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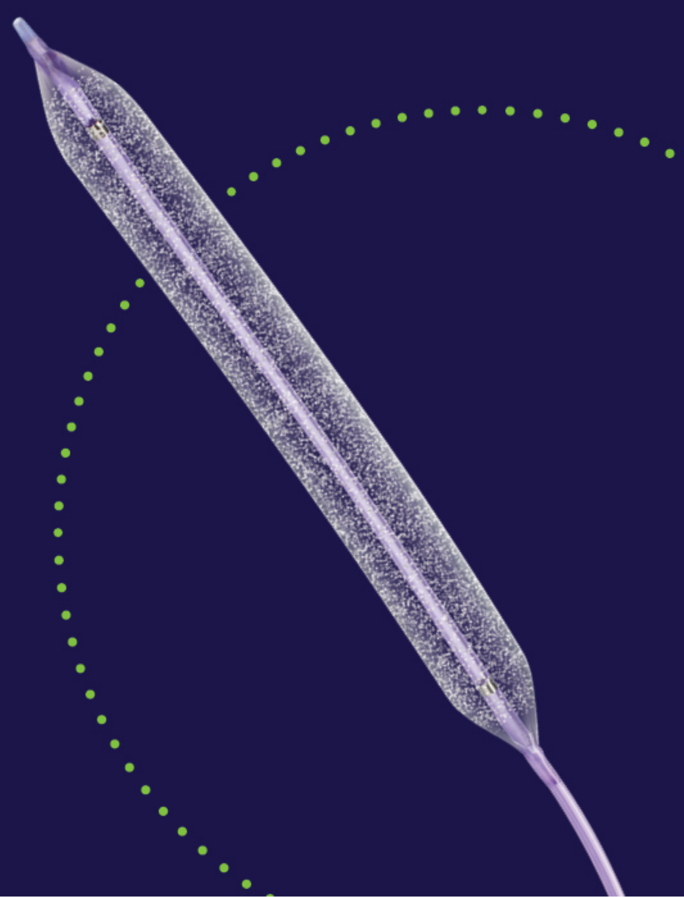

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# A mathematical approach to severe hyponatremia and hypernatremia in renal replacement therapies

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## Abstract

Severe dysnatremias are perplexing problems in patients undergoing renal replacement therapy on a chronic or acute basis. The ability to manipulate sodium concentration in the dialysate or replacement solutions is limited. Compounding dialysate or replacement fluids to alter sodium concentration could result in errors. Rapid correction of hyponatremia or hypernatremia due to equilibrium with dialysate or replacement solutions could lead to osmotic demyelination syndrome or cerebral edema respectively. Continuous renal replacement therapy is the preferred dialysis modality in patients with severe dysnatremias. In this article, we present simple formulas to determine the rate of hypotonic or hypertonic solutions needed to mitigate rapid correction of dysnatremias. These formulas can be used readily by the clinician at bedside.

## 1 | INTRODUCTION

Many clinicians are confronted with patients who have severe hyponatremia or hypernatremia in the dialysis setting. Commonly, 5% dextrose in water solution (D5W) is given to mitigate rapid and/or overcorrection of hyponatremia, and 3% saline is given to mitigate rapid and/or overcorrection of hypernatremia based on the clinician's best estimate. Serum sodium concentration [Na] is checked frequently, and the rate of infusion is adjusted accordingly.

The formulas presented here will streamline this process. Checking [Na] frequently (every 1-2 hours) is critical. None of the formulas take into account other variables such as urine output, free water intake, other intravenous solutions used to infuse medications, or insensible losses. It is crucial to evaluate each patient for the duration of dysnatremia (acute vs chronic, <48 hours vs ≥48 hours, respectively) and any possible signs/symptoms secondary to dysnatremia (change in mental state, sensory or motor changes, seizure, etc). It is also important to slowly correct hyponatremia or hypernatremia prior to initiation of a regular hemodialysis (HD) session.

Complex mathematical models for [Na] flux during HD exist. They incorporate convection, diffusion, and other factors such as the Gibbs-Donnan effect.[1] The issue is complicated further due to frequent discrepancy between prescribed and measured dialysate [Na].[2]

## 2 | SEVERE HYPONATREMIA IN HD PATIENTS

In patients with normonatremia, dialysate [Na] is usually set around 137-140 mEq/L resulting in no net transfer of Na to the patient.

