Review Article

ISSN 1738-5997 (Print) · ISSN 2092-9935 (Online)
Electrolyte Blood Press 2022;20:64-75
https://doi.org/10.5049/EBP.2022.20.2.64

Management for Electrolytes Disturbances during Continuous Renal Replacement Therapy

Song In Baeg[1*], Kyungho Lee[2*], Junseok Jeon[2], Hye Ryoun Jang[2]

[1]*Division of Nephrology, Department of Internal Medicine, Myongji Hospital, Hanyang University Medical Center, Goyang;*
[2]*Division of Nephrology, Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea*

Received: October 31, 2022
Revised: December 18, 2022
Accepted: December 19, 2022
Corresponding Author: Hye Ryoun Jang, MD, PhD
Division of Nephrology, Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Irwon-ro 81, Gangnam-gu, 06351 Seoul, Korea
Tel: +82-2-3410-0782; Fax: +82-2-3410-0064
E-mail: shinehr@skku.edu

Despite the lack of proven superiority in mortality compared to intermittent hemodialysis, continuous renal replacement therapy (CRRT) is the preferred renal replacement therapy modality for critically ill patients with acute kidney injury (AKI) due to better hemodynamic stability and steady correction of electrolytes disturbances and volume overload. Multiple and complex electrolyte disorders in patients with AKI can be managed effectively with CRRT because controlled and predictable correction is feasible. Thus, CRRT has an advantage with safety over conventional hemodialysis, especially in patients with both renal dysfunction and electrolyte disorder that require a sophisticated treatment with avoidance of rapid correction. On the contrary, CRRT can potentially lead to paradoxical disturbance of electrolytes such as hypokalemia or hypophosphatemia, especially in patients under high dose or prolonged duration of CRRT treatment. These electrolytes related complications can be prevented with close monitoring followed by the appropriate use of CRRT fluids. Although there is a lack of solid evidence and standardized guideline for CRRT prescriptions, optimal management of various electrolyte disturbances can be achieved with individualized and tailored dialysate and replacement fluid prescriptions. Several commercially available CRRT solutions with varying compositions provide flexibility to manage electrolyte disorders and maintain the stability of electrolyte. In this review, we discuss various prescription methods to manage common electrolyte imbalances as well as preventative strategies to maintain electrolyte homeostasis during CRRT providing detailed protocols used in our center. This review may contribute to future research that can lead to the development of clinical practice guidelines.

Key Words: Continuous renal replacement therapy, Electrolyte, Dialysis, Acute kidney injury, Hemodialysis

INTRODUCTION

Continuous renal replacement therapy (CRRT) is often used in critically ill patients with acute kidney injury (AKI)[1,2]. Although previous studies failed to show the survival benefits of CRRT over conventional intermittent hemodialysis, CRRT is the preferred renal replacement therapy (RRT) in critically ill patients with renal failure since it allows better hemodynamic stability and continuous treatment with excellent efficacy[3]. Moreover, steady acid-base and electrolyte correction are known additional advantages of CRRT compared with intermittent hemodialysis[4,5].

Electrolyte disturbances are common in critically ill patients, and the incidence of complex electrolyte abnormality was found to be as high as 67%[6]. Many types of electrolyte disturbance can be effectively managed with CRRT with a continuous uninterrupted fashion[7]. Moreover, CRRT can

provide additional benefits to patients with several types of electrolyte disturbances such as severe hypernatremia or hyponatremia because CRRT can reduce the risk of rapid- or over- correction[8]. However, paradoxically, CRRT treatment can result in electrolyte complications, including hypophosphatemia, hypokalemia, and hypomagnesemia, especially in patients under prolonged duration or high dose of CRRT[5,9]. In order to treat electrolyte disturbance with CRRT and to minimize CRRT-induced paradoxical electrolyte disturbances in critically ill patients, the application and prescription of dialysate and replacement fluid should be tailored and individualized according to clinical situations[10].

In this review, we discuss clinical strategies to treat various types of electrolyte disturbances and avoid CRRT-induced electrolyte-associated complications.

Dysnatremia

Hypernatremia

Hypernatremia is a common complication in critically ill patients with AKI, occurring in 10% to 26% of patients[11]. In-hospital hypernatremia may be induced using diuretics or administration of hypertonic saline, and gastrointestinal loss[11,12]. Hypernatremia is associated with longer hospital stays and a greater risk of mortality compared with normonatremia[13]. Lowering sodium concentration induces the alteration of extracellular tonicity, leading to cellular swelling[14]. Generally recommended correction rate of serum sodium is $\leq$10 mmol/L over 24 h in patients with chronic hypernatremia[12,15]. However, unlike the strategy to treat hyponatremia, there is a lack of solid evidence that supports the need for slow correction in hypernatremia. Nevertheless, in hypernatremic patients who require RRT, it is important to note that concomitant dialytic removal of urea and uremic solutes may worsen brain edema and cause dialysis disequilibrium syndrome[16]. Thus, despite the controversy regarding the suggested correction rate for hypernatremia[17], hypernatremia should be carefully managed with slow correction rate in patients under RRT. In general, CRRT allows a slower sodium concentration change compared to intermittent hemodialysis[18], thus CRRT can be the best RRT modality in patients with severe chronic hypernatremia with renal failure.

In patients with severe hypernatremia who will undergo CRRT treatment, the correction rate can be managed by either hypertonic CRRT solutions or separate hypertonic saline infusions[19]. Given the lack of commercially available hypertonic CRRT fluids (Table 1), either sodium chloride or sodium bicarbonate can be added to the standard CRRT solutions to increase the sodium concentration to the desired level[18,19]. Sodium chloride can be mixed when patients have only hypernatremia without significant metabolic acidosis. When patients have both hypernatremia and metabolic acidosis, sodium bicarbonate can be considered as an initial choice. When continuous veno-venous hemodiafiltration (CVVHDF) mode is used, this method needs to

Table 1. Compositions of commercially available CRRT solutions in Korea

Composition (mmol/L)	Solutions*						
	MultiBic 0K (Fresenius)	MultiBic 2K (Fresenius)	MultiBic 4K (Fresenius)	Hemosol B0 (Fresenius)	Prismasol 2K (Baxter)	Prismasol 4K (Baxter)	Phoxilium (Baxter)
Na^+	140.0	140.0	140.0	140.0	140.0	140.0	140.0
K^+	0	2.0	4.0	0	2.0	4.0	4.0
Ca^{2+}	1.5	1.5	1.5	1.8	1.75	1.75	1.3
Mg^{2+}	0.5	0.5	0.5	0.5	0.5	0.5	0.6
Cl^-	109.0	111.0	113.0	109.5	111.5	113.5	116.0
HCO^{3-}	35.0	35.0	35.0	32.0	32.0	32.0	30.0
Lactate	0	0	0	3.0	3.0	3.0	0
Glucose	5.55	5.55	5.55	0	6.10	6.10	0
$HPO4^{2-}$	0	0	0	0	0	0	1.2

*Availability and trade names of the solutions may differ according to countries.

