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TREATMENT CONSIDERATIONS IN CONVENTIONAL HD—WHAT WE KNOW

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Dialysate potassium concentration: Should mass balance trump electrophysiology?

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Abstract

Nephrologists are faced with a difficult dilemma in choosing the ideal dialysis prescription to maintain neutral potassium mass balance. Should potassium mass balance goals prioritize the normalization of serum potassium levels using low potassium dialysate at the expense of provoking intradialytic arrhythmias, or should mass balance goals favor permissive hyperkalemia using higher dialysate potassium to avoid rapid intradialytic fluxes at the risk of more interdialytic arrhythmias? This review examines the factors that determine potassium mass balance among HD patients, the relationships between serum and dialysate potassium levels and outcomes, and concludes by examining currently available approaches to reducing risk of arrhythmias while managing potassium mass balance.

KEYWORDS
chronic hemodialysis, clinical epidemiology, electrolytes, end-stage kidney disease

1 | INTRODUCTION

End-stage kidney disease (ESKD) affects more than 650,000 patients per year in the United States and an estimated 2 million patients worldwide; the majority of these patients are maintained with regular hemodialysis treatment.[1] Besides clearance of uremic solutes, one of the fundamental goals of hemodialysis treatment is to maintain homeostasis of extracellular fluid and electrolyte levels; maintaining potassium homeostasis has always been a central focus due to the risk of fatal cardiac arrhythmias which can occur outside a narrow range of normal serum potassium levels. In the early years of low-efficiency hemodialysis, progressive lowering of dialysate potassium was needed to manage hyperkalemia. However, with modern advances in dialyzer efficiency combined with pressures to provide treatment in a shorter period of time, a new concern has emerged—the excess of cardiovascular events, arrhythmias, and sudden deaths occurring on hemodialysis treatment days, with the greatest frequency on the first HD treatment of the week after the long dialysis-free weekend. These events have been linked to the use of low potassium dialysate, suggesting that rapid dialytic removal of potassium during HD treatment may be the underlying cause.[2,3]

Thus, for the hyperkalemic dialysis patient, nephrologists are faced with a difficult dilemma. Should potassium mass balance goals prioritize the normalization of serum potassium levels using low potassium dialysate at the expense of provoking intradialytic arrhythmias, or should mass balance goals favor permissive hyperkalemia using higher dialysate potassium to avoid rapid intradialytic fluxes at the risk of more interdialytic arrhythmias? This review will examine the factors that determine potassium mass balance among HD patients, the relationship between serum and dialysate potassium levels and outcomes, and conclude by examining currently available approaches for managing potassium mass balance while reducing risk of arrhythmias.

2 | FACTORS AFFECTING POTASSIUM MASS BALANCE IN HEMODIALYSIS PATIENTS

Since urinary excretion of potassium is lost or greatly reduced in ESKD patients, potassium mass balance must be maintained using a combination of dietary potassium restriction and dialytic removal.

The goals of ideal dialytic management are to achieve an intradialytic negative potassium mass balance that equals the positive mass balance occurring between treatments so that both interdialytic hyperkalemia and intradialytic hypokalemia are prevented.[4]

The recommended daily potassium intake for hemodialysis patients is a restricted intake of about 60 mEq/day (420 mEq/week).[4] A typical dialysis treatment removes 70-100 mEq (210-300 mEq/week for thrice weekly hemodialysis patients) through a combination of diffusive and convective clearance. Therefore, assuming negligible urinary potassium clearance, some potassium elimination via the gastrointestinal tract is needed to maintain neutral potassium mass balance. This is accomplished via enhanced colonic excretion, which is a noted phenomenon in anuric patients due to enhanced activity of colonic AT1 receptors,[5,6] highlighting the importance of gut in maintaining potassium mass balance among dialysis patients.