In patients with severe hyponatremia requiring HD, dialysate [Na] can be lowered to 130 mEq/L. Most machines do not allow a dialysate [Na] <130 mEq/L. In the course of HD treatment serum [Na] will rise abruptly depending on dialysate [Na], blood flow rate (BFR; Qb) and dialysis duration. Serum [Na] will equal dialysate [Na] once equilibrium is achieved. The American and the European expert panels recommend a daily correction rate goal of 4-8 mEq/L (with a 10 mEq/L limit for day 1, and 8 mEq/L daily limit thereafter) for patients with low risk for osmotic demyelination syndrome (ODS). For patients at high risk for ODS (such as patients with alcoholism, liver disease, malnutrition, hypokalemia, or serum [Na] ≤105 mEq/L) the recommended daily limit is 8 mEq/L with a 4-6-mEq/L goal. These recommendations apply to chronic (≥48 hours) asymptomatic hyponatremia.[3] ODS is due to rapid shift of water out of the brain tissue resulting from rapid correction of chronic hyponatremia. ODS is encountered less often in HD patients since urea moves slowly across the blood-brain barrier, and the rapid decline in plasma urea during HD counteracts water movement out of the brain due to rapid correction of hyponatremia.[4] In other words, plasma urea and sodium levels move in opposite directions during HD. However, caution is still needed to prevent ODS in HD patients.

If initial serum [Na] is 124 mEq/L and dialysate [Na] is reduced to 130 mEq/L, serum [Na] will be close to 130 mEq/L at the end of a regular HD treatment (3-4 hours HD duration, BFR [Qb] 300-400 mL/min). In this example, no further action is required as long as precautions are taken to avoid further rise in serum [Na] in the first 24 hours.

In the case of severe chronic hyponatremia (for example, serum [Na] 118 mEq/L, ≥48 hours duration), even if one utilizes the reduced dialysate [Na] of 130 mEq/L, the rise of serum [Na] by 12 mEq/L in 3-4 hours could potentially lead to ODS. The rate of rise should be lowered. We will explain why this is challenging if HD is chosen and why continuous renal replacement therapy (CRRT) is the preferred approach. Let us determine the rate of rise in [Na] in the course of a HD treatment.

Ri [Na] = Rate of rise in serum [Na] by the end of a HD session

$$\text{Ri [Na]} = \frac{\text{Total transferred Na during HD session}}{\text{Total body water (L)}}$$

$$\text{Ri[Na]} = \frac{\text{Dialysate [Na]} - \text{Serum [Na]} \times \text{Qb}\ \frac{L}{min} \times \text{duration of HD (minutes)}}{\text{Total body water (L)}}$$

$$\boxed{\text{Ri [Na]} = \frac{\Delta\ \text{Na}\ \left(\frac{\text{mEq}}{\text{L}}\right) \text{x Qb} \left(\frac{L}{min}\right) \text{x T (minutes)}}{\text{TBW (L)}}}$$

**Formula 1: Rate of rise in serum [Na] in the course of a HD treatment**

In women total body water (TBW) (L) = body weight (kg) × 0.5

In men TBW (L) = body weight (kg) × 0.6

**Example 1** The patient is a female who weighs 50 kg, TBW 25 L

Initial serum [Na] 113 mEq/L

Dialysate [Na] 130 mEq/L, delta[Na] = 17 mEq/L

Qb 100 mL/min = 0.1 L/min

Dialysate flow rate (Qd) 600 mL/min

Dialysis duration 3 hours = 180 min

$$\text{Ri[Na]} = \frac{17 \times 0.1 \times 180}{25} = 12\ \text{mEq/L}$$

Despite such a low Qb, her serum [Na] will rise by nearly 12 mEq/L over a 3 hours period. This is a rapid rate of serum [Na] correction. Higher Qb would have raised her serum [Na] more rapidly in equilibration with the dialysate [Na], and thus, would have been more problematic.

To determine a Qb that would result is a slower rise in serum [Na], we need to re-arrange the above formula:

$$\boxed{\text{Qb}\ \left(\frac{\text{L}}{\text{min}}\right) = \frac{Ri\ \left(\frac{mEq}{L}\right) x\ TBW\ (L)}{\Delta\ \text{Na}\ \left(\frac{\text{mEq}}{\text{L}}\right)\ \text{x T (min)}}}$$

**Formula 2: Blood flow rate (Qb) needed for a slow rise in [Na]**

**Example 2** We can calculate Qb needed to raise serum [Na] by only 6 mEq/L, over 3 hours of HD, in the above patient:

$$\text{Qb} = \frac{6 \times 25}{17 \times 180} = 0.049 \left(\frac{\text{L}}{\text{min}}\right) = 49 \left(\frac{\text{mL}}{\text{min}}\right)$$

Such a low Qb is problematic for obvious reasons. It requires selecting a pediatric option on the dialysis machine.[5] It is likely to result in clotting of the dialyzer and inadequate dialysis. Many patients may have significant hyperkalemia and/or metabolic acidosis prior to dialysis, and these metabolic derangements are unlikely to improve if Qb is kept at this low rate. Reducing dialysis time to lessen the transfer of Na from dialysate to the patient may not be feasible in case of significant hyperkalemia, metabolic acidosis, or hypervolemia.

