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Special Report

Improving Clinical Outcomes Among Hemodialysis Patients: A Proposal for a "Volume First" Approach From the Chief Medical Officers of US Dialysis Providers

Daniel E. Weiner, MD, MS,[1,2] Steven M. Brunelli, MD, MSCE,[3] Abigail Hunt, PhD,[3] Brigitte Schiller, MD,[4] Richard Glassock, MD,[5] Frank W. Maddux, MD,[6] Douglas Johnson, MD,[2] Tom Parker, MD,[7] and Allen Nissenson, MD[3,8]

Addressing fluid intake and volume control requires alignment and coordination of patients, providers, dialysis facilities, and payers, potentially necessitating a "Volume First" approach. This article reports the consensus opinions achieved at the March 2013 symposium of the Chief Medical Officers of 14 of the largest dialysis providers in the United States. These opinions are based on broad experience among participants, but often reinforced by only observational and frequently retrospective studies, highlighting the lack of high-quality clinical trials in nephrology. Given the high morbidity and mortality rates among dialysis patients and the absence of sufficient trial data to guide most aspects of hemodialysis therapy, participants believed that immediate attempts to improve care based on quality improvement initiatives, physiologic principles, and clinical experiences are warranted until such time as rigorous clinical trial data become available. The following overarching consensus opinions emerged. (1) Extracellular fluid status should be a component of sufficient dialysis, such that approaching normalization of extracellular fluid volume should be a primary goal of dialysis care. (2) Fluid removal should be gradual and dialysis treatment duration should not routinely be less than 4 hours without justification based on individual patient factors. (3) Intradialytic sodium loading should be avoided by incorporating dialysate sodium concentrations set routinely in the range of 134-138 mEq/L, avoidance of routine use of sodium modeling, and avoidance of hypertonic saline solution. (4) Dietary counseling should emphasize sodium avoidance.

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When dialysis adequacy is discussed, small-molecule clearance, as measured by urea kinetics, is the metric used. However, in the modern era of hemodialysis, when high-efficiency dialyzers are the rule and large surface area membranes are affordable, achieving a threshold of urea clearance is not difficult, and perhaps what is meant by "adequate dialysis" should be reconsidered. Although it is widely accepted that truly adequate dialysis encompasses a variety of other outcomes, including volume control and patient quality of life, in its most common current use the term "adequacy" often is narrowly applied to measures of small-solute removal. This critical point, that sufficient dialysis is more than just small-molecule clearance, is recognized in clinical guidelines. For example, the 2006 NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) clinical practice guideline recommendations for dialysis adequacy have sections for both hemodialysis and peritoneal dialysis that focus on volume control. To date, the critical importance of volume control as an element of sufficient dialysis may not be emphasized adequately by the broader dialysis community, likely because volume control, unlike small-solute clearance, remains difficult to assess and even more challenging to quantify in a standardized manner. Volume control and the means of achieving volume control are critical elements of dialysis care that likely have huge implications for patient morbidity and mortality and require active attention from all members of the dialysis team, especially the patient.

In March 2013, the chief medical officers of 14 of the largest dialysis providers in the United States, along with affiliated clinicians, nurses, and dieticians,

From [1]Tufts Medical Center, Boston, MA; [2]Dialysis Clinic, Inc, Nashville, TN; [3]DaVita Clinical Research, Minneapolis, MN; [4]Satellite Healthcare Inc, San Jose; [5]University of California at Los Angeles, Geffen School of Medicine, Los Angeles, CA; [6]Fresenius Medical Care North America, Waltham, MA; [7]Renal Ventures Management, Lakewood; and [8]DaVita HealthCare Partners Inc, Denver, CO.

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Address correspondence to Daniel E. Weiner, MD, MS, William B. Schwartz Division of Nephrology, Box 391, Tufts Medical Center, 800 Washington St, Boston, MA 02111. E-mail: dweiner@tuftsmedicalcenter.org

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responsible for treating >80% of dialysis patients nationally, convened a symposium to share their experiences in order to address meaningful approaches to improve dialysis patient outcomes. This meeting was notable as much for what was not discussed as for what was addressed in detail: anemia management was discussed only briefly and urea clearance was not mentioned at all. The consensus among attendees was that the most consequential factors for improving the lives of dialysis patients included volume control, nutrition, dialysis access, and transitions in care, including the transition to dialysis therapy and the transition to and from a hospital. This report focuses on the critical issue of redefining the concept of sufficient dialysis to include volume control, calling attention to both quality initiatives by dialysis providers and the dearth of research and limited tools currently available to optimize volume management among hemodialysis patients.

