Continuous Renal Replacement Therapy for the Management of Acid-Base and Electrolyte Imbalances in Acute Kidney Injury

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Continuous renal replacement therapy (CRRT) is used to manage electrolyte and acid-base imbalances in critically ill patients with acute kidney injury. Although a standard solution and prescription is acceptable in most clinical circumstances, specific disorders may require a tailored approach such as adjusting fluid composition, regulating CRRT dose, and using separate intravenous infusions to mitigate and correct these disturbances. Errors in fluid prescription, compounding, or delivery can be rapidly fatal. This article provides an overview of the principles of acid-base and electrolyte management using CRRT.

Key Words: CRRT, Hyponatremia, Acidosis, Alkalosis, Hyperkalemia

INTRODUCTION

Acute kidney injury (AKI) may present with life-threatening electrolyte or acid-base disorders. Intermittent or continuous forms of renal replacement therapies (RRTs) are used for blood purification in AKI. Critically ill patients who require renal support are often hemodynamically unstable and may require continuous renal replacement therapy (CRRT) for the management of acid-base and electrolyte imbalances.

Occasionally, the CRRT prescription may also need to be individualized depending on the duration and/or severity of a specific disorder. A variety of CRRT techniques may be applied in such settings to achieve controlled correction of electrolytes such as adjustment of replacement fluid (RF) or dialysate composition, regulation of CRRT dose based on kinetic modeling, or using separate electrolyte infusion(s). As CRRT can be most effective over longer periods of time, serious disturbances in electrolyte homeostasis may occur in the absence of thoughtful design and monitoring of the intervention. Understanding the principles of electrolyte and acid-base management with CRRT is necessary as errors in fluid prescription, compounding, or delivery may lead to significant complications or even death.

The makeup of the dialysate/RF in combination with the specifics of the dialysis technique is of paramount importance in safely accomplishing treatment goals.

DIALYSATE OR REPLACEMENT FLUID QUALITY

In the United States, sterile substitution fluid is used in continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration. The fluid is either prepared and prepackaged by a manufacturer or occasionally custom-made in a compounding pharmacy. Customized injection (spiking) of electrolyte solutions into commercial fluid bags by the pharmacy or at the bedside should be avoided and considered only when absolutely necessary as with cases of severe dysnatremia. Spiking of CRRT fluids carries the risk of contamination with endotoxins or bacteria and the risk of human error (incorrect dose).[1,2]

FLUID COMPOSITION

Many commercial, sterile CRRT solutions with varying electrolyte compositions are available and provide a range of fluid options to treat different electrolyte disorders. There is little practical difference in the composition of replacement or dialysate fluid, however, and many dialysate fluids are used off-label as RF. These solutions contain the following concentrations of electrolytes and glucose: sodium 136 to 140 mEq/L, chloride 100 to 113 mEq/L, potassium 0 to 4 mEq/L, calcium 1.5 to 3.0 mEq/L, magnesium 1.0 to 1.5 mEq/L, and glucose 0 to 100.0 mg/dL. Hyponatric and calcium-free solutions are also available and seem to be designed for use with regional citrate anticoagulation (RCA); although this may not be explicitly stated. Lactate or bicarbonate is used as the alkalinizing anion in a concentration range of 25 to 40 mEq/L. When RCA is used for maintaining the patency of the CRRT circuit, the citrate also serves as a source of base to replace bicarbonate losses across the filter. Patients receiving high-volume exchanges or those with severe tissue acidosis and/or liver failure may be unable to convert the lactate or citrate load effectively, resulting in hyperlactatemia or hypercitratemia and metabolic acidosis.[3,4] Bicarbonate-based fluids are available as twin-bag systems, one containing the bicarbonate solution and the other at least glucose and the divalent cations calcium and magnesium, and the 2 compartments are mixed immediately before use.[5] Most commercially available CRRT solutions do not

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contain phosphate, and separate phosphate supplementation is generally required to prevent hypophosphatemia during CRRT.