For HD patients with severe hyponatremia, some have suggested limiting dialysis to 1 hour at a time, alternating dialysis with isolated ultrafiltration if needed for management of hypervolemia. Qb is kept at <2 mL/kg/min, dialysate [Na] is lowered to 130 mEq/L and serum [Na] is checked every 30-60 minutes during HD treatment.[6]

Another option to mitigate the problem of too rapid correction of serum [Na] is to lower dialysate [Na] to 130 mEq/L and to initiate D5W infusion at the start of dialysis. The patient should be monitored for hyperglycemia and hypervolemia.

To determine the volume of D5W needed to slow down the rate of correction of serum [Na], let us consider the following:

*V* = Volume of D5W (L)

$[\text{Na}]_t$ = Terminal serum [Na] at the end of dialysis, which is the same as dialysate [Na] due to equilibrium (especially if Qb is kept in the usual range of 300-450 mL/min over 3-4 hours of HD) if no D5W is infused.

$[\text{Na}]_d$ = Desired serum [Na] at the end of dialysis

TBW = Total body water (L)

Note that total body [Na] remains the same after infusion of D5W (which contains no Na).

$$[\text{Na}]_t \times \text{TBW} = [\text{Na}]_d \times (\text{TBW} + V).$$

Solve for V.

$$[Na]_t \times TBW = [Na]_d \times TBW + [Na]_d \times V,$$

$$[Na]_d \times V = [Na]_t \times TBW - [Na]_d \times TBW = ([Na]_t - [Na]_d) \times TBW.$$

$$V = \frac{([Na]_t - [Na]_d) \times TBW}{[Na]_d},$$

and dialysis disequilibrium syndrome (DDS) [7]; therefore, CRRT is preferable. We should emphasize that the pathogenesis of DDS is complex but clearly involves a component of cerebral edema. DDS is unlikely to result solely from rapid correction of hypernatremia.[8] It is conceivable that rapid correction of azotemia is more likely to result in DDS, especially if another cause of hyperosmolality, such as hyperglycemia or hypernatremia, is rapidly corrected at the same time.[9]

$$\text{Volume of D5W (L)} = \frac{(\text{dialysate [Na]} - \text{Desired serum [Na]}) \text{ x TBW (L)}}{\text{Desired serum [Na]}}$$

**Formula 3: Volume of D5W needed to slow down the rate of correction of serum [Na]**

**Example 3** In a 50 kg female (TBW = 25 L) whose serum [Na] is 117 mEq/L our desired [Na] at the end of dialysis would be (117 + 6 = 123 mEq/L), however with dialysate [Na] of 130 mEq/L the patient's serum [Na] will become 130 mEq/L at the end of dialysis treatment unless we infuse 1.4 L D5W during dialysis.

$$D5W = \frac{(130 - 123) \times 25}{123} = 1.4(L)$$

The volume of infused D5W increases with the severity of hyponatremia and with the increase in TBW.

**Example 4** If the patient is a man who weighs 80 kg (TBW = 48 L), initial serum [Na] 108 mEq/L, the desired serum [Na] 114 mEq/L, then the volume of D5W using the same formula is 6.7 L. This can result in significant hyperglycemia and hypervolemia.

## 3 | SEVERE HYPERNATREMIA IN HD PATIENTS

Dialysate [Na] can be set up to 150-155 mEq/L. If serum [Na] is close to that value (within 2 mEq), no further action is needed. Based on expert recommendation, dialyzing a patient with severe hypernatremia using dialysate that is significantly lower in [Na] (lower by greater than 5 mEq) may result in cramping, hypotension

If serum [Na] is significantly higher than dialysate [Na], one can infuse 3% saline at the initiation of dialysis to mitigate against a sudden drop in serum [Na]. The amount and the rate of 3% saline should vary from case to case. The following formula can be used to calculate the volume of 3% saline (Na content is 513 mEq/L) that is needed:

$$\text{Volume of 3\% saline (L)} = \frac{\text{TBW (L) x (desired [Na]} - \text{dialysate [Na])}}{\text{513 (mEq/L)}}$$

**Formula 4: Volume of 3% saline needed to mitigate rapid decline is serum [Na]**

The difference between the desired serum [Na] and dialysate [Na] multiplied by TBW (L) indicates the total amount of Na (mEq) needed. If we divide the product by the Na content of 3% saline (513 mEq/L), the result is the volume (L) of 3% saline solution that should be infused.

**Example** If a patient presents with a serum [Na] of 160 mEq/L, we raise dialysate [Na] to 150 mEq/L. Dialyzing against a [Na] gradient of 10 mEq/L is undesirable because of possible cramping and hypotension. A target serum [Na] of 156 mEq/L is reasonable. If the patient is a 70 kg man, his TBW is 0.6 × 70 = 42 L, the volume of 3% saline using the above formula is:

$$\text{Volume of 3\% saline} = \frac{42 \times (156 - 150)}{513} = 0.491 \text{ L}$$

## 4 | SEVERE HYPONATREMIA AND CRRT

As we have seen above, HD may not be practical for patients with severe hyponatremia.