THE CHALLENGE TO DIALYSIS PROVIDERS

Although there have been improvements in morbidity and mortality rates during the past decade, morbidity and mortality remain unacceptably high among dialysis patients. According to the US Renal Data System 2013 *Annual Data Report*, only 52% of patients are still alive 3 years after the initiation of dialysis therapy.[1] Cardiovascular (CV) disease is the greatest cause of hospitalizations and mortality in the dialysis population, accounting for 164 deaths per 1,000 patient-years at risk in the second month after starting dialysis therapy and 76 deaths per 1,000 patient-years at risk at the end of the first year. This is not limited to the United States; for example, in Australia, although CV mortality has improved in dialysis patients, this has not kept pace with improvements in the general population.[2]

Traditionally, CV risk modification in hemodialysis patients has focused on more tangible factors, addressing atherosclerotic disease by blood pressure, lipid, or calcium-phosphorus control. However, it seems that adequate volume control is equally if not more important than these factors. Emerging evidence suggests that fluid overload may lie at the heart of the high rates of morbidity and mortality observed in patients treated with hemodialysis. Fluid overload is common in hemodialysis patients[3] and is associated with elevated blood pressure, left ventricular (LV) hypertrophy, and other adverse CV events, as well as increased mortality.[4,5] Moreover, higher interdialytic weight gain (IDWG) is associated with elevated risk of all-cause and CV mortality.[6,7]

Accordingly, fluid overload may be a key contributor to vascular stiffness, as well as the initially adaptive but eventually maladaptive cardiac remodeling that occurs when the left ventricle responds to pressure and volume overload (Fig 1). These pathophysiologic changes, in conjunction with other traditional and nontraditional CV risk factors in dialysis patients, predispose to subendocardial ischemia, reflecting a mismatch between the increased perfusion demands of a thickened ventricle and the reduced supply encountered with impaired coronary vasodilatory capacity and decreased coronary perfusion during diastole. Notably in the setting of perfusion changes during the hemodialysis procedure itself, cardiac ischemia may become increasingly manifest, with cardiac stunning and ultimately fibrosis and heart

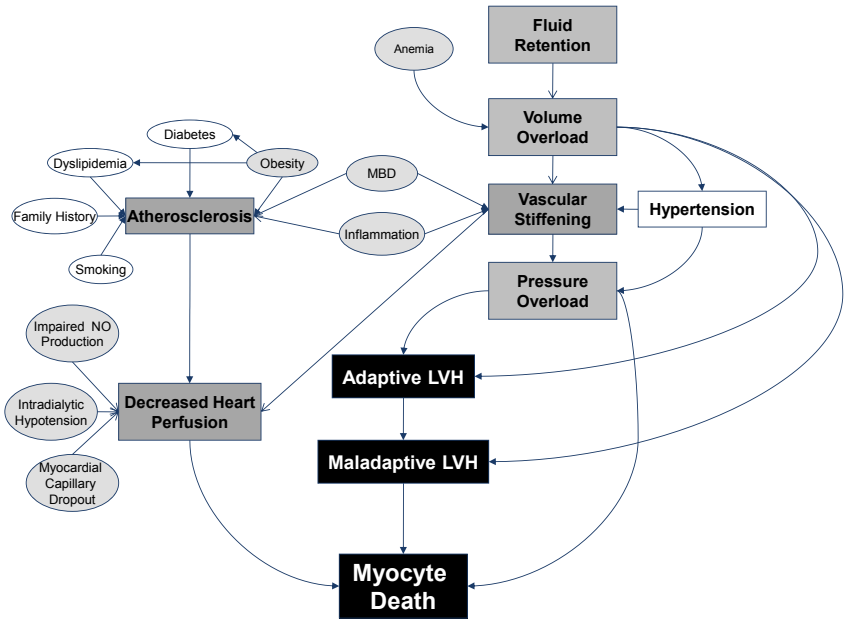

Figure 1. Proposed pathogenesis of cardiac disease in hemodialysis, simplified. Gray ovals are nontraditional cardiovascular disease risk factors, white ovals are traditional cardiovascular disease risk factors, light boxes represent key processes along the causal pathway, and dark boxes represent structural cardiac manifestations. Hypertension is both a key process and a traditional risk factor. Abbreviations: LVH, left ventricular hypertrophy; MBD, mineral and bone disorder; NO, nitric oxide.

failure occurring.[8,9] Critically, the heart is not the only organ at risk, with recent data also suggesting similar effects on the brain.[10]

