) \]

\[ \Sigma \text{Na}(1440) = 124 \text{ mM} \times (48.0 \text{ L} - 0.15 \text{ L/h} \times 24 \text{ h}) - (116 \text{ mM} \times 48.0 \text{ L}) = -62.4 \text{ mmol} \]

\[ \text{Q}_{UF}(t) = \frac{[(\text{Na}_{Post} \times V) - (\text{Na}_{Pre} \times V)]}{(\text{Na}_{Post} \times t)} = \frac{(V \times \Delta \text{Na})}{(\text{Na}_{Post} \times t)} \]

\[ \text{Q}_{UF}(t) = \frac{(V \times \Delta \text{Na})}{(\text{Na}_{Post} \times t)} = (48 \text{ L} \times 8 \text{ mM})/(124 \text{ mM} \times 1440 \text{ min}) = 0.00215 \text{ L/min} = 3.1 \text{ L per 24 hours} \]

**Modeling Sodium Balance**

For patients vulnerable to volume excess/overload, \( \Sigma \text{Na} \) should be modeled a priori, and we demonstrate this concept as follows.

Figure 4. | Plasma sodium concentration increases are time- and volume-dependent. Data are derived from a hypothetical 42-year-old, 178-cm, 90-kg man (\( M \); see text, Case 1) with Watson volume 48.0 L and a 42-year-old woman (\( W \)) with Watson volume 39.1 L. The baseline plasma and replacement fluid sodium concentrations of both patients are 116 mM and 136 mM, respectively. Continuous venovenous hemofiltration treatment parameters are as follows: \( Q_P \), 225 ml/min; \( Q_{RF} \), 18.3 ml/min; \( Q_{UF} \), 0 ml/min; and treatment time, 4320 minutes. The \( \text{P}_{Na} \) of the woman is greater at all time points due to her smaller Watson volume. \( Q_P \), plasma flow rate; \( Q_{RF} \), replacement fluid flow rate; \( Q_{UF} \), net ultrafiltration fluid rate; \( \text{P}_{Na} \), plasma sodium concentration.
Case 2. A 30-year-old man with heart failure and stage 3B CKD develops AKI and dyspnea. The admission weight is 2 kg more than his last-reported hospital discharge weight. His vital signs are as follows: height, 170 cm; weight, 80 kg; temperature, 36.5°C; heart rate, 118 bpm; blood pressure 130/80 mm Hg; respiratory rate, 18 per minute; and Watson volume, 44.85 L. His laboratory data are as follows: NaPre, 120 mM; BUN, 50 mg/dl; serum creatinine, 4.2 mg/dl; and hematocrit, 0.33. Urine output is 0.05 ml/kg h. A 24-hour NaPost target of 126 mM is planned. Predilution CVVH is begun with parameters of QP 200 ml/min, QRF 50 ml/min, QUF 2.5 ml/min, and treatment time, 1440 minutes. At end treatment, NaAR is 0.74 and PNa increases from 120 mM to 126 mM (top plot). Negative sodium balance begins at t = 240 minutes. Cumulative sodium loss is 185 mmol at end treatment (bottom plot).

![Graph](image1.png)

Figure 5. Plasma sodium concentration elevation without sodium accumulation is achieved by net ultrafiltration during predilution continuous venovenous hemofiltration. Treatment parameters during predilution continuous venovenous hemofiltration of a hyponatremic, 170-cm, 80-kg, 30-year-old man with Watson volume 44.85 L are as follows (see text, Case 2): NaRF2, 128 mM; Qp, 200 ml/min; QRF2, 50 ml/min; QUF, 2.5 ml/min; and treatment time, 1440 minutes. At end treatment, NaAR is 0.74 and PNa increases from 120 mM to 126 mM (top plot). Negative sodium balance begins at t = 240 minutes. Cumulative sodium loss is 185 mmol at end treatment (bottom plot).

![Graph](image2.png)

Table 4. Effects of intravenous solutions and urine output on the effective replacement fluid sodium concentration

| Solution | RF | 0.45% | Solution A | Solution B | UO | 4-Hour Results
|-----------|----|------|------------|------------|----|----------------|
| Flow rate, L/h | 2.0 | Single dose | Single dose | Single dose | -0.1 | —
| Time, h | 4.0 | 4.0 | — | — | 4.0 | —
| [Na], mM | 130.0 | 77.0 | 154.0 | 40.0 | 50.0 | —
| Volume, L | 8.0 | 0.10 | 0.10 | 0.25 | -0.40 | 8.05
| Cation, mmol | 1040.0 | 7.7 | 15.4 | 10.0 | -20.0 | 1053.1
| Eff-NaRF, mM | 130.0 | 129.3 | 130.3 | 127.3 | 134.2 | 130.8

The replacement fluid is infused simultaneously with three separate solutions as shown, with ongoing urine output. To simplify calculations, the RF-potassium concentration is assumed equal to plasma potassium concentration and not described. RF, replacement fluid with [Na] 130 mM; UO, urine output; [Na], sodium concentration; Eff-NaRF, effective [Na] of RF and one of the solutions listed and/or UO.