Electrolytes management is significantly easier in CRRT. Management of severe hyponatremia with CRRT was presented at the Nephrology Quiz and Questionnaire Session at the 2018 Kidney Week.[10]

To simplify matters, first we will assume that all replacement fluids will be administered prefilter at a rate of 2 L/h (33 mL/min) and [Na] in the replacement fluid is the standard 140 mEq/L (280 mEq in 2 L). The patient will be on continuous venovenous hemofiltration CVVHF (no dialysate). Filtration fraction (FF) will be kept <25%, giving replacement fluids prefilter will help in achieving that goal.

If BFR is 200 mL/min and hematocrit (Hct) is 30%, then:

$$\text{Plasma flow rate (PFR)} = \text{BFR} \times (1 - \text{Hct}) = 200 \times (1 - 0.3) = 140\,\text{mL/min}.$$

If net fluid removal is 0 and ultrafiltration rate (UFR) is 2000 mL/60 min (33 mL/min), we can calculate the FF using the following formula:

$$\text{FF}(\%) = \frac{\text{UFR}\left(\frac{\text{mL}}{\text{min}}\right)}{\text{PFR}\left(\frac{\text{mL}}{\text{min}}\right) + \text{Prefilter replacement fluid rate}\left(\frac{\text{mL}}{\text{min}}\right)}$$

$$\text{FF} = \frac{33}{140+33} = 19\%$$

If the same replacement fluid is administered postfilter:

$$\text{FF} = \frac{\text{UFR}}{\text{PFR}} = \frac{33}{140} = 24\%$$

Now we will determine the desired $[\text{Na}]_d$ level and the volume of D5W to be given postfilter to achieve that target.

$V$ = Volume of D5W (L) that has 0 Na content

Replacement fluid $[\text{Na}]_r$ = 140 mEq/L (280 mEq Na in 2 L)

$$[\text{Na}]_d = \frac{280+0}{2+V}$$

Solve for $V$:

$$2[\text{Na}]_d + V \times [\text{Na}]_d = 280,$$

$$V \times [\text{Na}]_d = 280 - 2[\text{Na}]_d$$

$$V = \frac{280 - 2[\text{Na}]_d}{[\text{Na}]_d}$$

$$\text{Volume of D5W}\left(\frac{\text{L}}{\text{h}}\right) = \frac{280 - 2[\text{Na}]_d}{[\text{Na}]_d}.$$

Now we can re-write the above formula to account for any volume of replacement fluids irrespective of [Na] content to achieve a desired serum $[\text{Na}]_d$: If volume of replacement fluid is $V_r$ and [Na] in replacement fluid is $[\text{Na}]_r$, then $V_r \times [\text{Na}]_r$ will be the total Na in replacement fluids, and:

$$\text{D5W}\left(\frac{\text{L}}{\text{h}}\right) = \frac{\text{Vr [Na]r} - \text{Vr[Na]d}}{\text{[Na]d}}$$

**Formula 5: Volume of D5W needed to mitigate rapid decline in serum [Na] in CVVHF**

**Example 1** See Figure 1: If the initial serum [Na] is 124 mEq/L and the desired serum $[\text{Na}]_d$ is 130 mEq/L, and replacement fluid is at 2 L/h with [Na] of 140 mEq/L:

$$\text{D5W}\ \frac{\text{L}}{\text{h}} = \frac{(2 \times 140) - (2 \times 130)}{130} = 0.153\ \text{L}$$

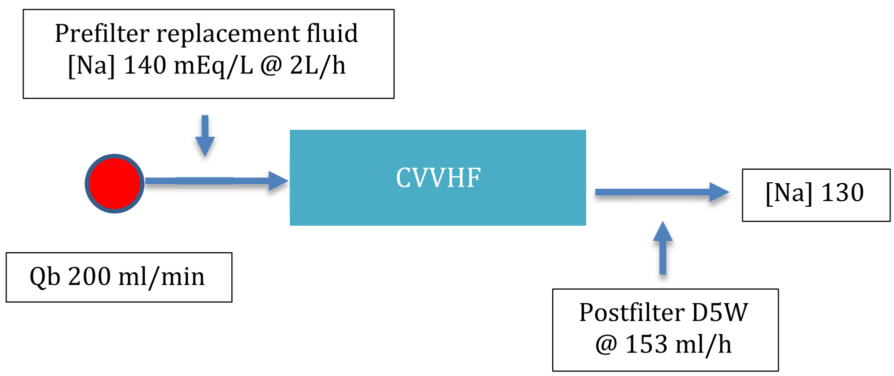


FIGURE 1 Correction of hyponatremia by dextrose in water solution (D5W) infusion in Continuous Veno-venous Hemofiltration (CVVH) [Color figure can be viewed at wileyonlinelibrary.com]