SODIUM

Sodium disorders can be present with dialysis-requiring AKI, CKD, or ESRD.[6-8] The treatment guidelines (2013 Expert Panel Recommendations, 2014 European Hyponatraemia Guideline Development Group) do not address the unique situation where dysnatremias and dialysis-requiring kidney failure coexist. However, although the overall strategy for the management of dysnatremias must include RRT in renal failure, the rate of correction should not be different from the nondialysis population. Controlled correction of sodium disorders is necessary to avoid development of cerebral edema in hypernatremic patients and osmotic demyelination syndrome in hyponatremic patients. For serum sodium that is only mildly decreased or increased, the hemodialysis dialysate sodium could be adjusted to stay within 6 to 8 mEq/L above or below the patient's serum sodium. However, patients with more extreme dysnatremia (<120 mEq/L or >165 mEq/L) would be best treated using CRRT.

Strategies to avoid overly rapid correction of chronic dysnatremias include adjusting the dialysate or the RF sodium concentration,[8-10] regulating the overall and hourly clearance delivered by RRT,[8] with or without the additional use of separate hypotonic or hypertonic infusions.

CLINICAL SUMMARY

- Controlled, predictable correction of electrolyte and acid-base derangements is feasible with continuous renal replacement therapy (CRRT).
- Eliminating CRRT system downtime and declining dialyzer performance preferably with regional citrate anticoagulation may enhance our ability to apply simplified kinetic modeling to the CRRT control of select solutes, for example, sodium and bicarbonate.
- CRRT can mitigate and thereby mask profound pathophysiologic processes that are disturbing the electrolyte and acid-base balance.
- Embracing a kinetic analytical approach to the understanding of solute fluxes during CRRT allows for the prompt recognition of pathologic conditions such as ongoing tissue breakdown and ischemia.

MANAGEMENT OF CHRONIC HYPONATREMIA WITH RENAL FAILURE

Diluting Dialysate/RF [Na^+] in CRRT

Commercial hyponatric dialysate or RFs are lacking. The few available hyponatric dialysate solutions (sodium 120-130 mEq/L range) are calcium-free and used with RCA along with hypertonic sodium citrate– and calcium-containing infusions, making them impractical for highly predictable and safe correction of severe hyponatremia. Therefore, commercially available CRRT fluids need to be diluted with free water to achieve any desired sodium concentration in institutions with adequate pharmaceutical support. A stepwise switch every 24 hours to fluid bags with 8 to 10 mEq/L higher sodium concentration than the patient's current serum sodium can be considered. This approach of using solutions with successively higher sodium may be reliable in avoiding any overcorrection in the serum sodium due to CRRT. The dilution can be achieved by injecting free water into the dialysate/RF bag or exchanging a specific volume of dialysate/RF with an equivalent amount of water. We have previously described both methods in detail.[8]

Controlling Sodium Change in Hyponatremia with CRRT by Applying Kinetic Principles

Changes in sodium are slower with CRRT when compared with hemodialysis due to the lower delivered sodium dialysance with the low volumes of dialysate/RF used per hour and/or the lower blood flow rates. Nevertheless, attention should be given to factors that influence the rate of change in serum sodium for each individual during the CRRT procedure. Sodium kinetic models have been shown to predict end-dialysis plasma water sodium concentration.[11] Most reported equations are complex and may be prohibitive for daily use. Instead, a single-pool, fixed-volume, sodium kinetic equation may be used in a manner similar to urea kinetics for the quantification of sodium changes during CRRT.[8] This is because sodium and urea have similar dialyzer solute transfer characteristics as both are nonprotein-bound small solutes with similar effective blood water flow (QBe). Therefore, effective urea clearance (K) can be used to estimate sodium dialysance (D).[12] Modifiers introduced by the Donnan effect and the laboratory reporting of serum sodium cancel each other and may be ignored while preserving clinically acceptable accuracy.