*Aggregate effect of solutions and urine output on Eff-NaRF.

*Isolated effect of each solution or urine output on Eff-NaRF.
ultrafiltration of 2.14 L per 24 hours is required, as shown below. Ultrafiltration beyond 24 hours produces net total body sodium loss. Figure 5 depicts the evolution of $P_{Na}(t)$ and $\Sigma Na(1440)$ if $Q_{UF}$ is 3.6 L per 24 hours.

$$Q_{UF}(1440) = \frac{(V \times \Delta Na)}{(Na_{post} \times t)} = \frac{(44.85 \times 6 \text{ mM})}{(126 \text{ mM} \times 1440 \text{ min})} = 0.00148 \text{ L/min} = 2.14 \text{ L per 24 hours}$$

Sodium Balance with Edema
If the entire 2-kg excess weight is assumed isotonic to plasma, total body sodium balance must be recalculated. The Watson volume of the 78-kg man was 44.18 L and increased to 46.18 L from 2 L of edema. Achieving zero sodium balance requires just 0.06 L of more net ultrafiltration. However, there is a 160-mmol sodium excess if edema is considered isotonic plasma (Equation 15). To shed the sodium surplus, an additional 1.27 L of net ultrafiltration is required. Overall, net ultrafiltration of 3.47 L attains a $P_{Na}(1440)$ of 126 mM at 76.53 kg.

$$Q_{UF}(1440) = \frac{(V \times \Delta Na)}{(Na_{post} \times t)} = \frac{(46.18 \times 6 \text{ mM})}{(126 \text{ mM} \times 1440 \text{ min})} = 0.00153 \text{ ml/min} = 2.2 \text{ L per 24 h}$$

(Equation 15)

$$\Sigma Na(0) = P_{Na}(0) \times (\text{adjusted } V + \text{ edema [kg]}) = 120 \text{ mM} \times (44.18 + 2) \text{L} = 5542 \text{ mmol}$$

$$\Sigma Na(0) = P_{Na}(0) \times (\text{unadjusted } V) = 120 \text{ mM} \times 44.85 \text{ L} = 5382 \text{ mmol}$$

$\Delta$Total body sodium = 5542 mmol – 5382 mmol = 160 mmol

Additional ultrafiltration volume = 160 mmol/126 mM = 1.27 L

Influence of Exogenous Fluids and Urine Output on Replacement Fluid Sodium Concentration
During SBO, the influence of exogenous cation (sodium and potassium)-containing fluids on $P_{Na}$ and $\Sigma Na$ must be tallied. Only cationic effects require analysis as anions follow pari passu. The RF [Na] is altered by infusions of exogenous fluids and/or urine output and produces a blended solution with an effective [Na] (Eff-$Na_{RF}$). Table 4 illustrates the 4-hour effects on Eff-$Na_{RF}$ in a patient who receives three intravenous fluids, 0.45% saline and hypothetical solutions A and B. By evaluating a short time interval, the singular and collective effects of each fluid on Eff-$Na_{RF}$ are exposed early on. In aggregate, with consideration of all inputs and outputs, the 4-hour effects on Eff-$Na_{RF}$ and extracellular fluid volume are +0.8 mM and +0.05 L, respectively. Extrapolation of this analysis to a 24-hour interval may oblige readjustments of $Na_{RF}$ and/or $Q_{UF}$. Lastly, elaboration of hypotonic urine increases Eff-$Na_{RF}$ minimally, unless urine output is copious, i.e., >4 L per day.

Acute Sodium Loading
Sodium loading can benefit individuals who are normotensive with acute brain swelling. In patients who are hypotensive and hypovolemic, sodium loading may be carried out abruptly by delivery of several small-volume, hypertonic saline boluses (e.g., 100-ml boluses of 23.4% saline) (7,23). Subsequent maintenance of the hypertonic state can be achieved with CRRT modalities. Importantly, the gradual sodium loading of SBO should not supplant urgent volume resuscitation where indicated. In brief, the associated risk of sodium loading must be weighed at the outset of SBO, particularly in patients who are volume overloaded or edematous.