3 | FACTORS MODULATING DIALYTIC POTASSIUM REMOVAL

Hemodialysis removes potassium from the extracellular fluid compartment, which contains only 2% of total body potassium; the remainder is found in the intracellular space. Diffusion accounts for 85% of dialytic potassium clearance,[7,8] and the rate and amount of potassium removal are largely a function of the serum-dialysate potassium gradient.

During the first hour of dialysis, the serum-dialysate potassium gradient is largest and the rate of potassium decline is the most rapid; a 1 mEq/L fall is typical, but this fall can be greater with larger serum-dialysate gradients. After the initial acute fall in serum potassium levels in the first hour, a more gradual decline of an additional 1 mEq/L occurs over next 2 hours as the serum-to-dialysate potassium gradient narrows. During the final hour, serum potassium levels remain steady even though diffusive clearance is still occurring, indicating equilibrium between the rates of potassium removal and the rate of re-equilibration from intracellular space.[8] At the conclusion of treatment, there is a subacute "rebound" of serum potassium levels with continued movement of potassium from intracellular space to extracellular space.

Figure 1 illustrates the impact of the size of the serum-dialysate gradient on intradialytic and postdialytic serum potassium levels as studied by Blumberg et al.[9] High serum-dialysate gradients result in a more rapid fall in serum potassium levels during treatment as well as a more rapid postdialysis rebound of potassium levels compared to smaller gradients.

There are several other aspects of the dialysis prescription besides the serum-dialysate potassium gradient that influence the rate of potassium removal. First, alkalosis enhances the activity of Na/K/ATPase channels and promotes shifts of potassium into the intracellular space; thus, increased dialytic transfer of bicarbonate can promote more severe intradialytic falls in serum potassium. This was demonstrated experimentally in a randomized crossover study comparing the effect of three different dialysate bicarbonate concentrations (39 mEq/L, 35 mEq/L and 27 mEq/L) on the rate of serum potassium decline while keeping the serum-dialysate potassium gradient constant.[10] The highest bicarbonate concentration was associated with the greatest decline in serum potassium levels compared to standard and low concentrations, but there was no significant difference in the total potassium removal, concordant with enhanced acute intracellular potassium shifts rather than enhanced potassium removal.

Second, although the effect of dialysate magnesium concentration on potassium kinetics has not been studied, low dialysate magnesium could potentiate risks associated with low potassium

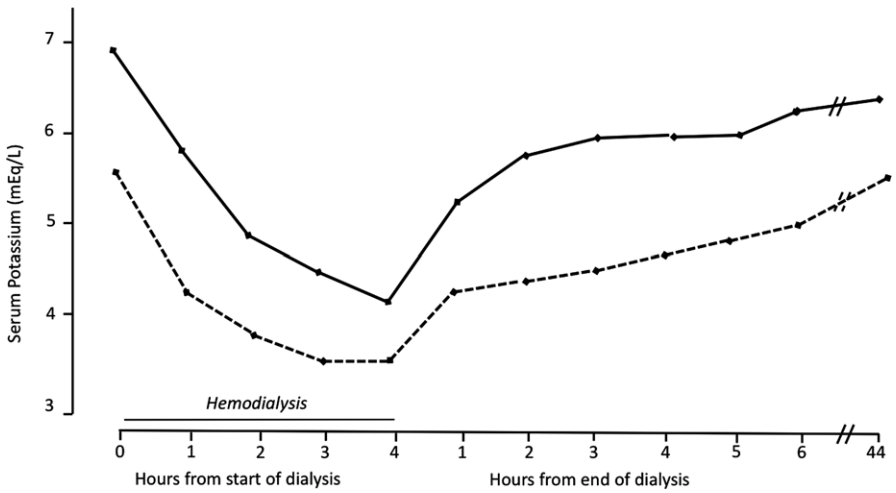

FIGURE 1 Comparison of intradialytic and postdialytic potassium levels between a serum-dialysate gradient of 5.8 mEq/L (solid line, predialysis serum potassium 6.8 mEq/L, dialysate potassium 1 mEq/L) and a gradient of 4.7 mEq/L (dashed line, predialysis serum potassium 5.7, dialysate potassium 1 mEq/L). The high serum-dialysate gradient condition results in a total excursion of serum potassium levels of ~5 mEq/L (3 mEq/L fall and 2 mEq/L rebound) in the 10 h following the start of treatment, compared to ~3 mEq/L with the lower gradient condition. Adapted from Blumberg et al[9,50]