Table 2. Changes in the sodium concentration of a standard 5 L CRRT fluid (Na 140 mmol/L) after adding different amounts of extra sodium

Sodium added (mmol)	Sodium final (mmol/L)
20	144
40	148
60	152
80	156
100	168
120	172

*Sodium can be added as a sodium-chloride or sodium-bicarbonate

Table 3. Changes in the sodium concentration of a standard 5 L CRRT fluid (Na 140 mmol/L) after adding or exchanging sterile water

Adding volumes			Exchanging volumes	
Volume added (mL)	Na final concentration (mmol/L)	Volume, final (L)	Volume exchanged (mL)	Na final concentration (mmol/L)
0	140.00	5	0	140.00
250	133.33	5.25	250	133.00
500	127.27	5.5	500	126.00
750	121.74	5.75	750	119.00
1,000	116.67	6	1,000	112.00
1,250	112.00	6.25	1,250	105.00

be applied to both dialysates and replacement fluids[15,20]. Example concentrations after adding different amounts of sodium are presented in Table 2. The recommended sodium concentration for the initial CRRT solution is set to be 5-10 mmol/L lower than that of the patient[15,20]. Serial changes in serum sodium concentration should be frequently monitored. If the sodium concentration decreases by 2 or more within the first 6 hours after CRRT initiation, we recommend adjustment of the CRRT dose or sodium concentration of the CRRT solution[21].

Administration of 3% saline intravenously with a separate intravenous access or into the return line of CRRT blood circuit can also be used as an alternative strategy to prevent rapid correction of hypernatremia[18,19]. When this method is applied, 3% saline should be discontinued when CRRT delivery is interrupted or discontinued to avoid exacerbating hypernatremia[19].

If patients have suspected or proven to have increased intracranial pressure and require CRRT treatment, therapeutic hypernatremia as an osmotherapy can be induced or maintained by using hypertonic CRRT fluid as mentioned above[22]. For this purpose, the recommended serum sodium concentration has been suggested as 150-155 mmol/L[22,23].

Hyponatremia

In patients with renal failure and severe hyponatremia, the initiation of CRRT can potentially result in a rapid correction of hyponatremia that increases the risk of osmotic demyelination syndrome[24]. The lower the initial sodium concentration, the higher risk of overcorrection[25]. If sodium concentration decreases by 2 or more within the first 6 hours after CRRT initiation, lowering the CRRT dose or sodium concentration of CRRT solution should be considered[21,26]. Since there is a lack of commercially available hypotonic CRRT solutions (Table 1), there are two available strategies to prevent a rapid correction of hyponatremia: dilution of CRRT fluid; and concomitant intravenous infusion of 5 or 10% dextrose water solution.

The dilution of CRRT fluid can be achieved by either adding various volumes of sterile water or by exchanging equal volumes of the CRRT fluid with sterile water to achieve a desired sodium concentration[19,26-29]. When CVVHDF mode is used, this dilution method needs to be applied to both dialysates and replacement fluids[29]. For continuous venovenous hemofiltration (CVVHF) and CVVHDF, diluted fluid may be used as pre- or/and post-filter replacement fluid[26]. Sodium concentration of post-filter replacement fluid exerts a slightly stronger impact on plasma serum sodium concentration compared to sodium concentration of pre-filter replacement fluid[30]. When the same CRRT fluids with supraphysiologic sodium concentration are used as both pre-filter and post-filter replacement fluids, the expected sodium correction rate will increase as the proportion of post-filter replacement flow rate increases compared to pre-filter replacement flow rate[30]. The calculated final concentrations following adding or exchanging different volumes of sterile water are presented in Table 3. However, the following caveats should be considered when this method is applied. The former method has a volume limitation that will fit in the manufacturer's bag and can cause the CRRT machine's

scale alarm when a large volume is added. The latter method requires an additional volume removal process from CRRT fluid bag before adding distilled water and increases the risk of contamination[27].

A concomitant intravenous infusion of dextrose water solution into a separate intravenous access or return bloodline of the CRRT circuit can be an alternative strategy to reduce the sodium correction rate[8]. Our center has used an infusion of 5% dextrose water solution with a separate intravenous access starting with the rate of 1.5 mL/kg/h with serum electrolyte follow-up every 4 hr. Although this method is less cumbersome compared to diluting CRRT fluid, a large volume of 5% dextrose water infusion with high rate (more than 200 cc/h) is frequently inevitable to prevent rapid correction in hyponatremic patients prescribed with a high dose of CRRT treatment due to other metabolic derangements.

Dyskalemia

Hyperkalemia

Potassium homeostasis is primarily controlled by renal excretion. Potassium is an essential element for maintaining cellular function. An abnormal serum potassium concentration can cause deleterious consequences such as cardiac arrhythmia and sudden cardiac death. Hyperkalemia is a major complication of AKI, which occur in 8.8-32.2%[31]. Adrenal insufficiency and medications such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and potassium-sparing diuretics can contribute to the development of hyperkalemia[32]. A U-shaped association between baseline serum potassium and all-cause mortality was reported in critically ill patients[33,34]. In patients requiring CRRT, mortality significantly increased when pre-CRRT potassium level $\leq$3.4 mmol/L or $\geq$4.5 mmol/L[35].