The validity of using single-pool urea kinetics to describe intradialytic urea changes during sustained low-efficiency hemodialysis and CRRT has been demonstrated.[13,14] 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, its generation rate (nonisotonic sodium and potassium gain or loss from the body), and apparent volume of distribution (total body water). The application of kinetic modeling to CRRT will also require elimination of system downtime, which could be best achieved by effective anticoagulation. Although kinetic models may be helpful in predicting the rate of change in sodium level with a certain CRRT dose, frequent laboratory confirmation is still advised. Variables that affect sodium change may change over time, and readjustment of the CRRT dose may be necessary.

A clinical application of the sodium kinetic model during CRRT treatment to a patient presenting with severe hyponatremia and AKI has been described by our group.[8] By applying fixed-volume single-pool

kinetic principles to sodium, the dialysance and/or dialysate/RF rate for a desired sodium change in any period could be estimated. The serum sodium at any time $[Na^+](t)$ during CRRT treatments may be described by the following equation:

$$[Na^+](t) = [Na^+]_{RF} + \Delta[Na^+](t) \quad (1)$$

Where $[Na^+]_{RF}$ is the dialysate/RF sodium concentration, and $\Delta[Na^+](t)$ is the gradient between the $[Na^+]_{RF}$ and the patient's systemic sodium concentration at time = t during CRRT. The rate of change in serum sodium concentration is determined by 2 main forces: effect of CRRT on altering the initial serum sodium toward equilibrium with the dialysate/RF and the effect of CRRT on "net" nonisotonic fluid gains or losses in the body pool and defined by Equation 2:

$$\Delta[Na^+](t) = \left([Na^+]_i - [Na^+]_{RF}\right) \times \left(e^{\frac{-Dt}{V}}\right) + \frac{G}{D} \times \left(1 - e^{\frac{-Dt}{V}}\right) \quad (2)$$

Where $[Na^+]_i$ is the initial serum sodium concentration, D is effective sodium dialysance, which is nearly equal to effective urea clearance K, and G (mEq/h) is net sodium generation. V is total body water volume and can be determined by using Watson's formula applied to the patient's estimated dry weight, obtained from prior electronic health records data or using a best guess, and adding to this any measured intensive care unit weight gain (current weight − estimated dry weight) as estimated 100% edema (water) volume.[15] The second term of the aforementioned equation may be approximated to be zero when nonisotonic fluid gain/loss in the total body water is negligible, yielding:

$$[Na^+](t) = [Na^+]_{RF} + \left([Na^+]_i - [Na^+]_{RF}\right) \times \left(e^{\frac{-Dt}{V}}\right) \quad (3)$$

A daily sodium Dt/V of 1.2 (near equivalent to urea Kt/V) will increase the serum sodium by about 70% of the initial gradient between dialysate/RF and plasma sodium.

By rearranging Equation 3, the required D needed for a desired sodium change at any elapsed time or for every 24-hour period could be estimated:

$$D = -\frac{V}{24\ hrs} \times \ln\left(1 - \frac{[Na^+](t) - [Na^+]_i}{[Na^+]_{RF} - [Na^+]_i}\right) \quad (4)$$

Where $[Na^+]_{RF} > [Na^+](t) > [Na^+]_i$ when treating hyponatremia. The dialysate/RF flow rate could be simply adjusted to achieve the calculated D and keep the sodium change within 6 to 8 mEq/L target with a specific dialysate/RF sodium concentration level. In cases of severe hyponatremia, and if using a commercial 140 mEq/L sodium dialysate or RF, the flow rate and hence sodium dialysance needs to be considerably decreased to stay within desired daily limits of correction especially in those with small total body water. The required CRRT dose in such cases may be lower than the recommended CRRT dose for uremic clearance. For example, a patient with a V 25 L, $[Na^+]_i$ 110 mEq/L, $[Na^+]_{RF}$ 140 mEq/L, the D should not exceed 0.32 L/h in the "first" 24 hours to keep sodium changes to ≤8 mEq/L. In the second 24 hours, 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. For example, if sodium is 118 mEq/L at the start of the second 24-hour interval, the D could be increased to 0.47 L/h for a desired increase of 8 mEq/L in the next 24 hours. In those with concomitant significant abnormalities of other solutes (eg, uremia, hyperkalemia), higher CRRT dose will be required, and thus, dialysate/RF sodium lowering or hypotonic fluid administration in a separate infusion line with hypotonic fluids may be required to maintain sodium within a desired range while providing adequate solute clearance.