dialysate in a similar fashion via promotion of intracellular potassium shifts, given the effects of hypomagnesemia on risk of hypokalemia.[11] Third, convective clearance of potassium plays a small but significant role in total dialytic potassium removal; recent mass balance studies have shown that potassium mass removed by ultrafiltration accounts for approximately 6% of the total potassium mass removed.[8] Finally, glucose-free or low glucose containing dialysate solutions can also lead to higher potassium removal via suppression of insulin-mediated shifts of potassium to the intracellular space.[12,13]

4 | SERUM POTASSIUM LEVELS AND ARRHYTHMIC RISKS IN HEMODIALYSIS PATIENTS

Normal extracellular potassium levels are critical to maintain a stable transmembrane potential of about −85 mV to permit normal cardiac and skeletal muscle function; deviations in membrane potential due to changes in serum potassium levels can lead to muscle paralysis and fatal cardiac arrhythmias.[14,15] Although the normal range for serum potassium levels is typically reported between 3.5 and 5.0 mEq/L in the general population, epidemiologic data support the notion that the optimal range to reduce arrhythmic risk is higher in dialysis patients. In a study of 2,134 HD patients, a predialysis serum potassium level of 5.1 mEq/L was associated with the lowest risk of peridialytic sudden cardiac arrest, while potassium levels above and below 5.1 were associated with increasing risk.[16]

Another study examining predialysis serum potassium levels and survival within a cohort of 81,013 hemodialysis patients found that potassium concentrations between 4.6 and 5.3 mEq/L were associated with the lowest incidence of all-cause mortality.[17] In this study, elevated potassium levels ≥5.6 mEq/L were most strongly associated with increased mortality after adjustment for confounders related to comorbidities and nutritional status, whereas the association of potassium levels <4.6 mEq/L with mortality was mostly explained by factors related to malnutrition.

A more recent study of 55,183 patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS) multinational cohort confirmed these findings with the lowest risk of death among patients with predialysis serum potassium levels between 4 and 5.5 mEq/L, a significant increase in the risk of death and arrhythmia outcomes at levels ≥5.6; risk associations with potassium levels <4 mEq were attenuated after accounting for potential confounding from malnutrition indicators.[18]

Even if risks associated with low potassium levels are not entirely mediated through malnutrition and inflammation-related factors, predialysis hypokalemia is encountered less frequently compared to hyperkalemia, making hyperkalemia management a more pressing public health concern. In two studies, surveying predialysis serum potassium values obtained within a large dialysis organization, approximately 20% of all measurements were ≥5.5 mEq, and about 12.5% of measurements were ≥6.0,[19] whereas predialysis potassium levels <4.0 accounted for only 9% of all measurements.[17]

The prevalence and prognostic significance of immediate postdialysis potassium levels and in particular, postdialysis hypokalemia, are unknown, since postdialysis levels are not routinely measured. Regardless, the potential impact of falling potassium levels during and after the hemodialysis procedure is concerning. In a study of ESKD patients who had wearable defibrillators in place, 70.0% of the captured arrhythmia events occurred during the session and 2.8% were captured immediately after the dialysis procedure.[20] The results of several recent prospective arrhythmia monitoring studies using implantable loop-monitoring devices also demonstrate increased risk of significant arrhythmias during and after the dialysis procedure, particularly during the first dialysis treatment of the week when potassium shifts are largest.[21-23] However, in these studies, the highest frequency of arrhythmias were noted in the immediate predialysis period following the long dialysis-free weekend interval, pointing to potassium accumulation and hyperkalemia as a significant contributor to the overall arrhythmic burden in hemodialysis patients.