Although CRRT can be used as a treatment for hyperkalemia, in patients with severe hyperkalemia with EKG changes, intermittent hemodialysis should be considered as a first-line RRT modality rather than CRRT since the removal rate of conventional hemodialysis is higher than that of CRRT[36]. Approximately 70-100 mmol of potassium can usually be removed during 4 hours of dialysis[31,37]. CRRT can also be used as a treatment for hyperkalemia when hemodialysis is not feasible[18]. CRRT can effectively correct hyperkalemia by increasing the dialysate or replacement flow rate and using low potassium or potassium-free CRRT fluids[38]. The potassium concentration of CRRT solutions ranges from 0 to 4 mmol/L (Table 1). In patients with life-threatening hyperkalemia, potassium-free solutions with a higher CRRT dose should be applied initially. Mild hyperkalemia can be corrected by using CRRT solutions with a potassium concentration of 2 mmol/L[18,20,39]. In patients with progressive tissue damage such as rhabdomyolysis, tumor lysis syndrome, or hemolysis, ongoing potassium load should be considered when choosing CRRT solutions based on their serum potassium concentrations[35,39].

If hyperkalemia persists while the maintenance of appropriately prescribed CRRT, it should be considered that there can be an ongoing tissue breakdown such as rhabdomyolysis or hemolysis as well as hypercatabolic states such as severe sepsis or burn[35,39]. Particularly, in patients using extracorporeal membrane oxygenation or ventricular-assisted devices, hemolysis should be excluded[35,39]. Insufficient actual delivered dose than the prescribed dose possibly due to frequent interruptions of CRRT, decreased dialyzer efficiency, or recirculation of vascular access may also cause persistent or recurrent hyperkalemia[35].

Hypokalemia

Hypokalemia is less frequent than hyperkalemia in critically ill patients with AKI[35], but it occurs more frequently as a complication of CRRT with an incidence as high as 24%[5,9]. When a conventional dose (20-25 mL/kg/h) of CVVHDF with potassium-free dialysate and replacement fluids is prescribed, hypokalemia was reported to occur as early as the first 24 hours after CRRT initiation[40]. Since significant hypokalemia can induce respiratory muscle weakness and cardiac arrhythmias[41,42], avoiding hypokalemia in critically ill patients is important. Moreover, given the fact that chronic potassium depletion can lead to renal tubular cell damage and dysfunction, hypokalemia should be avoided in AKI patients for better renal recovery[43].

Hypokalemia during CRRT can be treated or prevented with oral/intravenous potassium supplementation and/or

Table 4. An example of CRRT fluid protocol according to serum potassium and phosphate concentrations using commercially available phosphate and potassium-containing CRRT fluids

(K: mmol/L) (P: mg/dL)	Dialysate[+]		Pre-filter replacement fluid[+]	
	Serum P ≥3.6	Serum P ≤3.5	Serum P ≥3.6	Serum P ≤3.5
Serum K ≤4.5	Multibic 4K	Phoxilium	Multibic 4K	Phoxilium
4.6 ≤ serum K ≤5.0	Multibic 4K	Phoxilium	Hemosol B0	Hemosol B0
Serum K ≥5.1	Hemosol B0	Hemosol B0	Hemosol B0	Hemosol B0

[*]Post-filter replacement fluid is fixed with Hemosol B0
[+]This protocol is based on the application of the same flow rate for dialysate and replacement fluid (The used ratio for pre- and post-filter replacement fluid flow rates ranged from 1:1 to 4:1).

using potassium-containing CRRT solutions[18]. Compared to potassium-free CRRT solutions, patients treated with potassium-enriched CRRT solutions showed significantly higher serum potassium concentration during CRRT[40]. Using potassium-containing CRRT solutions can reduce the intensive care unit (ICU) workloads and frequency of intravenous supplementation[44].

Thus far, there is a lack of consensus on recommended potassium concentration in CRRT fluids. Many centers use protocols to prescribe CRRT dialysate based on serum potassium and phosphate level. An example of a CRRT fluid prescription algorithm based on patients' potassium concentration is presented in Table 4. We use CRRT solutions with a potassium concentration of 4 mmol/L as dialysate fluid and pre-filter replacement fluid when the patient's serum potassium is ≤4.5 mmol/L. When serum potassium concentration is 4.5-5.0 mmol/L, solutions with a potassium concentration of 2 or 4 mmol/L were used. When serum potassium >5 mmol/L, solutions with a potassium concentration of 0 mmol/L were used. Most centers do not use a potassium concentration 4 mmol/L solutions for post-filter replacement fluid to avoid potential risk of hyperkalemia. Potassium concentrations should be monitored every 4 to 8 hours depending on the patients' condition[20,44].

Dyscalcemia

Hypercalcemia

Calcium is associated with cellular injury and is known to be an important factor in maintaining cellular function [45,46]. Hypercalcemia induces vasoconstriction which reduces the glomerular filtration rate, and decreases renal reabsorption of water in kidneys, leading to volume depletion[47]. Hypercalcemia can aggravate AKI by promoting renal tubular injury[48]. Hypercalcemia can occasionally occur in AKI patients with malignancy or immobilization or in those taking vitamin D-containing drugs[47,49-51].

In patients with severe hypercalcemia, aggressive fluid resuscitation with normal saline is required to restore intravascular volume. RRT need to be considered for patients who are unsuitable for aggressive fluid therapy due to volume overload or refractory to medications such as intravenous bisphosphonate and calcitonin[51]. The ionized calcium concentration of the commercial CRRT solutions is about 1.25-1.75 mmol/L (2.5-3.5 mEq/L) (Table 1), thus calcium balance during CRRT is neutral or mildly positive[18,39].

When performing CRRT in AKI patients with significant hypercalcemia, calcium-free solutions can be used as dialysate and replacement fluid. In general, CRRT solutions usually consist of two separate chambers, one (compartment A) containing sodium bicarbonate and sodium chloride and the other (compartment B) containing calcium chloride and magnesium chloride. This system is designed to prevent precipitations of bicarbonate with calcium and magnesium by reconstituting two compartments immediately before its use[18]. In patients with significant hypercalcemia, only the calcium-free chamber (compartment A) can be utilized without the reconstitution of the two compartments. We use this strategy in patients with serum ionized calcium concentration ≥1.4 mmol/L. By applying this method for replacement fluid, our center lowered hypercalcemia incidence during CRRT. However, this method can potentially induce hypomagnesemia since calcium containing compartment B contains magnesium as well. Therefore, frequent monitoring of serum calcium and magnesium concentration is mandatory to avoid hypocalcemia and hypomagnesemia[20].