Likely reflecting a combination of perturbations in volume during hemodialysis as well as the effects of chronic volume overload on hemodialysis patients, multiple observational studies have demonstrated an association between rapid ultrafiltration and increased mortality.[6,11-13] Consequently, one of the key factors to improving volume control is increasing a patient's time on hemodialysis. Boiled down to its essentials, addressing volume overload is a straightforward concept; patients must attain euvolemia and thereafter to maintain euvolemia, intake must equal output (Fig 2). Therefore, addressing both intake and output are critical to addressing volume. Unfortunately, simple solutions remain elusive, particularly when presented with the challenges of in-center hemodialysis schedules and other provider factors, the lack of technology to accurately assess volume status, patient factors, and the paucity of clinical trials throughout nephrology and particularly in dialysis.[14] Even if consistent attainment of postdialysis intravascular euvolemia were achievable, it would not solve the volume problem entirely: IDWG ensures that on a time-averaged basis, patients experience some degree of extracellular volume expansion. Nonetheless, routinely achieving postdialysis euvolemia would represent an important step forward. Reassuring data exist; in patients treated with frequent hemodialysis (planned 6 times per week) in the very select FHN (Frequent Hemodialysis Network) Trial population, a schedule that is accompanied by reduced IDWG and lower ultrafiltration rates (UFRs), antihypertensive medications could be reduced, blood pressure control could be improved, and LV hypertrophy could be regressed.[15,16] Of note, the FHN trials were not powered to detect a difference in all-cause mortality.

There are at least 6 major barriers that providers must overcome to more consistently achieve normovolemia in hemodialysis patients (Box 1). First, there are no widely available gold-standard tools with which dry weight can be accurately ascertained, although current or future roles may exist for relative plasma volume monitoring (RPVM), bioelectrical impedance monitoring, and other novel technologies. Second, dialysis facility staff may be reluctant to implement longer treatment times because individualizing treatment times may create logistical challenges. Third, additional fluid removal, even with careful monitoring, may result in more frequent hemodialysis-associated symptoms (such as intradialytic hypotension and cramping) that must be managed by facility staff and may adversely affect patients' experience of care. Fourth, although for some patients, 4 and even 5 or 6 treatments a week can improve fluid management, payers do not consistently reimburse fourth treatments and even less frequently reimburse fifth and sixth treatments. Fifth, many patients are unwilling to lengthen treatment time or increase treatment frequency, and many fear that either increased fluid removal or longer treatment will cause them more symptoms. Additionally, patients may have difficulty with sodium restriction, reflecting long-standing dietary habits, taste preferences, and cost.

Box 1. Major Provider Barriers to Achieving Normovolemia in Dialysis Patients

1. Absence of widely available validated gold-standard tools for dry weight assessment.
2. Potential logistical challenges associated with longer treatment times.
3. Possibility of more frequent dialysis-associated symptoms, such as hypotension and cramping, with additional fluid removal.
4. Inconsistent reimbursement and payment policy for additional dialysis sessions, particularly 5th or 6th treatments.
5. Patient reluctance to lengthen treatment time, increase treatment frequency, and reduce dietary sodium intake.
6. Physician factors, including limitations in extracellular volume status assessment, dietary counseling, and timely adjustment of the dialysis prescription.

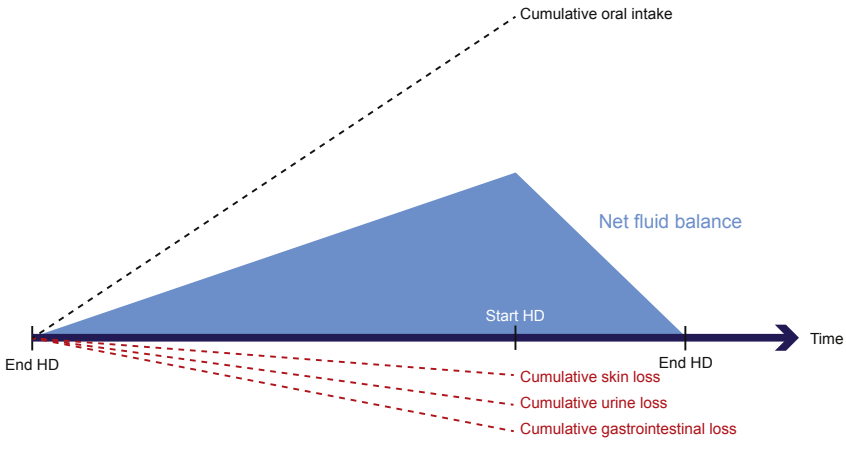

Figure 2. Fluid balance in hemodialysis (HD). Net fluid excess is a function of interdialytic intake versus insensible, urine, and gastrointestinal losses, such that fluid removal during the dialysis session needs to equal this fluid excess.