Administering a Hypotonic Fluid in a Separate Infusion Line

Infusing electrolyte free water as a 5% dextrose water (D5W) solution into the patient or into the return limb of the CRRT blood circuit is another reasonable approach to decrease the rate of correction of the systemic sodium concentration. The D5W infusion can be considered as an additional post-filter RF. The rise in the systemic sodium can then be controlled by changing the fraction of overall clearance delivered by D5W vs a 140 mEq/L sodium dialysate/RF fluid. This offers advantages over customizing solutions in that the overall CRRT sodium target could be changed easily and quickly at the bedside in institutions without adequate pharmacy support to dilute CRRT fluid bags. In addition, overall clearance can be maintained while sodium changes remain within desired targets. Safety concerns with this technique include the theoretical risk of worsening hyponatremia with filter clotting and rapid correction of sodium if consecutive D5W bags run out while the CRRT continues. The method could be adopted for both CVVH and CVVHD using standard dialysate/RF solutions.

$$D5W\ rate = \frac{140 - target\ [Na^+]}{140} \times desired\ clearance \quad (5)$$

For example, using post-dilution CVVH in a patient with initial sodium of 110 mEq/L with target sodium concentration of 120 mEq/L at a desired clearance of 2.5 L/h using RF/dialysate with 140 mEq/L of sodium, the D5W infusion rate would be 357 mL/h = 0.36 L/h, and the dialysate/RF rate should be 2.14 L/h. The net ultrafiltration setting should be increased by the rate of the D5W infusion = 0.36 L/h. For each 5% post-dilution infusion contribution by D5W to overall clearance, the overall CRRT-targeted systemic sodium concentration decreases by 7 mEq/L (see Table 1).

Table 1. Effect of Adding Intravenous D5W at 3 Different Fractions of Total Clearance in CVVH or CVVHD

Hypotonic CVVH/CVVHD	Na concentration (mEq/L)	Rate (mL/h)
Replacement fluid/dialysate	140	0.9 × desired clearance
Post-filter D5W	0	0.1 × desired clearance
Final hypotonic fluid	126	
Replacement fluid/dialysate	140	0.85 × desired clearance
Post-filter D5W	0	0.15 × desired clearance
Final hypotonic fluid	119	
Replacement fluid/dialysate	140	0.8 × desired clearance
Post-filter D5W	0	0.2 × desired clearance
Final hypotonic fluid	112	

Abbreviations: CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; D5W, 5% dextrose water; Na, sodium.

MANAGEMENT OF CHRONIC HYPERNATREMIA WITH RENAL FAILURE

Spiking of the Dialysate/Replacement Fluid [Na^+] in CRRT

Patients with renal failure and chronic, extreme hypernatremia (sodium > 165 mEq/L) are best treated using CRRT. Intermittent hemodialysis machines cannot be programmed to deliver dialysis fluid sodium > 155 mEq/L, and dialysis with such relatively hypotonic dialysate and usual sodium dialysance ≥200 mL/min could lead to brain edema. Using prepackaged 140 mEq/L sodium CRRT solutions, the sodium concentration can be increased to any desired value by adding hypertonic saline and the sodium dialysance can be reduced to very low, < 50 mL/min, levels as needed. We spike any standard CRRT solution bag with 23.4% hypertonic saline which contains 4 mEq of sodium per each mL of solution. A stepwise switch to fluid bags with 10 mEq/L lower sodium than patient's current serum sodium can be considered every 24 hours. Using this approach, overcorrection may be avoided. To avoid contamination of the fluid, an aseptic technique must be used.