Table 5. An example of CRRT fluid protocol for patients with significant hypercalcemia

(K: mmol/L) (P: mg/dL)	Dialysate[†]		Pre-filter replacement fluid[†] (Optional)		Post-filter replacement fluid[†]
	P ≥ 3.6	P ≤ 3.5	P ≥ 3.6	P ≤ 3.5	
K ≤ 4.5	Multibic 4K	Phoxilium	[*]Hemosol B0 without A bag mixed with 1 bottle of KCl 20 mmol/NS 100 mL	Phoxilium without A compartment	Hemosol B0 without A compartment
4.6 ≤ K ≤ 5.0	Multibic 4K	Phoxilium	Hemosol B0 without A compartment		Hemosol B0 without A compartment
K ≥ 5.1	Hemosol B0	Hemosol B0	Hemosol B0 without A compartment		Hemosol B0 without A compartment

[*]Frequent monitoring of serum magnesium is required to avoid hypomagnesemia.
[†]This protocol is based on the application of the same flow rate for dialysate and replacement fluid (The used ratio for pre- and post-filter replacement fluid flow rates ranged from 1:1 to 4:1).

An example of a detailed algorithm for patients with hypercalcemia in conjunction with serum potassium and phosphate concentrations is presented in Table 5.

CRRT with regional citrate anticoagulation (RCA) can also be used for the treatment of hypercalcemia. Several case series have been reported successfully treated hypercalcemic crises using RCA-CRRT with a low rate of calcium replacement[52,53].

Hypocalcemia

Hypocalcemia is commonly encountered in the ICU and known to be a predictor of increased mortality in critically ill patients with AKI. The mortality rate of critically ill patients with hypocalcemia was found to be as high as 50% [54-56]. Serum calcium concentration was inversely correlated with the severity of AKI with the lowest in the patients with uremic encephalopathy[57]. Hyperphosphatemia, parathyroid hormone (PTH) insufficiency, decreased production of renal calcitriol, sepsis, and various medications can cause hypocalcemia in critically ill patients[58].

In RCA-based CRRT, citrate is infused into the pre-filter bloodline, and the citrate chelates ionized calcium. Therefore, RCA-based CRRT has a higher incidence of hypocalcemia than heparin-based CRRT. To prevent hypocalcemia during RCA-based CRRT, calculating the rate of calcium loss and administrating intravenous calcium is needed to maintain. The infusion rate of calcium supplementation should be adjusted according to the serial changes in serum ionized calcium concentration[59,60]. Ionized calcium levels from pre-filter and post-filter sites should be monitored every 6-8 hours[61]. One center's protocol suggested starting 5% calcium chloride infusion at 5.5 mmol/h (25 ml/h) and increasing the rate by 2 ml/h when systemic ionized calcium concentration ranges from 0.8 to 1.0 mmol/L. The rate of calcium infusion can be reduced by 2 ml/h if systemic ionized calcium ranges from 1.2 to 1.4 mmol/L[62]. Additionally, it is important to note that total calcium concentration should be monitored at least once daily to calculate the calcium gap or ratio. Since an assay to directly measure calcium-citrate complex is currently unavailable, increasing a gap between total calcium and ionized calcium or total/ionized calcium ratio can be used as an indicator of citrate accumulation[63,64]. In the case of citrate accumulation, the available management includes reducing/stopping the citrate infusion, decreasing blood flow rate to decrease blood-citrate coupling, increasing dialysate and/or filtration rate to enhance citrate clearance, and increasing calcium infusion to avoid or treat ionized hypocalcemia [63,64].

Evidence for adequate calcium replacement such as threshold and the appropriate dose is lacking[65]. To normalize serum ionized calcium levels in hypocalcemic patients under CRRT, calcium gluconate or calcium chloride can be injected by bolus or continuous infusion[66]. Several studies have reported that ionized calcium concentration increases immediately after calcium administration but is not maintained until after 3 to 6 hours[67]. Further study regarding calcium supplementation strategies such as threshold, appropriate dose, timing, and duration in AKI patients undergoing CRRT is required[65].

Dysphosphatemia

Hyperphosphatemia

Phosphate is an intracellular anion and essential for cellular biologic function[68]. Serum phosphate concentration is determined by the renal excretion capacity of dietary phosphate intake. Although phosphate balance can be maintained by increased PTH and fibroblast growth factor 23 by decreasing proximal tubular reabsorption, urinary excretion cannot reach adequate phosphate excretion once GFR decline below 20-25 mL/min. Hyperphosphatemia was reported to be associated with adverse patient outcome[69,70], but it is unclear whether hyperphosphatemia has direct toxicity like other electrolytes, or it simply reflects severity of underlying catabolic conditions. However, acute severe hyperphosphatemia in catabolic conditions may contribute to organ dysfunction by inducing hypocalcemia and precipitating calcium phosphate crystals[71] In these conditions, calcium supplementation and correction of metabolic acidosis can further promote calcium phosphate crystal formation. Therefore, severe hyperphosphatemia-induced symptomatic hypocalcemia should be considered as an indication of RRT, especially in patients with excess tissue breakdown such as tumor lysis syndrome[72]. Hyperphospha- temia can be easily managed by CRRT treatment since phosphate is readily removed by diffusion and convection[9], but the evidence supporting the beneficial effect of treating hyperphosphatemia in AKI is lacking.

Hypophosphatemia

Since phosphate concentration of most CRRT solutions is 0 mmol/L (Table 1), the incidence of hypophosphatemia was reported as high as 65% while using these non-phosphate-containing CRRT solutions[5,9]. Thus, hypophosphatemia is considered as one of the most serious complications in patients who underwent CRRT. Hypophosphatemia is associated with respiratory muscle weakness, and myocardial dysfunction, arrhythmia, leukocyte dysfunction, rhabdomyolysis, and increased mortality[73,74]. Given that phosphate depletion is associated with impaired phagocytosis leading to immune dysfunction[75,76], avoiding hypophosphatemia is a critical issue in critically ill patients. Notably, in a study that applied the protocol-driven phosphate repletion with a sophisticated calculation of urinary and CRRT-derived phosphate loss, the net phosphate balance remained constantly negative[77]. Although negative phosphate balance is usually necessary during early period of CRRT in AKI patients due to hyperphosphatemia caused by reduced renal phosphate excretion, persistent negative phosphate balance exerts a potentially harmful effect particularly in patients under a prolonged course of CRRT treatment. Furthermore, catecholamine administration, which is frequently required in patients under CRRT, can result in intracellular shifting of phosphate, which further contributes to CRRT-associated hypophosphatemia[78].