Sixth, clinicians may not evaluate patients frequently enough or carefully enough to allow them to assess optimally extracellular volume status, counsel about salt and water consumption, or adjust the hemodialysis prescription in a timely manner. These factors can lead to slow but progressive volume gain over time, particularly if target weight reassessment fails to keep pace with lean body mass loss.

Dealing with these challenges requires a multifaceted approach spanning all stakeholders in dialysis care, including patients and their families. Facilities should emphasize the importance of controlling extracellular fluid volume. All staff, including nurses, technicians, dietitians, social workers, and physicians, should pay regular attention to target weight and be alert to possible changes in lean body mass. Given data, albeit limited, that support cognitive behavioral therapy to modify patient habits in dialysis,[17] patient and family education must communicate effectively the distinction between fluctuations in weight attributable to extracellular fluid and weight changes attributable to increases or decreases in lean body mass. When this concept is firmly established and patients and family members demonstrate their understanding by teaching it back, patient and family education should give major emphasis to restriction of sodium and water intake.[17-19] Physicians should examine available data to determine the best ultrafiltration strategies for their patients, discuss these strategies with their patients and the treatment team, and implement them. Industry should develop and refine instruments and techniques to guide ultrafiltration. Stakeholders should encourage and fund research into strategies for optimizing dialysis care, which to date remain insufficient, particularly given the high costs of dialysis care.[14] Payers should allow providers the latitude to incorporate new technologies and treatment strategies.

The rest of this conference report focuses on specific strategies to address volume control. Noting the success of the Fistula First Breakthrough Initiative, we propose several Volume First statements that may improve outcomes among hemodialysis patients, along with research recommendations to further dialysis care (Box 2). These statements form our consensus opinion, which is based on broad experience across multiple dialysis providers, but unfortunately, to date, often is reinforced by only observational and frequently retrospective studies.

Box 2. Research Recommendations to Enhance Volume Management in Hemodialysis

Extracellular fluid status should be a component of sufficient hemodialysis
- Clinical trials evaluating the impact of technologies to assess volume status during hemodialysis on patient experience, hospitalization, and mortality outcomes
- Evaluation of the utility of biomarkers, such as natriuretic peptides, to guide ultrafiltration
- Evaluation of the effects of improved volume control on clinical outcomes, including cardiac morphology and function, as well as other highly prevalent conditions in dialysis patients such as sleep apnea and physical and cognitive functional impairment

Fluid removal should be gradual
- Evaluation of the impact of dialysis duration on important clinical outcomes
- Clinical trials evaluating the effect of dialysate temperature on clinical outcomes and patient experience
- Clinical trials evaluating ultrafiltration rate thresholds and the association between ultrafiltration rate and cardiac and brain manifestations

Intradialytic sodium loading should be avoided
- Calibration of prescribed dialysate sodium to delivered dialysate sodium
- Clinical trials evaluating dialysate sodium concentration strategies, including dialysis based on the serum to dialysate sodium gradient, on mortality

Dietary counseling should emphasize sodium avoidance
- Development of culturally diverse educational tools and interventions to reduce dietary sodium intake
- Quality improvement studies evaluating patient and patient family interventions to reduce dietary sodium intake

Note: With support of regulatory agencies and dialysis providers, many of these trials can be pragmatic and/or cluster randomized to enable more prompt generation of data and lower costs. This approach could facilitate more ready conduct of well-designed, large, practical, and generalizable clinical trials that assess clinical decisions made daily in the care of dialysis patients.

CONSENSUS OPINIONS

1: Extracellular Fluid Status Should Be a Component of Sufficient Hemodialysis

Currently, in most cases, dry weight is assessed by fairly crude subjective and objective clinical measures with little scientific data supporting use of these measures to determine ultrafiltration targets. Many nephrologists may recall being taught that dry weight is the lowest achieved weight before a patient ends up in the Trendelenburg position. Not surprisingly, excessive ultrafiltration can occur both when challenging patients' dry weight and when treating to prescribed dry weight, and these episodes may result in adverse clinical events, such as hypotension, cramping, and syncope, in addition to potential longer term sequelae that may occur as a consequence of cardiac and other organ stunning.[20] Furthermore, episodes of intradialytic hypotension are associated with earlier loss of residual kidney function,[21] which appears to be associated with poorer survival and worse quality of life in hemodialysis patients.[22]

Conversely, when target weight is overestimated (either inadvertently or to minimize the likelihood of

symptomatic hypovolemia), patients remain chronically volume expanded, which can have both immediate (eg, pulmonary edema) and chronic consequences (eg, maladaptive changes in cardiac structure). Often this is addressed with additional use of antihypertensive agents to control elevated blood pressure, a condition that itself often is a manifestation of volume overload in dialysis patients, either in lieu of or in conjunction with efforts to control volume. We believe that the use of antihypertensive agents as a primary strategy to control elevated blood pressure in dialysis patients should be discouraged in favor of gradual correction of volume overload while concomitantly tapering antihypertensive medications.