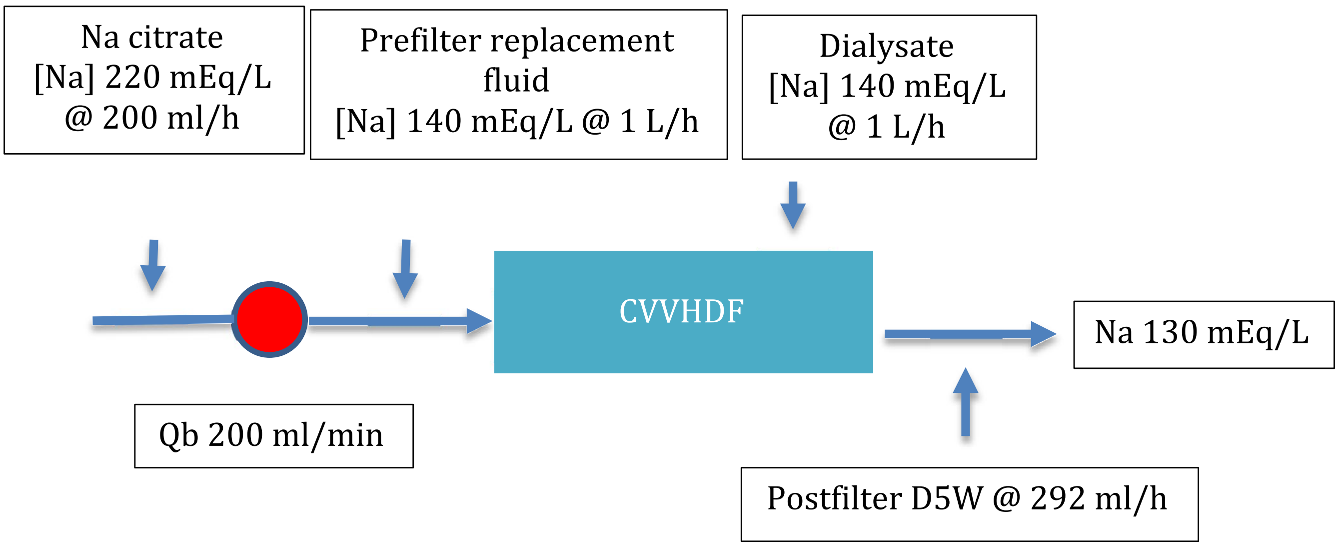


FIGURE 2 Correction of hyponatremia by dextrose in water solution (D5W) infusion in continuous venovenous hemodiafiltration (CVVHDF) [Color figure can be viewed at wileyonlinelibrary.com]

We give 153 mL/h of D5W.

**Example 2** If the desired serum $[Na]_d$ is 120 mEq/L, and the replacement fluid is at a rate of 1.5 L/h with $[Na]_r$ of 135 mEq/L.

$$D5W\left(\frac{L}{h}\right)=\frac{(1.5\times 135)-(1.5\times 120)}{120}=0.187\ L$$

We give 187 mL/h of D5W.

An online calculator is available to perform the same calculations with great ease.[11]

The same formula can be used in other CRRT modalities such as continuous venovenous hemodiafiltration (CVVHDF) with citrate anticoagulation.

*V* in this case is the total volume of fluids containing [Na] (Na citrate + dialysate +prefilter and/or postfilter replacement fluids). $[Na]_d$ is the desired final serum [Na]. See Figure 2.

$$D5W\left(\frac{L}{h}\right)=\frac{(\text{citrate solution [Na]}+\text{dialysate [Na]}+\text{replacment fluid [Na]})-V\,[Na]d}{[Na]d}$$

**Formula 6: Volume of D5W needed to mitigate a rapid rise in serum [Na] in CVVHDF**

**Example 3** If [Na] in Na citrate solution used for anticoagulation is 220 mEq/L and the solution is run at 200 mL/h, total Na in that solution will be 220 × 0.2 = 44 mEq.

Standard dialysate [Na] is 140 mEq/L, so if dialysate is run at 1 L/h, Na content will be 140 mEq. Standard replacement fluid [Na] is 140 mEq/L, and if prefilter replacement fluid is run at 1 L/h, Na content will be 140 mEq. The desired serum $[Na]_d$ is 130 mEq/L in this example.

$$D5W\left(\frac{L}{h}\right)=\frac{(44+140+140)-2.2(130)}{130}=0.292\ L$$

D5W is given at 292 mL/h. Giving a solution such as D5W at this rate will increase the dose of CRRT.