As a preventative intervention, oral or intravenous phosphate replacement can be applied, or phosphate can be added to CRRT solutions. For example, 15 mmol sodium phosphate can be intravenously injected over 4 hours twice to 3 times per day during CRRT treatment. Although there was a concern about adding phosphate to CRRT solution due to the potential risk of calcium phosphate precipitation, it has been studied that potassium phosphate can be added to calcium-containing CRRT solution without calcium phosphate precipitation up to 2 days nor adverse events in patients under CRRT[79]. A study that sophisticatedly measured ionized calcium and phosphate concentrations in the solution bag after adding potassium phosphate found no change in either of them for up to 5 hours[80]. Therefore, adding potassium phosphate to CRRT solution right before its application to the patient is likely a safe strategy in centers where commercialized phosphate-containing CRRT solutions are not available.

The commercialized phosphate-containing CRRT solution was approved by US Food and Drug Administration in 2015. Since then, many centers have adopted phosphate-containing solutions with potential advantages in avoiding medical error and contamination[81,82]. Our center uses premixed phosphate-containing CRRT solution with a phosphate concentration of 1.2 mmol/L (3.7 mg/dL) as a dialysate fluid and pre-filter replacement fluid when patients' serum phosphate level is $\leq$3.5 mg/dL before initiation of CRRT treatment or during the treatment[20]. More specifically, considering that phosphate-containing CRRT solutions have high

potassium concentration (4.0 mmol/L) (Table 1), we apply phosphate-containing solution as both dialysate and pre-filter replacement fluid in patients with serum potassium <4.5 mmol/L and serum phosphate <3.5 mg/dL (Table 4). In patients with a serum potassium concentration of ≥4.6 and ≤5.0, we apply it as a dialysate only (Table 4). After using this protocolized application of phosphate-containing CRRT solution, the variability of the serum phosphate concentration during CRRT treatment was significantly reduced in our center[20].

A recent retrospective single-center study demonstrated that the use of non-phosphate solution has 8-fold higher risk of hypophosphatemia compared to the phosphate-containing solution[82]. Furthermore, patients who received phosphate-containing CRRT solution showed shorter hospital stays and longer ventilator-free days[83].

Dysmagnesemia

Hypermagnesemia

Magnesium is a physiologically important electrolyte involved in muscle contraction and relaxation as well as neurotransmission[84]. Hypermagnesemia can occur in patients with impaired renal function and increased intake of magnesium because renal excretion is the only route of magnesium elimination[85]. In line with the experimental studies showing that magnesium mediates vasorelaxation[86], epidemiologic studies demonstrated an association between hypermagnesemia and lower blood pressure as well as increased vasopressor requirements[87]. Particularly, hypermagnesemia can cause vasoactive drug refractory hypotension with cardiac depression[88]. If medical treatments including aggressive intravenous saline administration and loop diuretics fail to effectively reduce magnesium concentration in symptomatic severe hypermagnesemic patients, hemodialysis or CRRT should be considered to remove excess magnesium. Given that severe hypermagnesemia frequently occurs in the setting of increased magnesium absorption due to impaired bowel motility and hypermagnesemia per se can further aggravate ileus with the interference of smooth muscle extraction and contraction coupling [89], it is important to note that continuous absorption may exist in hypermagnesemic patients even after discontinuation of magnesium intake or administration. As such, CRRT can be a suitable treatment option for hypermagnesemic patients because its continuity by preventing rebound hypermagnesemia[90].

Hypomagenesemia

Hypomagnesemia can derive Na-K-ATPase dysfunction altering cardiac repolarization, which can contribute to cardiac arrhythmia in critically ill patients[91]. Hypomagnesemia can also result in respiratory muscle weakness in critically ill patients[92]. Commercial CRRT fluids have 0.5-0.75 mmol/L (1-1.5 mEq/L) of magnesium (Table 1). Especially in the setting of RCA, hypomagnesemia can happen more frequently because magnesium is chelated by citrate, and magnesium-citrate complexes have high diffusive and convective clearance[93].

There is a lack of recommendations for magnesium supplementation in patients undergoing CRRT. If hypomagnesemia occurs in patients under CRRT, intravenous magnesium can be administered[94]. A widely available intravenous magnesium formulation is magnesium sulphate ($MgSO_4$), where 1 g of $MgSO_4$ contains 100 mg, corresponding to 4 mmol (8 mEq) of elemental Mg^{2+} [95]. MgSO4 1 g can increase serum magnesium concentration by 0.18 mg/dL within 18-30 hours. It is important to note that intravenous magnesium supplementation can cause arrythmia, hypotension, and neuromuscular depression[96]. In RCA protocols, a continuous infusion of 2-4 g/day of $MgSO_4$ is generally administered.

SUMMARY and CONCLUSIONS

Multiple and complex electrolyte disturbances are common in critically ill patients with AKI, and many of them can be effectively managed by CRRT. Furthermore, for the electrolyte imbalances that require slow correction such as dysnatremia, CRRT has the advantage compared to conventional intermittent hemodialysis. However, unintended electrolyte complications may occur during CRRT, especially with prolonged duration and high intensity of treatment. Close monitoring of electrolytes accompanied by tailored prescriptions of CRRT solutions, intravenous fluids, and sup-

plementary medications are required in CRRT treatment. Recently, several centers introduced protocol-driven CRRT prescription strategies, showing improved electrolyte stability and reduced labor-intensive repetitive electrolyte replacement and medical costs. We believe that a sophisticated algorithm-based approach in CRRT management can improve patients' outcomes and prevent treatment-related adverse effects. Thus far, there is a lack of consensus regarding electrolyte management among CRRT. The development of a systemized operation protocol by prospective clinical trials is warranted to improve the outcomes of patients and augment the advantages of CRRT treatment.

Acknowledgment

We thank the CRRT nursing team of Samsung Medical Center for their dedicated efforts to perform CRRT properly and motivate the development of our own protocol.

Conflict of Interest

The authors have no conflicts of interest to declare.