Step 6: Troubleshooting
Slow or No Plasma Sodium Concentration Elevation
If $P_{Na}$ fails to increase during SBO, the osmotherapy prescription must be reexamined. Equipment and extracorporeal circuit integrity must be checked, and the effects of all fluid inputs and outputs must be reevaluated. If $V$ is underestimated, the rise of $P_{Na}$ is mathematically inhibited by an NaAAR that is lower than calculated. A $Q_{UF}$ increase will not remedy the situation because $D_{Na}$ and NaAAR are essentially...
Inaccurate NaAR
When BUN is relatively low, e.g., 30–40 mg/dl, calculation of NaAR may be inaccurate. This may transpire when sodium ion and urea clearance are discordant, i.e., abnormal rate of urea metabolism. Accordingly, a ΔNa of 25–40 ml/min can be prespecified by empirically establishing VNa, QP, QRF, and, optionally, QUF.

Additional Considerations
Hyperglycemia from Dextrose-Containing Solutions
If RF solutions cannot be altered, delivery of a parallel, posthemofilter D5W infusion in pre-/postdilution CVVH may provoke concern for induction of hyperglycemia. However, this concern is unwarranted. A maximal rate of carbohydrate infusion of 4 mg/kg/min has been suggested to prevent lipogenesis (24). At this metabolic threshold, the patient of Case 1 can tolerate a posthemofilter D5W infusion of 300 ml/h, without hyperglycemia (Table 5). Absent carbohydrate metabolism, this infusion rate, in an extracellular volume of 16 L, increases plasma glucose (PGlu) from 100 to 2150 mg/dl. However, at a submaximal rate of glucose metabolism of 2.65 mg/kg/min, PGI60 remains stable at 100 mg/dl. Notably, the effective PNa entering the hemofilter is changed minimally. Prefilter D5W infusions have minimal potential for generating severely elevated PGI60 due to rapid glucose sieving through the hemofilter. If D5W or sterile water infusion rates are eschewed, less hypotonic solutions can be used, e.g., 0.225% or 0.45% saline solution.

Regional Citrate Anticoagulation
Regional citrate anticoagulation with trisodium citrate (TSC) solutions of 4% ([Na], 408 mM) or 2.2% ([Na], 224 mM) have been used during SBO (25–27). Nevertheless, hypertonic TSC infusions can greatly increase plasma toxicity, necessitating reduction of RF [Na] and/or dialysate [Na] to prevent untoward elevations of PNa. If TSC is used during SBO, a priori sodium modeling is advised with appropriate laboratory monitoring at 4- to 8-hour intervals, including ionized calcium levels that will decline with untoward PNa elevations if hypercitratemia occurs.

SBO by Other CRRT Modalities
Aside from predilution CVVH, other CRRT modalities and protocols are available, and some employ pre- and posthemofilter RF delivery (19). When QRF is partitioned pre- and postfilter versus prefILTER alone, there is an incremental postfilter PNa elevation. Table 6 represents a quantitative analysis for pre- and posthemofilter CVVH and reveals only a 0.5-mM increment with a 30/70 division of QRF between pre- and postfilter fractions. TSC has been exploited to increase PNa from normal to supranormal levels in patients with cerebral edema (6). However, in acute cerebral edema, rapid induction of hypertonicity via hypertonic saline boluses (4 M) is favored when prompt elevation of plasma toxicity is critical (7).

Summary
In conclusion, advective SBO by predilution CVVH may be therapeutically exploited in hypotonic conditions with hyponatremia and oligo-anuria. We recommend a six-step approach prevents treatment-based sodium loading (Box 1).

Author Contributions
S. Frinak was responsible for methodology; S. Frinak, T. Gradinariu, N. Mohiuddin, and J. Yee were responsible for formal analysis; S. Frinak, J. Uduman, and J. Yee conceptualized the manuscript S. Frinak and J. Yee were responsible for supervision and validation; N. Mohiuddin and J. Yee were responsible for visualization; all authors wrote the original draft of the manuscript, and reviewed and edited the manuscript.