Administration of a solution such as D5W will increase the dose of CRRT. Knowledge of TBW is critical to predict the changes in serum [Na] over the course of the CRRT treatment. Let us take Example 1. above, after 1 hour of CRRT, the net gain in Na is: total Na in replacement fluids (after dilution with D5W) − total Na in UF fluid = 2 × 130 − 2 × 124 = 12 mEq, for a patient who weighs 60 kg with TBW of 30 L, the rise in serum [Na] after the first cycle will be 12/30 = 0.4 mEq/L. Contrast that with a patient with liver cirrhosis, massive ascites and TBW of 60 L. In that case the rise in serum [Na] will only be 0.2 mEq/L in the first hour of CRRT.

With continuation of CRRT, the patient's serum [Na] will rise progressively, and the net Na gain will decrease. Therefore, it is mandatory to check serum [Na] every 1-2 hours, once the desired serum [Na] is achieved, the same formula is used to calculate the next serum [Na] target until gradual serum [Na] correction is achieved.

$$\text{Increase in serum [Na] }\left(\frac{\text{mEq}}{\text{L}}\right) = \frac{\text{Vr [Na]d} - \text{Vr[Na]i}}{\text{TBW}}$$

**Formula 7: The increase in serum [Na] after 1 hour of CRRT**

## 5 | SEVERE HYPERNATREMIA AND CRRT

In case of hypernatremia we will use the same assumptions as above. Here we need to determine the volume of 3% saline to be infused postfilter.

$[Na]_d$ = Desired serum [Na]

$V$ = Volume (L) of 3% saline (513 mEq Na/L)

Prefilter replacement fluids [Na] 140 mEq/L at 2 L/h (280 mEq Na)

$$[Na]_d = \frac{280\left(\frac{\text{mEq}}{2\text{L}}\right) + V(\text{L}) \times 513\left(\frac{\text{mEq}}{\text{L}}\right)}{2(\text{L}) + V(\text{L})}.$$

Solve for $V$:

$$2[Na]_d + V \times [Na]_d = 280 + V \times 513,$$

$$2[Na]_d - 280 = V \times 513 - V \times [Na]_d,$$

$$2[Na]_d - 280 = V(513 - [Na]_d),$$

$$V = \frac{2[Na]_d - 280}{513 - [Na]_d}$$

$$\text{Volume of 3\% saline }\left(\frac{\text{L}}{\text{h}}\right) = \frac{2[Na]_d - 280}{513 - [Na]_d}.$$

**Example 1** If the initial serum $[Na]_i$ is 160 mEq/L, the desired serum $[Na]_d$ is 150 mEq/L, and we are running replacement fluid [Na] 140 mEq/L at a rate of 2 L/h in CVVHF modality:

$$V = \frac{(2 \times 150) - 280}{513 - 150} = 0.055\,\text{L}$$

We give 55 mL/h of 3% saline.

Now we can re-write the above formula to account for all types of replacement fluids irrespective of their [Na].

$[Na]_d$ = Desired serum [Na]

$[Na]_r$ = Replacement fluid [Na]

$V$ = Volume of pre- and/or post- filter replacement fluids and dialysate

$V$ Na = Sum of Na content of all replacement fluids and dialysate, then:

$$\text{Volume of 3\% saline }\left(\frac{\text{L}}{\text{h}}\right) = \frac{\text{V x [Na]d} - \text{V x [Na]r}}{513 - \text{[Na]d}}$$

**Formula 8: Volume of 3% saline needed to mitigate rapid rise in serum [Na] in CVVHF**

**Example 2** If the desired serum $[Na]_d$ is 160 mEq/L, and we are running replacement fluids containing [Na] 145 mEq/L at a rate of 1.5 L/h in CVVHF modality:

$$\text{3\% saline} = \frac{(1.5 \times 160) - (1.5 \times 145)}{513 - 160} = 0.063\,\text{L}$$

We give 63 mL/h of 3% saline.

**Example 3** If the desired serum $[Na]_d$ is 155 mEq/L in CVVHDF modality, and the patient is receiving Na citrate solution for anticoagulation with [Na] 220 mEq/L at a rate of 300 mL/h (the amount of Na delivered per hour is 220 × 0.3 = 66 mEq/h), with standard dialysate [Na] 140 mEq/L at a rate of 1 L/h, and standard replacement fluid [Na] 140 mEq/L at a rate of 1 L/h, given prefilter, the volume of 3% hypertonic saline to be infused is:

$$\text{Volume of 3\% saline} = \frac{(2.3 \times 155) - (66 + 140 + 140)}{513 - 155} = 0.029\,\text{L}$$

We give 29 mL/h of 3% saline.

$$\text{Volume of 3\% saline }\left(\frac{\text{L}}{\text{h}}\right) = \frac{\text{total V x [Na]d} - \text{total Na content of solutions}}{513 - \text{[Na]d}}$$

**Formula 9: Volume of 3% saline needed to mitigate rapid rise in serum [Na] in CVVHDF**

Administration of 3% saline will increase the dose of CRRT. It is mandatory to check serum [Na] every 1-2 hours.