REFERENCES

1. Uchino S, Bellomo R, Morimatsu H, et al.: Continuous renal replacement therapy: A worldwide practice survey. The beginning and ending supportive therapy for the kidney (B.E.S.T. kidney) investigators. Intensive Care Med 2007;33(9):1563-1570.
2. An JN, Kim SG, Song YR: When and why to start continuous renal replacement therapy in critically ill patients with acute kidney injury. Kidney Res Clin Pract 2021;40(4):566-577.
3. Augustine JJ, Sandy D, Seifert TH, Paganini EP: A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. Am J Kidney Dis 2004;44(6):1000-1007.
4. De Vriese AS, Colardyn FA, Philippé JJ, et al.: Cytokine removal during continuous hemofiltration in septic patients. J Am Soc Nephrol 1999;10(4):846-853.
5. Palevsky PM, Zhang JH, O'Connor TZ, et al.: Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008;359(1):7-20.
6. Adekola OO, Soriyan OO, Meka I, et al.: The incidence of electrolyte and acid-base abnormalities in critically ill patients using point of care testing (i-STAT portable analyser). Nig Q J Hosp Med 2012;22(2):103-108.
7. Uchino S, Bellomo R, Ronco C: Intermittent versus continuous renal replacement therapy in the ICU: impact on electrolyte and acid-base balance. Intensive Care Med 2001;27(6):1037-1043.
8. Rosner MH, Connor MJ, Jr.: Management of Severe Hyponatremia with Continuous Renal Replacement Therapies. Clin J Am Soc Nephrol 2018;13(5):787-789.
9. Bellomo R, Cass A, Cole L, et al.: Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009;361(17):1627-1638.
10. Murugan R, Hoste E, Mehta RL, et al.: Precision Fluid Management in Continuous Renal Replacement Therapy. Blood Purif 2016;42(3):266-278.
11. Pokaharel M, Block CA: Dysnatremia in the ICU. Curr Opin Crit Care 2011;17(6):581-593.
12. Overgaard-Steensen C, Ring T: Clinical review: practical approach to hyponatraemia and hypernatraemia in critically ill patients. Crit Care 2013;17(1):206.
13. Han SS, Bae E, Kim DK, et al.: Dysnatremia, its correction, and mortality in patients undergoing continuous renal replacement therapy: A prospective observational study. BMC Nephrol 2016;17:2.
14. Kovesdy CP: Significance of hypo- and hypernatremia in chronic kidney disease. Nephrol Dial Transplant 2012;27(3):891-898.
15. Dangoisse C, Dickie H, Tovey L, Ostermann M: Correction of hyper- and hyponatraemia during continuous renal replacement therapy. Nephron Clin Pract 2014;128(3-4):394-398.
16. Ronco C, Bellomo R, Brendolan A, Pinna V, La Greca G. Brain density changes during renal replacement in critically ill patients with acute renal failure. Continuous hemofiltration versus intermittent hemodialysis. J Nephrol 1999;12(3):173-178.
17. Chauhan K, Pattharanitima P, Patel N, et al.: Rate of Correction of Hypernatremia and Health Outcomes in Critically Ill Patients. Clin J Am Soc Nephrol 2019;14(5):656-663.
18. Claure-Del Granado R, Bouchard J: Acid-base and electrolyte abnormalities during renal support for acute kidney injury: Recognition and management. Blood Purif 2012;34(2):186-193.
19. Yessayan LT, Szamosfalvi B, Rosner MH: Management of dysnatremias with continuous renal replacement therapy. Semin Dial 2021;34(6):472-479.
20. Baeg SI, Jeon J, Kang D, et al.: Impact of protocolized fluid management on electrolyte stability in patients undergoing continuous renal replacement therapy. Front Med (Lausanne)