Table 6. Effect of pre- and posthemofilter replacement fluid infusion on end treatment plasma sodium concentration

| Variable                  | Units | Predilution Only | Pre-/Postdilution | Pre-/Postdilution |
|---------------------------|-------|------------------|-------------------|-------------------|
| QP                        | ml/min| 200.0            | 1.0/0.0           | 0.3/0.7           |
| QRF                       | ml/min| 50.0             | 50.0              | 50.0              |
| Replacement fluid         |       | 1.0/0.0          | 0.5/0.5           | 0.3/0.7           |
| ΔNa                       | ml/min| 40.0             | 44.4              | 46.5              |
| NaAR                      |       | 0.76             | 0.80              | 0.81              |
| PNa(1440)                 | mM    | 127.6            | 128.0             | 128.1             |

A hypothetical patient with Watson volume 40 L and PNa(0) 120 mM undergoes 24 hours of continuous venovenous hemofiltration with the following parameters: NaRF, 130 mM; QP, 200 ml/min, and QRF, 3 L/h. Three simulations are shown: predilution only and pre- and postdilution with QRF pre- and postdilution ratios of 0.5/0.5 and 0.3/0.7. ΔNa, NaAR, and PNa(1440) increase with an increasing proportion of postdilution QRF. The maximal PNa(1440) difference among the three pre-/posthemofilter combinations is 0.5 mM. QP, plasma flow rate; QRF, replacement fluid flow rate; ΔNa, dialysis rate of sodium; NaAR, sodium concentration adjustment ratio; PNa(0), PNa at t (0); PNa(1440), PNa at t = 1440 minutes; NaRF, replacement fluid [Na].
Box 1. Osmotherapy by Predilution Continuous Venovenous Hemofiltration

(1) Define $\Delta Na$ from time (0) to time (t) by defining $Na_{Post}$, e.g. 8 mM after 24 hours
$\Delta Na = Na_{Post} - Na_{Pre}; Na_{Pre} = P_{Na}(0); t = end\ treatment\ time$

(2) Define sodium concentration adjustment ratio (NaAR) from time (0) to t via urea reduction ratio (URR), e.g., 30%–70% over 24 hours
$NaAR \approx URR = (BUN(0) - BUN(t))/(BUN(0) - BUN_{Dialysate})$

(3) Define $\nabla N(a)(0)$
$\nabla N(a)(0) = \Delta Na/NaAR = (Na_{Post} - Na_{Pre})/NaAR = Na_{RF2} - Na_{Pre}$

(4) Calculate $Na_{RF2}$
$Na_{RF2} = Na_{Pre} + \nabla N(a)(0)$

(5) Adjust $Na_{RF1}$ to $Na_{RF2}$ by methods 1–4 (Figure 3)

(6) Calculate dialysance of sodium ($D_{Na}$) from NaAR, Watson volume (V), and t
$D_{Na} = -(V/t) \times LN(1 - NaAR)$

(7) Calculate predicted continuous venovenous hemofiltration at specified $Q_{RF}$ and $Q_{RF}$ to determine $Q_{UF}(t)$ (see below)

Monitor $P_{Na}$ at 4- to 6-hour intervals

(8) Calculate $Q_{RF}$ from $D_{Na}$ and $Q_{B}$
$Q_{RF} = Q_{B} \times (D_{Na} - Q_{UF})/(Q_{B} - D_{Na}); Q_{UF} = 0$

Model predilution continuous venovenous hemofiltration

(9) Model predilution continuous venovenous hemofiltration at specified $Q_{RF}$ and $Q_{RF}$ to determine $Q_{UF}(t)$ (see below)

$Q_{UF}(t) = [Na_{Pre} \times V] / (Na_{Pre} \times t) = (Na_{Post} - Na_{Pre}) \times V / (Na_{Post} \times t)$

Disclosures
J. Yee discloses honoraria from the American Society of Nephrology. S. Frinak, T. Gradinariu, N. Mohiuddin, and J. Udman have nothing to disclose.

Funding
None.