As we discussed earlier with severe hyponatremia and CRRT, knowledge of TBW is critical to predict the changes in serum [Na] over the course of the CRRT treatment. Let us take Example 1 of hypernatremia. After 1 hour of CRRT, the net loss of Na is: total Na in UF fluid − total Na in replacement fluids (after reaching the desired concentration with addition of 3% saline) = 2 × 160 − 2 × 150 = 20 mEq, for a patient who weighs 60 kg with TBW of 30 L, the fall in serum [Na] after the first cycle will be 20/30 = 0.66 mEq/L. Contrast that with a patient with liver cirrhosis, massive ascites and TBW of 60 L. In that case the fall in serum [Na] will only be 0.33 mEq/L in the first hour of CRRT.

With continuation of CRRT, the patient's serum [Na] will decrease progressively, and the net Na loss will decrease. Therefore, it is mandatory to check serum [Na] every 1-2 hours, once target serum [Na] is achieved, the same formula is used to calculate the next desired serum $[\mathrm{Na}]_d$ until gradual serum [Na] correction is achieved. The following formula can be used to estimate Na loss.

$$\text{Decline in serum [Na]}\ \left(\frac{\text{mEq}}{\text{L}}\right) = \frac{\text{Vr [Na]i} - \text{Vr[Na]d}}{\text{TBW}}$$

**Formula 10: The decline in serum [Na] at 1 hour of CRRT**

correction of [Na] was defined as >0.5 mEq/L/h and slow correction as ≤0.5 mEq/L/h. There was no difference in 30-day mortality between the rapid and the slow correction groups. Moreover there were no cases of seizures, cerebral edema or altered consciousness in either group. The study was retrospective in nature and did not identify the optimal rate of [Na] correction in hypernatremia. The study did not provide data on the type of intravenous fluids used for correction of hypernatremia. In an accompanying editorial, Dr Stern indicated that current recommendations for the management of hypernatremia in adults are based on studies done in pediatric populations.[17] The editorial emphasized the fact that adaptation to hyponatremia is more rapid than adaptation to hypernatremia, and that hypernatremia is not hyponatremia in reverse. Therefore, a daily correction rate of <10-12 mEq/L may be prudent but is not evidence-based.

Continuous renal replacement therapy is the preferred method in patients with severe hyponatremia or hypernatremia requiring renal replacement therapy.[18] In patients with severe hypernatremia, 3% saline can be infused postfilter to avoid too rapid correction. As data on the safe rate of correction of hypernatremia continue to emerge, the rate of 3% saline and its utility will need to be reevaluated.

## 6 | DISCUSSION

The movement of Na across dialysis membrane is by diffusion and convection.[12] Diffusion is governed mainly by the gradient between plasma [Na] and dialysate [Na], and to a lesser extent by plasma protein concentration. The kinetics of Na transport by convection (where Na follows water) is mainly affected by plasma protein concentration. Plasma consists of approximately 94% water and 6% proteins and lipids. If plasma [Na] is 140 mEq/L, plasma water [Na] will be 149 mEq/L (140/0.94 = 149). [Na] in the ultrafiltrate decreases relative to plasma [Na] as plasma protein concentration increases. If dialysate [Na] is kept slightly below serum [Na] (eg, 3 mEq/L lower), no Na diffusion occurs.[13] This is due to the Gibbs-Donnan effect exerted by the negatively charged protein on cations such as Na to maintain electroneutrality.[14]

Ultrafiltrate removes approximately 140 mEq/L of [Na] by convection.[15]

In chronic hypernatremia, the traditional paradigm has been to lower serum [Na] at a rate that does not exceed 10-12 mEq/24 h. Chauhan et al recently questioned this view, indicating that it was based on expert opinion, rather than evidence-based guidelines.[16] In their study the authors assessed data on 449 critically ill patients with hypernatremia (approximately one-fourth had hypernatremia on admission and the rest developed hypernatremia during hospitalization). Hypernatremia was defined as [Na] ≥ 155 mEq/L. Rapid correction of [Na] was defined as >0.5 mEq/L/h and slow correction as ≤0.5 mEq/L/h.

The above formulas described for CRRT are not intended for use in prolonged intermittent renal replacement therap.