The mEq of sodium to be added to a standard dialysate/RF bag to achieve a desired dialysate/RF sodium concentration can be calculated by the following equation:

$$mEq\ Na^+ = desired\ \left[Na^+\right]_{RF} \times V_f - initial\ \left[Na^+\right]_{RF} \times V_i \quad (6)$$

V_f is the RF final volume, and V_i is RF initial volume. The volume of the required 23.4% hypertonic saline is negligible. Therefore, the RF final volume is nearly equal to RF initial volume, and Equation (6) will be reduced to:

$$mEq\ Na^+ = V \times \left(desired\ \left[Na^+\right]_{RF} - initial\ \left[Na^+\right]_{RF}\right) \quad (7)$$

For example, to increase the RF sodium from 140 mEq/L to 160 mEq/L of a 5-L RF bag, 100 mEq Na or 25 mL of 23.4% hypertonic saline will be required.

Controlling Sodium Change with CRRT in Hypernatremia by Applying Kinetic Principles

Using the principles of sodium kinetics discussed previously, the serum sodium at any time during CRRT is predictable by the following equation, allowing controlled correction of hypernatremia.

$$\left[Na^+\right](t) = \left[Na^+\right]_{RF} + \left(\left[Na^+\right]_i - \left[Na^+\right]_{RF}\right) \times \left(e^{\frac{-Dt}{V}}\right) \quad (8)$$

Frequent laboratory monitoring is recommended, as predictor variables may change over time necessitating adjustment of CRRT dose. To maintain a desired sodium change ≤ 10 mEq/L, the required sodium dialysance using a dialysate/RF with a specific Na level is estimated by Equation 4, however, when treating hypernatremia obviously $[Na^+]_{RF} < [Na^+](t) < [Na^+]_i$. In a large patient with $[Na^+]_i$ 170 mEq/L, V 50 L, and using a commercial dialysate/RF solution with sodium concentration of 140 mEq/L, the required D for 10 mEq/L desired change over the next 24 hours is 0.85 L/h:

$$D = -\frac{50}{24} \times \ln\left(1 - \frac{-10 mEq/L}{[140] - [170]}\right) = 0.85 L/h$$

Administering a Hypertonic Infusion in a Separate Infusion Line

Running a separate infusion of 3% saline into the return limb of the CRRT blood circuit is another approach to mitigate hypernatremia in a controlled fashion during CRRT using standard 140 mEq/L dialysate or RF. The 3% saline infusion can be considered an additional post-filter RF and would contribute minimally to the overall clearance. The dialysate/RF infusion rate has to be adjusted to account for the 3% saline contribution to total clearance. Safety risks include worsening hypernatremia if CRRT is stopped while the infusion continues or if the 3% saline is given in a central vein although there is significant access recirculation, or rapid correction of hypernatremia if the 3% saline infusion is interrupted (for instance, if the 3% saline solution bag runs out without being replaced in a timely fashion while the CRRT continues).

The estimated post-dilution infusion rate of 3% saline when using a 140 mEq/L of sodium dialysate/RF can be approximated by this formula:

$$3\%\ infusion\ rate = \frac{target\ [Na^{+}] - 140}{(513 - 140)} \times desired\ clearance \quad (9)$$

For example, in a patient with an initial sodium 170 mEq/L with target sodium concentration of 160 mEq/L at a desired clearance of 2.5 L/h, the 3% saline infusion rate would be at 134 mL/h, and the RF rate should be 2.36 L/h, and the net ultrafiltration setting should be increased by the rate of the 3% saline infusion = 0.13 L/h.

POTASSIUM

Patients with AKI may have hyperkalemia at initiation of RRT. Using a recommended CRRT dose of 20 to 25 mL/kg/hr, most non–life-threatening cases of hyperkalemia can be managed with a dialysate/RF potassium concentration of 2 mEq/L with success. If a 0 mEq/L of potassium concentration is used, careful monitoring is necessary to avoid hypokalemia.