5 | ARRHYTHMIC RISKS ASSOCIATED WITH DIALYSATE POTASSIUM LEVELS

Since dialytic potassium removal is primarily determined by the dialysate potassium concentration, the challenge of selecting the appropriate dialysate potassium concentration is balancing two conflicting priorities. Nephrologists must choose between using a lower dialysate potassium to maximize potassium removal and prevent hyperkalemia at the risk of provoking hypokalemic intra- and postdialytic arrhythmias; the alternative is to select a higher dialysate potassium to reduce large dialytic shifts of potassium at the cost of failing to achieve neutral potassium mass balance and subjecting patients to hyperkalemic complications. Compounding the challenge is the current standard to only monitor serum potassium levels and change dialysate potassium once per month; thus, the effects of the dialysate choice extend to all treatments in a month. With this in mind, what evidence is available to help guide clinicians in this daunting task of selecting the best dialysate potassium?

5.1 | Evidence supporting the avoidance of low potassium dialysate

The safety of low potassium dialysate has been a focus of concern given the high risk of arrhythmias and sudden death during and after dialysis treatment as discussed above. Multiple large retrospective studies have investigated associations between dialysate potassium levels, predialysis serum potassium levels, and risk of sudden death, cardiac events, and all-cause mortality. Although subject to indication bias and other sources of confounding, in general, large cohort studies have identified increased risks of sudden cardiac death (SCD) associated with use of low potassium dialysate <2 mEq/L,[16,24] with one study identifying an increased risk of SCD among patients exposed to dialysate potassium <3 mEq/L as compared to ≥3 mEq/L.[25]

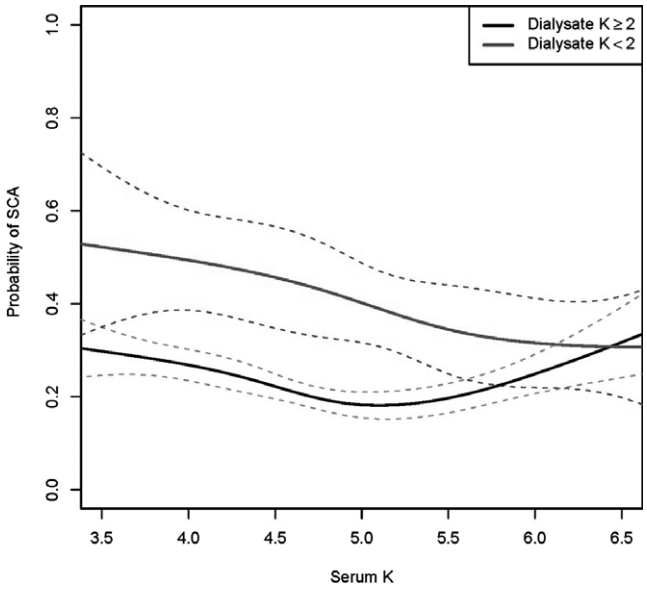

FIGURE 2 Sudden cardiac arrest (SCA) risk according to serum and dialysate potassium. The risk of SCA of lower potassium dialysate <2 mEq (gray line) is highest among patients with lower predialysis serum potassium levels but is equivalent (overlapping confidence intervals) to ≥2 mEq (black line) among hyperkalemic patients. From Pun et al[16,50]

Not surprisingly, the risks associated with low potassium dialysate are principally seen among patients with low to normal predialysis serum potassium (Figure 2); importantly, no study has demonstrated a significant risk increase in sudden death or mortality associated with low potassium dialysate among patients with predialysis serum potassium levels ≥5. Perhaps the strongest evidence supporting the risk of large serum-dialysate gradients comes from a large retrospective study examining short-term outcomes of 62,388 patients contributing data from 830,741 potassium gradient measurements. Although there were no significant associations with mortality, larger gradients (driven by use of dialysate potassium <2 mEq/L as well as higher serum potassium levels) were associated with increased risks of same or next day all-cause hospitalization and emergency room presentation.[26]