Current and future technologies may be able to assist in the optimization of fluid status in hemodialysis patients. RPVM uses optics to noninvasively monitor hematocrit, oxygen saturation, and change in intravascular blood volume during the dialysis session, with dialysis staff acting on the hypothesis that excessive hemoconcentration suggests a failure to refill the vascular space and altering the ultrafiltration plan accordingly.[23] Several small studies suggest that RPVM may assist in establishing appropriate dry weights, resulting in a reduced incidence of intra- and postdialytic morbidities.[24-26] A recent facility-level quality improvement initiative performed in 15 hemodialysis units also described a reduction in fluid-related hospitalizations in facilities implementing dry weight determinations using an educational training program in conjunction with RPVM (CritLine; Fresenius Medical Care) versus the educational training program alone.[27] Critically, this study was designed as a quality improvement initiative, was not powered to show statistical significance, and is not published in the traditional peer-reviewed literature. In contrast, the only patient-level randomized trial published in the peer-reviewed literature assessing the use of RPVM found higher hospitalization and mortality rates in RPVM-treated patients compared with controls.[28] Importantly, volume assessment tools are only a means to an end and their efficacy is only as good or bad as the interventions levied in response. Therefore, heterogeneous findings are not surprising, and importantly, no single positive or negative study should be interpreted as definitive evidence in favor of or against their potential clinical effectiveness.

The use of bioelectrical impedance spectroscopy to measure body composition is another potential approach to determine appropriate dry weight empirically.[29] In a prospective study of 52 patients in whom fluid status was assessed regularly using body composition monitoring over the course of 1 year, fluid overload was reduced by 2 L in patients with fluid overload $>$ 15% of extracellular water without an increase in the incidence of intradialytic adverse events.[30] A reduction in both systolic blood pressure and use of antihypertensive medication also was observed. Furthermore, in a recent randomized controlled study, objective measurement of fluid overload with bioelectrical impedance spectroscopy was associated with a reduction in time-averaged fluid overload values (-0.5 ± 0.8 L), regression of LV mass index (from 131 ± 36 to 116 ± 29 g/m^2 in the intervention group), and decreases in blood pressure and arterial stiffness parameters.[31] The most notable study to date evaluating bioimpedance-guided fluid management was a pilot study that randomly assigned 131 patients from a single hemodialysis center in Romania. During 2.5 years of follow-up, among individuals managed using bioimpedance, there was a greater decline in arterial stiffness and relative fluid overload, although there was no difference in systolic blood pressure. Additionally, there were fewer deaths in the bioimpedance group, although with only 9 deaths total, the trial was underpowered to demonstrate a robust mortality benefit.[32]

We propose:

1. Approaching normalization of extracellular fluid volume should be a primary goal of dialysis care.
2. Barring objective evidence to the contrary, any patient with blood pressure $>$ 150/90 mm Hg at the predialysis assessment should be regarded as fluid overloaded and a program of gradual weight reduction and sodium restriction should be attempted prior to initiation or escalation of pharmacologic antihypertensive therapy. More frequent ultrafiltration also should be considered, incorporating additional in-center treatments, nocturnal hemodialysis if available, or home modalities, including both hemodialysis and peritoneal dialysis.
3. Providers and payers should facilitate robust evaluation of promising technologies and incorporation of effective novel technologies to enhance the safety and efficacy of attaining normal extracellular fluid volume.
4. Randomized clinical trials, including pragmatic clinical trials with broad generalizability and applicability and rigorous quality improvement initiatives, should be conducted to evaluate methods and promising technologies to facilitate achievement of sufficient volume control in dialysis patients.

2: Fluid Removal Should Be Gradual

Several observational studies have reported associations between more rapid UFR and adverse clinical outcomes. A retrospective analysis of 15,536 patients from 7 countries participating in DOPPS (Dialysis Outcomes Practice Patterns Study) showed that UFR $>$ 10 mL/h/kg was associated with significantly

increased risk of intradialytic hypotension and all-cause mortality.[13] Similarly a small multicenter prospective study of 287 prevalent hemodialysis patients in Italy reported an association between higher UFR and mortality. In this study, UFR < 12.4 mL/h/kg was associated with better survival at 5 years and each 1-mL/h/kg increase in UFR was associated with a 22% increase in mortality risk.[12] A post hoc analysis of data from the HEMO (Hemodialysis) Study categorized patients into 3 UFR groups (≤10, 10-13, and >13 mL/h/kg) and found that UFR > 13 mL/h/kg was associated independently with a 59% increase in risk of all-cause mortality and a 71% increase in risk of CV mortality,[11] while in the subgroup of HEMO Study participants with UFR of 10-13 mL/h/kg, there was a small increased mortality risk compared with those with UFR < 10 mL/h/kg. Notably, greater UFR was associated with increased mortality independent of IDWG,[6] suggesting that rate of fluid removal should be an important consideration when determining dialysis session length.