In cases of life-threatening hyperkalemia associated with arrhythmia and/or hemodynamic instability from potassium levels, in addition to medical treatment, hemodialysis should first be used.[16-18] Patients with rapid ongoing potassium generation, such as rhabdomyolysis, tissue ischemia, and tumor lysis syndrome, should be treated with hemodialysis first and then switched to CRRT. Maximizing blood flow and RF/dialysate rates may be needed. The switch to CRRT should be made if the potassium levels decrease and the steady state potassium levels on hemodialysis do not remain >5 mEq/L with dialysate ≤ 2 mEq/L. For example, in a patient with tissue ischemia and "persistent" serum potassium of 5.5 mEq/L on hemodialysis with dialysate 2 mEq/L with a plasma clearance of 200 mL/min, potassium removal and therefore generation in steady state can be estimated to be a minimum of 42 mEq/h (200 mL/min × 60 min/h × 0.001 L/mL × 3.5 mEq/L potassium gradient). This potassium load will exceed the removal capacity of CRRT modalities even with the use of higher dialysate/RF rates and a 0 or 1 mEq/L dialysate/RF potassium concentration. Conversely, persistent hyperkalemia on CRRT with low potassium dialysate/RF should also signal for the presence of significant tissue breakdown/ischemia in the absence of increased intake (errors with total parenteral nutrition [TPN], K-supplements). For example, in a patient with "persistent" serum potassium of ~6.0 mEq/L on CRRT with dialysate/RF 2 mEq/L and a plasma clearance of 2.5 L/h, potassium generation can be estimated to be 10 mEq/h (240 mEq/d) indicating the breakdown of 2 to 3 kg tissue per day,[19] with obvious grave implications for prognosis. These calculations assume that the prescribed hourly CRRT clearance is equal to the delivered clearance. Access recirculation and partial filter clotting will both reduce delivered clearance. In the CRRT-RCA program in our institution, the delivered clearance is automatically measured by the dialysis machine every 2 hours using the commercial ionic dialysance technology.[20]

Patients with AKI may occasionally present with hypokalemia. In such settings, they usually have preserved diuresis (>1 L/d or more) or a tendency for urinary potassium loss (such as toxic interstitial nephritis caused by aminoglycosides,[21] cisplatin,[22] amphotericin B[23]) or extrarenal losses of potassium (such as diarrhea). Hypokalemia in the patient on CRRT can be managed in the same manner as in non-CRRT patients. With intravenous or oral potassium replacement, the serum potassium can be normalized and maintained while the selection of a CRRT fluid potassium concentration of 4 mEq/L ensures no CRRT losses of potassium. The use of fluids with potassium levels greater than physiologic is unnecessary and will result in slow correction given the transfer kinetics and overall magnitude of positive potassium balance associated with CRRT.

CALCIUM

Hypo/hypercalcemia may coexist with AKI, and both disorders may be seen with CRRT modalities. Substitution fluids usually contain a calcium concentration similar to that of the ultrafilterable calcium in the plasma (about 60% of total plasma calcium). Therefore, dialysate/RF fluids containing about 3 mEq/L of calcium are generally used to obtain a neutral or mildly positive CRRT circuit calcium balance. Mild to moderate hypocalcemia is common in AKI and is primarily related to increases in serum phosphate. Symptomatic hypocalcemia should be treated with intravenous calcium while awaiting dialysis, and expedient RRT should be instituted in the presence of severe hyperphosphatemia (phosphorus > 8-10 mg/dL). Hypocalcemia can also complicate certain CRRT-RCA protocols if single-pass citrate extraction on the dialyzer and systemic citrate metabolism are simultaneously inadequate or when calcium supplementation is less than the CRRT circuit losses. The complications and troubleshooting of RCA are beyond the scope of this article. Hypercalcemia is rare in AKI and may occur in myeloma and in other malignancies especially with protracted immobilization and in the recovery phase of rhabdomyolysis when calcium is released from calcium-containing complexes in muscle. Both hemodialysis and CRRT are effective in decreasing serum calcium levels in these patients.[24-26]

MAGNESIUM

Hypomagnesemia may be seen occasionally in patients with AKI due to nephrotoxic agents (cisplatin, amphotericin B, and aminoglycosides). Magnesium in commercially available CRRT fluids ranges between 1 and 1.5 mEq/L equal to or exceeding the plasma ultrafilterable magnesium when RCA is not used. This level is clinically successful in maintaining normal plasma magnesium levels except in patients on RCA with normal 4 g/dL serum albumin levels (such patients may have ultrafilterable magnesium around 2 mEq/L in the CRRT circuit plasma prefilter). If hypomagnesemia occurs during CRRT, 2 to 4 g can be administered intravenously. Severe symptomatic hypermagnesemia should be managed with conventional intermittent hemodialysis.