While no prospective controlled studies have been conducted to examine the effect of low potassium dialysate on hard outcomes, several short-term crossover studies utilizing cardiac-monitoring devices have been conducted to assess subclinical arrhythmic events such as ventricular ectopy[27-29] premature ventricular complexes,[30] and changes in electrocardiographic conduction parameters such as the QT interval and QT dispersion.[31,32] Most, but not all studies observed higher rates of ventricular ectopy and QTc prolongation associated with lower potassium dialysates of 0 or 1 mEq/L compared to higher potassium dialysates. However, the validity of these markers as predictors of SCD and mortality is questionable, with long-term studies finding no association between these ECG markers and mortality.[33]

Overall, mostly circumstantial evidence points to the hazards of lower potassium dialysate <2 mEq/L, and the evidence for risk is strongest for patients with predialysis serum potassium levels <5 mEq/L. Whether lower potassium dialysate is appropriate or potentially beneficial for patients with higher predialysis serum potassium levels is unclear.

5.2 | Evidence against the use of high potassium dialysate

Using potassium dialysate concentrations ≥3 has also been associated with adverse outcomes. In a study of more than 81,000 US patients comparing outcomes according to various combinations of dialysate and predialysis serum potassium levels, patients exposed to high potassium dialysate > 3 mEq/L with predialysis serum potassium levels ≥ 5 had the highest risk of death.[17] Studies done among Canadian dialysis patients[34] and the DOPPS international cohort[18] have also observed an increased risk of death among users of dialysate potassium ≥3 mEq/L; however, in both studies, these risks were attenuated after adjustment for factors relating to malnutrition and inflammation. Since 3 mEq/L dialysate potassium is the most commonly prescribed dialysate potassium above the "standard" bath of 2 mEq/L, mortality and arrhythmia outcomes between these two dialysates were specifically compared in the latter study.[18] There was no significant mortality or arrhythmia benefit or harm associated with 3 mEq/L dialysate potassium compared to 2 mEq/L across the spectrum of predialysis serum potassium levels, even among patients with predialysis serum potassium >6 mEq/L and <4 mEq/L.

In summary, while no randomized controlled data exist to identify best dialysate potassium choices, current evidence most strongly supports the avoidance of low potassium dialysate <2 mEq/L among patients with known predialysis serum potassium levels ≤5. Little evidence exists to support the complete avoidance of dialysate potassium <2 mEq or >3 mEq/L when used appropriately with marked hyperkalemia or hypokalemia, respectively. However, given the reported risk associations, the use of these dialysate concentrates should be accompanied by reassessment of serum potassium levels and adjustment of the dialysate when serum levels come with the normal range. Ultimately, controlled randomized trials are needed to compare the impact of a strategy using lower potassium dialysate to reduce hyperkalemia-associated arrhythmias with one that uses higher potassium dialysate to avoid the potential arrhythmic hazards of increased serum-dialysate gradients.

6 | DIALYTIC APPROACHES TO ACHIEVE POTASSIUM MASS BALANCE AND REDUCE RISK OF ARRHYTHMIAS

Given the current "no-win" situation of current approaches to avoid hyperkalemia and also avoid large intradialytic potassium shifts, more physiologic dialytic approaches to achieve neutral potassium mass balance have been suggested. Using a separate dialysate potassium

proportioning system, dialysate potassium profiling gradually lowers dialysate potassium concentration as serum potassium levels fall, thereby maintaining a constant serum-dialysate potassium gradient.[35] This approach has been demonstrated to achieve a more gradual intradialytic fall in serum potassium levels[36] while maintaining the same total amount of potassium removal.[37] Additionally, dialysate potassium profiling has been shown to result in modest reductions in ventricular ectopy and improvements in QTc dispersion.[31] However, there are no current automated potassium-profiling capabilities in modern three-stream proportioning hemodialysis machines; profiling must be done by physically changing out the dialysate concentrate throughout the course of a treatment, making this impractical for everyday use.[38]