During hemodialysis, fluid is cleared directly from the intravascular space; this ultrafiltrate is replaced by shifts of fluid from the interstitial space into the vascular compartment. High UFR resulting in a fluid removal rate exceeding the resorptive capacity from the interstitial space results in intravascular hypovolemia and hypotension, which in turn can lead to reduced organ perfusion. Decreased myocardial blood flow and ischemia-induced cardiac stunning during hemodialysis is well described even in patients without significant coronary heart disease.[33-35] Abnormalities in LV wall motion are observed during and immediately after hemodialysis, whereas levels of cardiac troponin T, a marker of cardiac cell damage, increase after dialysis and are associated with the severity of hemodialysis-induced myocardial stunning.[36-38] Repeated ischemic episodes ultimately may result in cardiac remodeling and loss of contractile function.[39] Interestingly, cardiac stunning appears to be ameliorated in patients undergoing more frequent hemodialysis, possibly reflecting the lower UFRs and more consistent attainment of euvolemia experienced by these patients.[40] In addition to the well-described cardiac effects, high UFRs may result in ischemic insult to other organ systems, with some data suggesting that long-term brain hypoperfusion can lead to degradation of white matter, dementia, and depression.[41] Notably, the technique associated with RPVM during the intradialytic period has the potential to reduce the occurrence of such hypotensive episodes because ultrafiltration is matched to intravascular refilling.

Dialysis duration and UFR are tightly related. Consistent with observations of the effects of UFR on patient outcomes, the 2006 DOPPS analysis showed that dialysis treatment time longer than 240 minutes was associated independently with a 19% lower risk of all-cause mortality.[13] The reduction in mortality was evident in all geographic regions, but greatest in Japanese patients. A more recent retrospective analysis of data from 14,643 patients treated within a single large dialysis organization in the United States showed that session length shorter than 240 minutes was associated with increased all-cause mortality (hazard ratio, 1.32; 95% confidence interval, 1.30-1.69) compared to session length longer than 240 minutes.[6] Similarly, another retrospective analysis of 39,497 US in-center hemodialysis patients revealed a strong association between shorter dialysis session length and all-cause mortality, as well as incidence of CV events leading to hospitalization and death.[42] Currently, a 4-hour first strategy is being evaluated in the pragmatic TiME (Time to Reduce Mortality in End-Stage Renal Disease) Trial (ClinicalTrials.gov identifier, NCT02019225), a collaborative effort between the National Institutes of Health and 2 large dialysis organizations in the United States.

We Propose:

1. Based on the evidence summarized above, until further data are available, we propose a 4-hour first policy, such that the expected minimum duration of maintenance thrice-weekly hemodialysis is 4 hours, with treatment time adjusted up or down from 4 hours based on individualization of care and ability to consistently attain euvolemia, accounting for IDWG and UFR.
2. As dialysis duration is prescribed by the physician, we propose that prescribing physicians specifically comment on shorter durations of therapy in their patient assessments and reassess duration of dialysis regularly.
3. As described, modalities that incorporate more gradual ultrafiltration should be considered.

3: Intradialytic Sodium Loading Should Be Avoided

The electrolyte composition of dialysate is an important component of effective fluid management; however, the optimal sodium concentration for dialysate is uncertain. In the past several decades, higher dialysate sodium concentrations had been used in an attempt to reduce dialysis-associated symptoms and intradialytic hypotension, problems that became increasingly common as UFRs increased. Patients therefore frequently would undergo dialysis against a dialysate that may result in net diffusive movement of sodium into the patient, potentially contributing to greater IDWG, increased thirst, and higher blood pressure.[43,44] In a 1982 study by Van Stone et al[45] evaluating the effects of 3 different dialysate sodium

concentrations at similar ultrafiltration targets, less plasma volume loss occurred with higher dialysate sodium levels (~151 mEq/L) compared with dialysate sodium concentrations of 141 and 131 mEq/L. Similarly, Lambie et al[46] evaluated the effects of lower dialysate conductivity, noting greater initial sodium clearance, lower IDWG, and lower blood pressure with lower dialysate sodium concentrations.