PHOSPHORUS

Derangements of the serum phosphate level are common in the setting of AKI. Hyperphosphatemia is a frequent complication of AKI, whereas hypophosphatemia is extremely common with CRRT using phosphate-free dialysate or RF. The incidence of hypophosphatemia in patients on CRRT ranges from 11% to 65%, depending on the intensity and duration of treatment.[27,28] It can precipitate complications such as hemolysis, rhabdomyolysis, cardiac arrhythmias, and seizures[29-32] and is associated with respiratory failure and ventilator dependence in the critically ill.[33,34] Thus, the prevention of hypophosphatemia and its timely treatment are recommended.

Phosphate losses on the CRRT circuit with phosphate-free RF can be calculated assuming that 25 mL/kg/h plasma clearance is delivered (=0.6 L/kg/d or about 50 L/d for an 80-kg patient). If the steady-state plasma phosphate is kept normal around 1 mmol/L (3.1 mg/dL) by nutrition and supplements, then, the CRRT circuit loss will be 50 L × 1 mmol/L = 50 mmol. Because enteral nutrition of intensive care AKI patients is often provided with phosphate-restricted formulas and TPN typically is phosphate-free, patients on CRRT may need up to 40 to 50 mmol intravenous piggyback sodium phosphate supplements per day.

Hypophosphatemia can be prevented by prophylactic oral or intravenous phosphate replacement. We prescribe 15 mmol of intravenous sodium phosphate over 4 hours 2 to 3 times daily while on CRRT when the serum phosphate falls below 1.1 mmol/L (3.5 mg/dL). Sodium glycerophosphate injection may also be used to maintain the normal serum phosphorus level during CRRT for instance when sodium-phosphate is in short supply. Phosphate can also be added to parenteral nutrition. The phosphate-enriched TPN prescription must be modified when the CRRT is stopped so that hyperphosphatemia would not occur.

Finally, commercial phosphate-containing CRRT solutions are now available for use as replacement or dialysate fluids with CVVH, CVVHD, and continuous venovenous hemodiafiltration.[35,36] Precipitation of calcium-phosphate in bicarbonate-based, calcium- and phosphate-containing CRRT fluids might be a theoretical concern if the 2-chamber bag is not used for a prolonged time after mixing of its components and there is loss of CO_2 gas from the ready-to-use bag with a concomitant rise in fluid pH toward alkaline.[37]

ACID-BASE DISTURBANCES

Metabolic Acidosis

Hyperchloremic metabolic acidosis is the leading cause of acidosis in the early stages of AKI. This is due to the decreased regeneration of bicarbonate by the kidneys with an inability to excrete ammonium ions. Later, the accumulation of anions, such as phosphate, sulfate, urate, hippurate, propionate, and oxalate, may lead to high anion gap acidosis. Lactic acidosis is also common in critically ill patients with AKI in shock.