2022;9:915072.
21. Ostermann M, Dickie H, Tovey L, Treacher D: Management of sodium disorders during continuous haemofiltration. Crit Care 2010;14(3):418.
22. Ropper AH: Management of raised intracranial pressure and hyperosmolar therapy. Pract Neurol 2014;14(3):152-158.
23. Fülöp T, Zsom L, Rodríguez RD, et al.: Therapeutic hypernatremia management during continuous renal replacement therapy with elevated intracranial pressures and respiratory failure. Rev Endocr Metab Disord 2019;20(1):65-75.
24. Huang WY, Weng WC, Peng TI, et al.: Central pontine and extrapontine myelinolysis after rapid correction of hyponatremia by hemodialysis in a uremic patient. Ren Fail 2007; 29(5):635-638.
25. Yang H, Yoon S, Kim EJ, et al.: Risk factors for overcorrection of severe hyponatremia: A post hoc analysis of the SALSA trial. Kidney Res Clin Pract 2022;41(3):298-309.
26. Tandukar S, Kim C, Kalra K, et al.: Severe Hyponatremia and Continuous Renal Replacement Therapy: Safety and Effectiveness of Low-Sodium Dialysate. Kidney Med 2020;2(4): 437-449.
27. 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 2014;64(2):305-310.
28. Vassallo D, Camilleri D, Moxham V, Ostermann M: Successful management of severe hyponatraemia during continuous renal replacement therapy. Clin Kidney J 2012;5(2):155-157.
29. Neyra JA, Ortiz-Soriano VM, Ali D, Morris PE, Johnston CM: A Multidisciplinary Approach for the Management of Severe Hyponatremia in Patients Requiring Continuous Renal Replacement Therapy. Kidney Int Rep 2019;4(1):59-66.
30. Yee J, Mohiuddin N, Gradinariu T, Uduman J, Frinak S: Sodium-Based Osmotherapy in Continuous Renal Replacement Therapy: A Mathematical Approach. Kidney 360 2020;1(4):281-291.
31. Bianchi S, Aucella F, De Nicola L, et al.: Management of hyperkalemia in patients with kidney disease: A position paper endorsed by the Italian Society of Nephrology. J Nephrol 2019;32(4):499-516.
32. Hunter RW, Bailey MA: Hyperkalemia: Pathophysiology, risk factors and consequences. Nephrol Dial Transplant 2019; 34(Suppl 3):iii2-iii11.
33. Collins AJ, Pitt B, Reaven N, et al.: Association of Serum Potassium with All-Cause Mortality in Patients with and without Heart Failure, Chronic Kidney Disease, and/or Diabetes. Am J Nephrol 2017;46(3):213-221.
34. Gao XP, Zheng CF, Liao MQ, et al.: Admission serum sodium and potassium levels predict survival among critically ill patients with acute kidney injury: a cohort study. BMC Nephrol 2019;20(1):311.
35. Thongprayoon C, Cheungpasitporn W, Radhakrishnan Y, et al.: Association of serum potassium derangements with mortality among patients requiring continuous renal replacement therapy. Ther Apher Dial 2022.
36. Bhatla B, Nolph KD, Khanna R: Choosing the right dialysis option for your critically ill patient. What's right for a hyperkalemic patient may be wrong for one with shock. J Crit Illn 1996;11(1):21-24, 27, 31.
37. Hung AM, Hakim RM: Dialysate and serum potassium in hemodialysis. Am J Kidney Dis 2015;66(1):125-132.
38. Houzé P, Baud FJ, Raphalen JH, et al.: Continuous renal replacement therapy in the treatment of severe hyperkalemia: An *in vitro* study. Int J Artif Organs 2020;43(2):87-93.
39. Yessayan L, Yee J, Frinak S, Szamosfalvi B: Continuous Renal Replacement Therapy for the Management of Acid-Base and Electrolyte Imbalances in Acute Kidney Injury. Adv Chronic Kidney Dis 2016;23(3):203-210.
40. Besnard N, Serveaux M, Machado S, et al.: Electrolytes-Enriched Hemodiafiltration Solutions for Continuous Renal Replacement Therapy in Acute Kidney Injury: A Crossover Study. Blood Purif 2016;42(1):18-26.
41. Karaboyas A, Zee J, Brunelli SM, et al.: Dialysate Potassium, Serum Potassium, Mortality, and Arrhythmia Events in Hemodialysis: Results From the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 2017;69(2):266-277.
42. McGill RL, Weiner DE: Dialysate Composition for Hemodialysis: Changes and Changing Risk. Semin Dial 2017;30(2):112-120.
43. Relman AS, Schwartz WB. The nephropathy of potassium depletion; a clinical and pathological entity. N Engl J Med 1956;255(5):195-203.
44. Cho A, Lee YK, Park HC. Impact of electrolyte-rich dialysate during continuous renal replacement therapy on serum phosphate and potassium in ICU patients. PLoS One 2020; 15(9):e0238867.
45. Humes HD: Role of calcium in pathogenesis of acute renal failure. Am J Physiol 1986;250(4 Pt 2):F579-589.
46. Himmel HM, Whorton AR, Strauss HC: Intracellular calcium, currents, and stimulus-response coupling in endothelial cells. Hypertension 1993;21(1):112-127.
47. Bridoux F, Cockwell P, Glezerman I, et al.: Kidney injury and disease in patients with haematological malignancies. Nat Rev Nephrol 2021;17(6):386-401.
48. Edelstein CL, Alkhunaizi AA, Schrier RW: The role of calcium in the pathogenesis of acute renal failure. Ren Fail 1997;19(2):

199-207.
49. Liu S, Zhao J, Wang F: Acute kidney injury in cancer patients. Clin Exp Nephrol 2022;26(2):103-112.
50. Aihara S, Yamada S, Oka H, et al.: Hypercalcemia and acute kidney injury induced by eldecalcitol in patients with osteoporosis: a case series of 32 patients at a single facility. Ren Fail 2019;41(1):88-97.
51. AlZahrani A, Sinnert R, Gernsheimer J: Acute kidney injury, sodium disorders, and hypercalcemia in the aging kidney: diagnostic and therapeutic management strategies in emergency medicine. Clin Geriatr Med 2013;29(1):275-319.
52. Kindgen-Milles D, Kram R, Kleinekofort W, Morgera S: Treatment of severe hypercalcemia using continuous renal replacement therapy with regional citrate anticoagulation. Asaio J 2008;54(4):442-444.
53. Gradwohl-Matis I, Franzen M, Seelmaier C, et al.: Renal replacement therapy with regional citrate anticoagulation as an effective method to treat hypercalcemic crisis. Asaio J 2015;61(2):219-223.
54. Afshinnia F, Belanger K, Palevsky PM, Young EW: Effect of ionized serum calcium on outcomes in acute kidney injury needing renal replacement therapy: secondary analysis of the acute renal failure trial network study. Ren Fail 2013; 35(10):1310-1318.
55. Wang B, Li D, Gong Y, Ying B, Cheng B: Association of serum total and ionized calcium with all-cause mortality incritically ill patients with acute kidney injury. Clin Chim Acta 2019;494: 94-99.
56. Desai TK, Carlson RW, Geheb MA. Prevalence and clinical implications of hypocalcemia in acutely ill patients in a medical intensive care setting. Am J Med 1988;84(2):209-214.
57. Akman C, Ülker Çakır D, Bakırdöğen S, Balcı S: The Effect of Serum Calcium Levels on Uremic Encephalopathy in Patients with Acute Kidney Injury in the Emergency Department. Medicina (Kaunas) 2019;55(5).
58. Buckley MS, Leblanc JM, Cawley MJ: Electrolyte disturbances associated with commonly prescribed medications in the intensive care unit. Crit Care Med 2010;38(6 Suppl):S253-264.
59. Liu DL, Huang LF, Ma WL, et al.: Determinants of Calcium Infusion Rate During Continuous Veno-venous Hemofiltration with Regional Citrate Anticoagulation in Critically Ill Patients with Acute Kidney Injury. Chin Med J (Engl) 2016;129(14): 1682-1687.
60. Rhee H, Berenger B, Mehta RL, Macedo E: Regional Citrate Anticoagulation for Continuous Kidney Replacement Therapy With Calcium-Containing Solutions: A Cohort Study. Am J Kidney Dis 2021;78(4):550-559.e551.
61. Legrand M, Tolwani A: Anticoagulation strategies in continuous renal replacement therapy. Semin Dial 2021;34(6): 416-422.
62. Bi X, Zhang Q, Zhuang F, Lu W, Ding F: Optimized calcium supplementation approach in post-dilution CVVHDF using regional citrate anticoagulation. Int J Artif Organs 2021;44(3): 165-173.
63. Schneider AG, Journois D, Rimmele T: Complications of regional citrate anticoagulation: Accumulation or overload? Crit Care 2017;21(1):281.
64. Davenport A, Tolwani A: Citrate anticoagulation for continuous renal replacement therapy (CRRT) in patients with acute kidney injury admitted to the intensive care unit. NDT Plus 2009;2(6):439-447.
65. Forsythe RM, Wessel CB, Billiar TR, Angus DC, Rosengart MR: Parenteral calcium for intensive care unit patients. Cochrane Database Syst Rev 2008(4):Cd006163.
66. Drop LJ: Ionized calcium, the heart, and hemodynamic function. Anesth Analg 1985;64(4):432-451.
67. Auffant RA, Downs JB, Amick R: Ionized calcium concentration and cardiovascular function after cardiopulmonary bypass. Arch Surg 1981;116(8):1072-1076.
68. Takeda E, Taketani Y, Sawada N, Sato T, Yamamoto H: The regulation and function of phosphate in the human body. Biofactors 2004;21(1-4):345-355.
69. Jung SY, Kwon J, Park S, et al.: Phosphate is a potential biomarker of disease severity and predicts adverse outcomes in acute kidney injury patients undergoing contin- uous renal replacement therapy. PLoS One 2018;13(2):e0191290.
70. Jung SY, Kim H, Park S, et al.: Electrolyte and mineral disturbances in septic acute kidney injury patients undergoing continuous renal replacement therapy. Medicine (Baltimore) 2016;95(36):e4542.
71. Markowitz GS, Perazella MA: Acute phosphate nephropathy. Kidney Int 2009;76(10):1027-1034.
72. Howard SC, Jones DP, Pui CH: The tumor lysis syndrome. N Engl J Med 2011;364(19):1844-1854.
73. Geerse DA, Bindels AJ, Kuiper MA, et al.: Treatment of hypophosphatemia in the intensive care unit: A review. Crit Care 2010;14(4):R147.
74. Wang L, Xiao C, Chen L, Zhang X, Kou Q: Impact of hypophosphatemia on outcome of patients in intensive care unit: a retrospective cohort study. BMC Anesthesiol 2019; 19(1):86.
75. Craddock PR, Yawata Y, VanSanten L, et al.: Acquired phagocyte dysfunction. A complication of the hypophosphatemia of parenteral hyperalimentation. N Engl J Med 1974;290(25): 1403-1407.
76. Kiersztejn M, Chervu I, Smogorzewski M, et al.: On the