A 2011 study of 1,084 hemodialysis patients treated at Satellite Healthcare facilities revealed a mean predialysis plasma sodium concentration of 136.7 ± 2.0 mEq/L,[47] whereas in a small study of 15 nocturnal in-center hemodialysis patients, mean predialysis serum sodium concentration was found to be 136.2 ± 3.1 mEq.[48] A retrospective analysis of 1,549 individuals in the HEMO Study showed a mean predialysis sodium concentration of 138.2 ± 4.0 mEq/L.[49] An analysis of 11,555 patients from 12 countries in DOPPS showed a mean prehemodialysis serum sodium concentration of 138.5 ± 2.8 mEq, with Japanese patients having the highest (139.1 ± 2.6 mEq/L) and patients in Australia and New Zealand having the lowest levels (137.4 ± 2.8 mEq/L).[50] In this analysis, US patients were found to have a mean predialysis serum sodium concentration of 137.9 ± 2.8 mEq/L. Two other studies have assessed prehemodialysis serum sodium levels in US dialysis patients, reporting concentrations of 136.1 mEq/L in 2,272 hemodialysis patients treated at Satellite Healthcare facilities[51] and 137.9 mEq/L in 10,413 hemodialysis patients treated at DaVita HealthCare Partners facilities.[52]

Based on these observed predialysis serum sodium concentrations, dialysis against a dialysate sodium concentration of 140 mEq/L on average results in diffusive sodium gain, which may offset or potentially over-ride convective sodium removal. This may be an underestimate if the Gibbs-Donnan effect is taken into consideration—a proportion of serum sodium will complex to anionic proteins that do not diffuse across the dialysis membrane; thus, the effective serum sodium concentration is actually lower than that measured. The first Satellite Healthcare study described found that dialysate sodium prescriptions ranged from 136-149 (median, 140) mEq/L, with most patients being dialyzed against a positive sodium gradient and 91% of patients having a higher serum sodium level after dialysis.[47] This study also demonstrated a direct correlation between sodium gradient and both IDWG and postdialysis thirst. McCausland et al[51] also noted significant variation in dialysate sodium prescriptions across centers, with a fixed dialysate sodium concentration of 140 mEq/L being the most commonly used (in 47.9% of patients), and showed an association between higher dialysate sodium concentration and increased IDWG. Similarly, DOPPS showed that higher dialysate sodium prescriptions were associated with increased IDWG, equating to 0.17% of body weight per each 2-mEq/L higher dialysate sodium concentration.[53] The Satellite Healthcare study of nocturnal in-center hemodialysis patients described directly assessed the effect of reducing the dialysate sodium concentration from 140 mEq/L (in the first 12-week phase of the study) to 134 mEq/L (in the second 12-week phase of the study) and showed significant decreases in absolute IDWG, IDWG relative to dry weight, and systolic blood pressure (by 0.6 ± 0.6 kg, 0.6% ± 0.8%, and 8.3 ± 14.9 mm Hg, respectively) in the second phase compared with the first. Postdialysis plasma sodium concentrations also were decreased by 3.7 ± 1.9 mEq/L.[48]

Data for the association between dialysate sodium and mortality are inconsistent. McCausland et al[51] noted that higher dialysate sodium concentration is associated with greater mortality at higher serum sodium concentration, with no significant relationship noted at lower serum sodium levels. In contrast, Hecking et al,[50,53,54] analyzing international DOPPS data, noted that patients treated at hemodialysis facilities that use uniformly higher dialysate sodium concentrations do not have markedly higher predialysis systolic blood pressures and further noted lower mortality in patients with serum sodium levels < 137 mEq/L dialyzed against dialysate sodium prescriptions > 140 mEq/L, despite greater IDWG. Although reconciling these results is difficult, illustrating the need for clinical trials in this field, the juxtaposition of greater IDWG and lower mortality suggests possible residual confounding despite the rigorous statistical methodology applied by Hecking et al. Alternatively, transient hypotension may be more common with lower dialysate sodium concentrations, suggesting that interventions that address both sodium balance and effective ultrafiltration need to be implemented in concert.

One possible intervention to improve intradialytic sodium loading would be use of a sodium alignment protocol, in which the dialysate sodium concentration is set to the mean predialysis sodium level for the last 3 months for each patient. This process would allow individualized treatments and theoretically would make it less likely that a patient would dialyze against a positive sodium gradient. However, a concern expressed by nephrologists is that dialysis machines currently do not automatically reset to a certain sodium prescription between treatments. As a result, there may be increased risk for prescription errors if the sodium gradient prescription is not reset. This risk could be mitigated if dialysis machines were able to automatically reset to a specific default dialysate sodium prescription (eg, sodium of 138 mEq/L).

Critically, the multiple components of the dialysate affect the total dialysate sodium concentration, and there may be small but significant differences between prescribed and delivered dialysate sodium concentrations.