Adding hypertonic saline solution to the replacement fluid can be done cautiously to avoid devastating errors. It should be only done at centers with experience in compounding intravenous solutions. 1 mL of 30% NaCl (approximately 5 mEq Na/mL) added to 5 L bag of replacement solution will raise [Na] by 1 mEq/L. For example, to raise [Na] in a 5 L replacement solution from 140 to 160 mEq/L we need to add 20 mL of 30% NaCl (100 mEq of Na).[19] This volume of hypertonic saline is small and will not significantly affect the concentrations of other electrolytes, such as potassium, in the replacement solution.

Gotch and Keen described Na kinetic models predicting post dialysis serum [Na] based on dialysate [Na] and Kt/V.[20]

Yessayan et al reviewed management of electrolyte and acid-base disorders in patients with acute kidney injury requiring CRRT.[21] They described infusing D5W separately (eg., postfilter) to avoid rapid correction of hyponatremia using the following formula ([Na] in replacement fluid is the standard 140 mEq/L):

$$\text{D5W infusion rate} = \frac{140 - \text{desired [Na]}}{140} \times \text{desired clearance}$$

**Example** If the initial serum [Na] is 115 mEq/L and the desired [Na] is 121 mEq/L, with a CRRT clearance rate of 2 L/h and replacement fluid [Na] of 140 mEq/L, infusion rate of D5W would be 0.271 L/h. The sum of the replacement fluids and dialysate should be decreased to 1.729 L/h (2 − 0.271 = 1.729 L/h) in order to keep the desired clearance at 2 L/h and avoid hypervolemia.

In case of hypernatremia, the same authors proposed the following formula ([Na] in replacement fluid is the standard 140 mEq/L):

$$3\%\ \text{saline rate} = \frac{\text{desired [Na]} - 140}{(513 - 140)} \times \text{desired clearance}$$

**Example** If the patient's initial serum [Na] is 182 mEq/L, and the desired serum [Na] is 172 mEq/L, with a CRRT clearance rate of 2 L/h and replacement fluid or dialysate [Na] of 140 mEq/L, the infusion rate of 3% saline would be 0.171 L/h. As mentioned above the sum of the replacement fluids and dialysate should be decreased to 1.829 L/h (2 − 0.171 = 1.829 L/h) in order to keep the desired clearance at 2 L/h.

The same authors described the following formula to estimate serum [Na] at the end of CVVHF [22]:

$$Na_{(t)} = Na_{(i)} + (Na_{\text{dialysate}} - Na_{(i)}) \times (1 - e^{-Dt/V})$$

where $Na_{(t)}$ is serum [Na] at a desired time (eg 4 hours); $Na_{(i)}$ is the initial serum [Na] (at the start of CRRT); D is the Na dialysance which is roughly equal to urea clearance in L/h; (t) is time elapsed since the start of CRRT; V is TBW using Watson formula which derives TBW based on age, sex, weight and height.

The same formula can be utilized to determine serum [Na] at the end of an HD treatment. Na and urea are small solutes with similar dialyzer transfer properties. Therefore *Dt/V* in the above formula can be replaced by single-pool urea *Kt/V*.

**Example** In a 68 kg male, if initial serum [Na] is 120 mEq/L, dialysate [Na] 140 mEq/L, CRRT dose 25 ml/kg/h, D is 1.7 L/h (68 kg x 25 mL/kg/h = 1.7 L/hr), t is 2 hours, V (40 L, based on Watson formula for a 68 kg male, age 40, height 170 cm), serum [Na] after 2 hours will be 121.6 mEq/L. This is a rise by 1.6 mEq/L over 2 hours.

Our formulas differ from the formulas proposed by Yessayan et al because they allow for different permutations. For example, they can be utilized irrespective of [Na] concentration in replacement fluid or dialysate and with citrate anticoagulation.

Recently Yee et al expanded on the above concepts by describing a mathematical approach to the issue of hyponatremia via sodium-based osmotherapy while on CRRT.[23] The goal was to reduce cerebral edema in hypotonic hyponatremia. Intravenous solutions were administered in a controlled manner following a six-step protocol that utilized urea and Na kinetics.

## 7 | CONCLUSION

- A few mathematical formulas can be implemented at the bedside in patients with severe hyponatremia and hypernatremia requiring renal replacement therapy. The formulas estimate the volume of 5% dextrose in water or 3% saline needed to prevent too rapid correction of hyponatremia or hypernatremia, respectively.
- Continuous renal replacement therapy is the preferred dialysis modality in these patients.
- Frequent serum [Na] monitoring is mandatory because many variables are at play in these patients.
- The above formulas provide general guidance based on mathematical models and although logical, they have not been validated in clinical trials.
- Management of these complex problems should be guided by experienced clinicians.

### CONFLICT OF INTEREST

The authors find no conflict of interest in preparing this manuscript. The authors declare no competing financial and/or non-financial interests in preparing this manuscript.

### AUTHOR CONTRIBUTION

MT lead the concept, wrote the first draft. BB contributed in concept and editing the manuscript. Both authors approved the submitted version of the manuscript.

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