References
1. Shah SR, Bhave G: Using electrolyte free water balance to rationalize and treat dysnatremias. Front Med (Lausanne) 5: 103, 2018
2. Rose BD: New approach to disturbances in the plasma sodium concentration. Am J Med Sci 81: 1033–1040, 1986
3. Faber MD, Yee J: Hyponatremia. In: Ferri’s Clinical Advisor 2019, edited by Ferri FF, Philadelphia, PA, Elsevier, 2019, pp 751–753
4. Yun BC, Kim WR, Benson JT, Biggins SW, Therneau TM, Kremers WK, Rosen CB, Klintmalm GB: Impact of pretransplant hyponatremia on outcome following liver transplantation. Hepatology 49: 1610–1615, 2009
5. Zhu J, Al-Alkim F, Hussaini T, Vertinsky A, Byrne D, Erh SR, Stoessl AJ, Yoshida EM: Occult central pontine myelinolysis post liver transplant: A consequence of pre-transplant hyponatremia. Ann Hepatol 18: 651–654, 2019
6. Fülöp T, Zsom L, Rodríguez RD, Chabrier-Rosello JO, Hamrahian M, Koch CA: Therapeutic hypernatremia management during continuous renal replacement therapy with elevated intracranial pressures and respiratory failure [published correction appears in Rev Endocr Metab Disord 20: 77, 2019]. Rev Endocr Metab Disord 20: 65–75, 2019
7. Surani S, Lockwood G, Macias MY, Guntupalli B, Varon J: Hypertonic saline in elevated intracranial pressure: Past, present, and future. J Intensive Care Med 30: 8–12, 2015
8. Hoorn EJ, Zietse R: Diagnosis and treatment of hyponatremia: Compilation of the guidelines. J Am Soc Nephrol 28: 1340–1349, 2017
9. Wendland EM, Kaplan AA: A proposed approach to the dialysis prescription in severely hyponatremic patients with end-stage renal disease. Semin Dial 25: 82–85, 2012
10. Hamdi T, Yessayan L, Yee J, Szamosfalvi B: High sodium continuous veno-venous hemodialysis with regional citrate anticoagulation and online dialysate generation in patients with acute liver failure and cerebral edema. Hemodial Int 22: 184–191, 2018
11. Bender FH: Successful treatment of severe hyponatremia in a patient with renal failure using continuous venovenous hemodialysis. Am J Kidney Dis 32: 829–831, 1998
12. 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
13. Viktorsdottir O, Indridason OS, Palsson R: Successful treatment of extreme hyponatremia in an anuric patient using continuous venovenous hemodialysis. Blood Purif 36: 274–279, 2013
14. Rosner MH, Connor Jr. MJ: Management of severe hyponatremia with continuous renal replacement therapies. Clin J Am Soc Nephrol 13: 787–789, 2018
15. Sargent JA, Gotch FA: The analysis of concentration dependence of uremic lesions in clinical studies. Kidney Int Suppl 7: 35–44, 1975
16. I. NKF-K/DOQI clinical practice guidelines for hemodialysis adequacy: Update 2000 [published correction appears in Am J Kidney Dis 45: 791, 2005]. Am J Kidney Dis 37(Suppl 1): S7–S64, 2001
17. Dangoisse C, Dickie H, Tovey L, Ostermann M: Correction of hyper- and hyponatraemia during continuous renal replacement therapy. Nephron Clin Pract 128: 394–398, 2014
18. Hasegawa M, Taki F, Shimizu K, Aratani S, Fujimaru T, Aoki K, Komatsu Y: A case of continuous venovenous hemofiltration for anuric acute kidney injury with severe hyponatremia: A simple
method involving flexible adjustment of sodium replacement solution. Kidney Int Rep 1: 85–88, 2016.
19. Macedo E, Mehta RL: Continuous dialysis therapies: Core curriculum 2016. Am J Kidney Dis 68: 645–657, 2016
20. Worthley LIG: Hyperosmolar coma treated with intravenous sterile water. A study of three cases. Arch Intern Med 146: 945–947, 1986
21. Watson PE, Watson ID, Batt RD: Total body water volumes for adult males and females estimated from simple anthropometric measurements. Am J Clin Nutr 33: 27–39, 1980
22. Mercadal L, Ridel C, Petitclerc T: Ionic dialysance: principle and review of its clinical relevance for quantification of hemodialysis efficiency. Hemodial Int 9: 111–119, 2005
23. Murugan R, Hoste E, Mehta RL, Samoni S, Ding X, Rosner MH, Kellum JA, Ronco C; Acute Disease Quality Initiative (ADQI) Consensus Group: Precision fluid management in continuous renal replacement therapy. Blood Purif 42: 266–278, 2016
24. Guenst JM, Nelson LD: Predictors of total parenteral nutrition-induced lipogenesis. Chest 105: 553–559, 1994
25. Hofmann RM, Maloney C, Ward DM, Becker BN: A novel method for regional citrate anticoagulation in continuous venovenous hemofiltration (CVVHF). Ren Fail 24: 325–335, 2002
26. Munjal S, Ejaz AA: Regional citrate anticoagulation in continuous venovenous haemofiltration using commercial preparations. Nephrology (Carlton) 11: 405–409, 2006
27. 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