Other dialytic methods to reduce large potassium shifts while maintaining total potassium removal include conducting more frequent treatments using higher dialysate potassium baths and extending dialysis treatment time. Potassium kinetics during short daily hemodialysis has not been directly observed, but one recent study used kinetic data from the HEMO study to create a predictive model for expected potassium kinetics during quotidian dialysis modalities.[39] Comparing a six treatment per week schedule with a thrice weekly schedule and keeping total weekly dialysis duration the same, the model predicted that significantly higher dialysate potassium levels could be used with short daily dialysis to achieve equivalent total potassium removal rates, which in turn would reduce serum-dialysate gradients and rapid changes in serum potassium.

The effects of extending dialysis treatment time on potassium kinetics was examined in a crossover study comparing patients assigned to either a 4-hour or an 8-hour dialysis which were pair-matched for dialysate potassium concentration, total dialysate volume, and total ultrafiltration volume.[8] With the extended treatment times, there was a slower rate of serum potassium fall, a 15% overall increase in total potassium removal, and an identical end-of-treatment serum potassium in 8 hour treatments compared to 4 hour treatments. However, the limitation of both these approaches is that they are less available and generally less desirable for patients and dialysis providers alike.[4]

A point that should be emphasized is that it is critical that the dialysate potassium prescription be reviewed and adjusted regularly in response to predialysis serum potassium levels to avoid serum/dialysate potassium mismatches, particularly during vulnerable periods where serum potassium levels may be acutely altered, such as after hospitalization. Several dialysate potassium adjustment algorithms have been proposed to avoid these serum/dialysate mismatches and target safe serum potassium concentrations. An informal algorithm that has been commonly advocated for decades is the "rule of seven," in which the predialysis serum potassium level is subtracted from seven to determine the dialysate potassium that should be assigned. A summary of several other suggested adjustment algorithms is shown in Table 1.

A critically important aspect of any algorithm is the need to obtain more clinical context when reviewing and responding to changes in serum potassium levels; transient conditions such as hypokalemia from diarrhea or hyperkalemia from a missed dialysis treatment may simply require follow-up monitoring rather than a change in the dialysis prescription. If dialysate potassium is altered in response to acute changes in predialysis serum potassium levels without obtaining follow-up levels, serum/dialysate mismatches can easily occur when the acute condition resolves. This is particularly important if the treatment algorithm involves utilizing dialysate potassium concentrations >3 and <2 mEq/L, since these dialysates have been associated with harm among patients with normal predialysis serum potassium levels as discussed above.

If the workflow of the dialysis clinics makes the reliability of more frequent monitoring difficult to guarantee, a potential "do no

TABLE 1 Summary of suggested algorithms for managing dialysate potassium (dK) levels according to predialysis serum potassium

	Predialysis serum potassium (sK) Level (mEq/L)				
	<4	4.1-5.5	5.6-6.4	>6.5	Comments
"Rule of 7"	4 mEq/L	3 or 2 mEq/L	1 mEq/L	1 or 0 mEq/L	Potential for large serum-dialysate gradients; Potential for large mismatches without frequent follow-up of sK values.
Lee and Mendelsohn[4]	Increase current dK by 1 mEq/L to max of 4 mEq/L	Increase dK by 1 mEq/L to max of 3	2 mEq/L	2 mEq/L; Consider longer dialysis treatment time or frequent HD	Targets avoidance of low dK; found to result in only 4% of patients requiring dK changes after using algorithm for 5 months.
Abuelo[51]	Increase current dialysate by 1 mEq/L to max of 4 mEq/L	Maintain current dK level	Lower dK by 1 mEq to minimum of 0; consider other potassium lowering medications.		Targets avoidance of hyperkalemia
Pun and Middleton[50]	3 mEq/L; 4 mEq/L if persistent sK<3.5; Avoid dialysate magnesium <1 mEq/L and bicarbonate >35 mEq/L	2 mEq/L	2 mEq/L + Add potassium binder. + Dietary counseling + Lengthen treatment time If above measures inadequate, lower to 1 mEq/L or consider dialysate profiling		Frequent potassium monitoring at least once per week if utilizing dK>3 and <2 mEq/L and when sK <3.5 and >6.5.