Sodium modeling, whereby dialysate with a higher sodium concentration (145-160 mEq/L) is used early in dialysis and sodium levels are decreased over the course of dialysis toward or <140 mEq/L, is not recommended for routine use. Such an approach may increase the amount of sodium conferred upon dialysis to as much as 9 g,[55,56] and, although sodium modeling reduces the frequency of hypotension and cramping during dialysis in some patients, it also is associated with increased fatigue and thirst, higher IDWG, and higher blood pressure.[57-59]

Another widely used intervention to treat intradialytic hypotension is hypertonic saline solution, whereby 5-10 mL of 24.4% saline solution (containing 4 mEq/mL [234 mg] of sodium chloride) is infused rapidly. Hypertonic saline solution has remarkable effects, rapidly resolving cramps and hypotension,[60] potentially reflecting rapid upregulation of arginine vasopressin in addition to volume expansion.[61] However, this may come at a cost of increased sodium balance. Optimally, if available, technology to guide UFR can be used to prevent symptoms leading to administration of high osmolar solutions, particularly in patients with frequent cramping and hypotensive episodes during dialysis.

We Propose:

1. Dialysate sodium concentration typically should be prescribed in the range of 134-138 mEq/L, with deviations based on individual patient circumstances.
2. Because predialysis serum sodium concentrations have been shown to be stable over time in individual patients,[62] tailoring dialysate sodium concentration to the patient's particular sodium "set point" may have benefits.[63-65]
3. Dialysis machine manufacturers should consider changing settings such that the machine is reset to a default dialysate sodium concentration instead of the dialysate sodium concentration from the prior dialysis treatment.
4. Avoidance of hypertonic saline solution and avoidance of the routine use of sodium modeling.
5. Rigorous clinical trials should be conducted to determine optimal dialysate sodium concentrations and dialysate sodium gradients.

4: Dietary Counseling Should Emphasize Sodium Avoidance

Serum sodium concentration is affected by sodium and fluid removal during dialysis, as well as by dietary sodium and fluid intake. Lower sodium intake is associated with lower IDWG and lower blood pressure, as well as better survival. Maduell and Navarro[66] showed that restriction of salt intake without modification of the dialysate composition resulted in reduced IDWG and predialysis blood pressure. Unfortunately, clinical surveillance of dietary sodium intake is limited by inaccurate and imprecise measurement instruments, such as dietary recall, food frequency questionnaires, and food journals.[67-69]

The importance of dietary sodium to fluid management and patient outcomes places specific emphasis on the critical role of dietitians and their dietary counseling activities. Dietitians should be asked to shift their primary emphasis from phosphorus intake and phosphate-binder use to interdialytic sodium and water intake, as measured by IDWG. IDWG >3 kg or >3.5% of body weight should prompt intensive intervention by both the dialysis dietitian and the dialysis team as a whole. Dietary advice should account for specific patient circumstances, including the availability of fresh foods and the patient's financial situation, because restriction of sodium at the expense of lowering caloric intake also is undesirable. For example, work by McCausland et al[51] demonstrated that among hemodialysis patients, dietary sodium intake was not associated with mortality on a crude basis, but higher dietary sodium intake potentially was associated with greater mortality when calorie and protein intake was adjusted for; in other words, lower dietary sodium intake appears to be advantageous only if sodium can be restricted without inadvertently lowering intake other essential macronutrients.

We Propose:

Dialysis dietitians and other dialysis personnel should emphasize limiting sodium intake to the same or greater extent as other dietary counseling.

CONCLUSIONS

In summary, it is the belief of this coalition that good fluid management is one of the most essential unmet needs of contemporary dialysis populations in the United States and abroad. Addressing fluid intake and volume control requires alignment and coordination of patients, providers, dialysis facilities, and payers, potentially requiring a Volume First approach. In the absence of definitive clinical trials, few of which are being conducted or will be performed in the immediate future, we propose the following: (1) regular assessment of target weight goals; (2) gradual ultrafiltration with dialysis treatment times not routinely less than 4 hours without justification; (3) dialysate sodium concentration set routinely in the range of 134-138 mEq/L, with avoidance of the routine

use of sodium modeling and avoidance of hypertonic saline solution; and (4) aggressive but judicious dietary sodium counseling tailored to individual patients' needs. When possible, these interventions should be accompanied by data analyses to assess their efficacy and safety. Given the high morbidity and mortality rates among dialysis patients and the absence of sufficient trial data to guide dialysis therapy, we believe that attempts to improve care based on quality improvement initiatives, physiologic principles, and clinical experiences are warranted, with the ultimate goal of continuing to improve patient outcomes.

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