There is uncertainty about the need to correct mild to moderate metabolic acidosis in the setting of AKI. Furthermore, studies do not support the routine use of sodium bicarbonate infusion to treat lactic acidosis. However, most experts believe that the use of bicarbonate is appropriate in patients with severe lactic acidosis and acidemia (arterial pH < 7.1).[38] Such severe acidemia may produce hemodynamic instability as a result of reduced left ventricular contractility, arterial vasodilation, and impaired responsiveness to catecholamines.[39] In the setting of AKI, CRRT techniques are useful in treating cases of uncontrollable acidemia until the primary process causing the metabolic acidosis is reversed.[40-42] CRRT offers several practical advantages over bicarbonate infusions. Most importantly, massive amounts of bicarbonate may be given with CRRT without concurrent net sodium load (effectively exchanging other anions, eg, chloride, phosphate, or lactate with bicarbonate). This way, it is possible to maintain a neutral or even negative sodium balance using RF with a sodium level equal to the systemic serum sodium concentration with or without net ultrafiltration. CRRT with 3 mEq/L of calcium and 4 mEq/L of potassium content may also provide mildly positive calcium and potassium balance in hypocalcemic and hypokalemic patients and might make it easier to maintain ionized calcium and serum potassium at normal levels in the setting of effective bicarbonate addition.

Historically, lactate-based solutions were preferentially used as a buffer due to the instability of bicarbonate-based solutions, but, this problem has been practically solved with the twin-chamber fluid bags. Although lactate solutions are generally well tolerated during CRRT when infused at moderate flows of 2 to 3 L/h, severe hyperlactatemia may develop in situations of impaired lactate clearance such as liver failure and shock.[4] In such circumstances, infused lactate remains in circulation as a strong anion and endogenous bicarbonate is lost through the effluent/dialysate, leading to a high anion gap metabolic acidosis. The use of bicarbonate-based dialysate/RF during CRRT with typical small solute clearance of 2 to 3 L/h does not mask lactate overproduction, and therefore, systemic lactate may remain a reliable marker of tissue oxygenation in patients treated by CRRT. With prescribed CRRT clearances of 20 to 25 mL/kg/h, metabolic acidosis or alkalosis can be managed with commercially available bicarbonate solutions as long as sources of alkali or acid gain or loss are identified and stopped. If there is difficulty improving pH (highest available bicarbonate is 35 mEq/L), the dialysate or RF rate and hence the bicarbonate dialysance can be increased to accommodate the patient's needs. One could also spike the CRRT bags with amps of sodium-bicarbonate (1 mEq/mL of stock concentration); however, any increase achieved in the CRRT fluid bicarbonate level would be accompanied by a similar increase in sodium level, which may limit the feasibility of this approach. For instance, by adding a 50-mL sodium-bicarbonate amp to a 5-L CRRT fluid bag with starting sodium 140 and bicarbonate 35 mEq/L, the final bicarbonate would be 45 mEq/L with final sodium of 150 mEq/L, which is considerably hypernatremic.

Metabolic Alkalosis

Significant metabolic alkalosis is rare in AKI. Metabolic alkalosis in patients on CRRT occurs most commonly as a complication of the CRRT procedure itself with the provision of excess exogenous alkalis, such as seen in some citrate anticoagulation protocols. Other sources of alkali may include the transfusion of large volume of citrate-containing blood products,[43] or acetate-containing TPN. During CRRT, metabolic alkalosis can be managed by using acid-citrate-dextose A instead of 4% sodium citrate,[44,45] decreasing the infusion rate of citrate,[46] increasing single-pass extraction of citrate on the dialyzer,[47] or using a lower dialysate bicarbonate concentration,[48] and careful monitoring of other sources of alkali.

Severe alkalosis may rarely be seen in patients presenting with AKI as a complication of endogenous alkali generation with excess hydrogen chloride losses such as those that occur in Zollinger–Ellison syndrome.[49] In refractory cases of severe chloride depletion alkalosis (pH $>$ 7.55) or when immediate correction is necessary (eg, cardiac arrhythmia or hepatic encephalopathy), treatment options include the use of HCl infusion[50,51] or RRT.[43,49] Bedside application of a mathematical model of bicarbonate kinetics in such a setting has been described by Yessayan and colleagues.[49]

In conclusion, CRRT offers ways to effectively alter and tightly control plasma electrolyte composition in AKI. However, if CRRT is not carried out appropriately, significant complications may arise. Understanding of the kinetic principles of fluid and electrolyte management with CRRT and recognition of the factors that influence acid-base and electrolyte balance are crucial elements required to meet the individual needs of the AKI patient.

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