harm" approach is to avoid altogether using dialysate potassium <2 and >3 to prevent inadvertent mismatches. Tighter control of potassium mass balance using a wider variety of dialysate potassium levels and more frequent predialysis serum monitoring (perhaps using point-of-care handheld blood analyzers) could potentially reduce both the incidence of dialysis-associated arrhythmias and hyperkalemic events, but randomized controlled trials are needed to determine if this approach is superior to the current standard of care.

7 | NONDIALYTIC APPROACHES TO ACHIEVE POTASSIUM MASS BALANCE AND REDUCE RISK OF ARRHYTHMIAS

It is important not to discount the potential utility of nondialytic management strategies to achieve potassium mass balance and decrease the need to expose patients to the potential hazards of low dialysate potassium. Discontinuing angiotensin-converting enzyme inhibitors and spironolactone can lower serum potassium levels by 0.2-0.6 mEq/L in oligoanuric hemodialysis patients, presumably through abrogation of their effects on colonic secretion.[40,41] Fludrocortisone, a potent mineralocorticoid, has been reported in several case series to effectively reduce serum potassium levels in dialysis patients via enhanced colonic secretion,[42] but a randomized trial of 37 hemodialysis patients found no significant difference in predialysis serum potassium levels compared to controls after 3 months of treatment.[43]

The use of older potassium-binding resins including sodium polystyrene sulfonate and calcium polystyrene sulfonate is limited by poor gastrointestinal tolerability and the potentially fatal risk of colonic necrosis, and there is an absence of data demonstrating efficacy in the chronic setting.[44,45] Loop diuretics have been used to manage hyperkalemia, but their efficacy in hemodialysis patients is limited to only patients with residual renal function and associated with high, potentially ototoxic doses required to produce kaliuresis.[46] Thus, these agents have poor utility for the management of chronic hyperkalemia.

Two new oral potassium-binding agents (sodium zirconium cyclosilicate and patiromer) have been shown to be effective in reducing serum potassium levels among patients with moderate CKD.[47,48] These new medications have only been tested in small populations of hemodialysis patients,[49] but these new agents appear to be efficacious in potassium lowering and well-tolerated. If proven effective, well-tolerated, and safe in larger studies of hemodialysis patients, novel potassium-binding agents could represent an important advance in reducing dialysis-induced arrhythmias by allowing use of higher dialysate potassium levels while still maintaining potassium mass balance and avoiding interdialytic hyperkalemia.

8 | CONCLUSION

While identifying the optimal approach to managing hyperkalemia in hemodialysis patients is hampered by the absence of hard outcomes-based randomized controlled trials, some consensus can be reached based on existing data from multiple observational studies. First, dialysis patients appear to be tolerant of mild hyperkalemia up to 5.5 mEq/L without increases in arrhythmia or mortality risk; therefore, efforts to treat mild hyperkalemia by lowering dialysate potassium may not provide benefit and could introduce harm. Second, observational studies and circumstantial evidence suggest that extreme concentrations of dialysate potassium <2 and >3 mEq/L are associated with increased risk, especially when these dialysates are mismatched with serum potassium levels; use of these dialysates should be accompanied by more frequent follow-up of serum potassium levels compared to usual practice of measuring serum potassium only once a month.

While we await further data on novel approaches to manage hyperkalemia, multidisciplinary dialysis care teams can help reduce the significant arrhythmic burden borne by patients by being more attentive to serum and dialysate potassium levels and other factors which influence potassium mass balance.

DISCLOSURE

P.H.P has served on advisory boards for Relypsa, Inc.

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