mechanisms of impaired phagocytosis in phosphate depletion. J Am Soc Nephrol 1992;2(10):1484-1489.
77. Sharma S, Waikar SS. Phosphate balance in continuous veno-venous hemofiltration. Am J Kidney Dis 2013;61(6):1043-1045.
78. Liamis G, Milionis HJ, Elisaf M: Medication-induced hypophosphatemia: A review. Qjm 2010;103(7):449-459.
79. Troyanov S, Geadah D, Ghannoum M, Cardinal J, Leblanc M: Phosphate addition to hemodiafiltration solutions during continuous renal replacement therapy. Intensive Care Med 2004;30(8):1662-1665.
80. Hiremath S, Slivar S, Magner P: Phosphate Balance With Continuous Renal Replacement Therapy: A Simple Solution. American Journal of Kidney Diseases 2013;62(3):644.
81. Pistolesi V, Zeppilli L, Fiaccadori E, et al.: Hypophosphatemia in critically ill patients with acute kidney injury on renal replacement therapies. J Nephrol 2019;32(6):895-908.
82. Thompson Bastin ML, Adams PM, Nerusu S, et al.: Association of Phosphate Containing Solutions with Incident Hypophosphatemia in Critically Ill Patients Requiring Continuous Renal Replacement Therapy. Blood Purif 2022;51(2): 122-129.
83. Thompson Bastin ML, Stromberg AJ, Nerusu SN, et al.: Association of Phosphate-Containing versus Phosphate-Free Solutions on Ventilator Days in Patients Requiring Continuous Kidney Replacement Therapy. Clin J Am Soc Nephrol 2022; 17(5):634-642.
84. de Baaij JH, Hoenderop JG, Bindels RJ: Magnesium in man: implications for health and disease. Physiol Rev 2015;95(1): 1-46.
85. Felsenfeld AJ, Levine BS, Rodriguez M: Pathophysiology of Calcium, Phosphorus, and Magnesium Dysregulation in Chronic Kidney Disease. Semin Dial 2015;28(6):564-577.
86. Laurant P, Touyz RM: Physiological and pathophysiological role of magnesium in the cardiovascular system: Implications in hypertension. J Hypertens 2000;18(9):1177-1191.
87. Celi LA, Scott DJ, Lee J, et al.: Association of hypermagnesemia and blood pressure in the critically ill. J Hypertens 2013;31(11):2136-2141; discussion 2141.
88. Mordes JP, Swartz R, Arky RA: Extreme hypermagnesemia as a cause of refractory hypotension. Ann Intern Med 1975; 83(5):657-658.
89. Khairi T, Amer S, Spitalewitz S, Alasadi L: Severe Symptomatic Hypermagnesemia Associated with Over-the-Counter Laxatives in a Patient with Renal Failure and Sigmoid Volvulus. Case Rep Nephrol 2014;2014:560746.
90. Bokhari SR, Siriki R, Teran FJ, Batuman V: Fatal Hypermagnesemia Due to Laxative Use. Am J Med Sci 2018;355(4): 390-395.
91. Agus MS, Agus ZS: Cardiovascular actions of magnesium. Crit Care Clin 2001;17(1):175-186.
92. Tong GM, Rude RK: Magnesium deficiency in critical illness. J Intensive Care Med 2005;20(1):3-17.
93. Swartz R, Pasko D, O'Toole J, Starmann B: Improving the delivery of continuous renal replacement therapy using regional citrate anticoagulation. Clin Nephrol 2004;61(2):134-143.
94. Morabito S, Pistolesi V, Tritapepe L, Fiaccadori E: Regional citrate anticoagulation for RRTs in critically ill patients with AKI. Clin J Am Soc Nephrol 2014;9(12):2173-2188.
95. Ayuk J, Gittoes NJ: Treatment of hypomagnesemia. Am J Kidney Dis 2014;63(4):691-695.
96. Martin KJ, González EA, Slatopolsky E: Clinical consequences and management of hypomagnesemia. J Am Soc Nephrol 2009;20(11):2291-2295.