4. Dong L, Krewson EA, Yang LV: Acidosis activates endoplasmic reticulum stress pathways through GPR4 in human vascular endothelial cells. *Int J Mol Sci* 18: 278–292, 2017
5. Justus CR, Sanderlin EJ, Yang LV: Molecular connections between cancer cell metabolism and the tumor microenvironment. *Int J Mol Sci* 16: 11055–11086, 2015
6. Yaqoob MM: Acidosis and progression of chronic kidney disease. *Curr Opin Nephrol Hypertens* 19: 489–492, 2010
7. Banerjee T, Crews DC, Wesson DE, Tilea AM, Saran R, Ríos-Burrows N, Williams DE, Powe NR: Centers for disease control and prevention chronic kidney disease surveillance team: High dietary acid load predicts ESRD among adults with CKD. *J Am Soc Nephrol* 26: 1693–1700, 2015
8. Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, Wesson DE: Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. *Kidney Int* 78: 303–309, 2010
9. Goraya N, Simoni J, Jo C, Wesson DE: Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. *Kidney Int* 86: 1031–1038, 2014
10. Wesson DE, Simoni J, Broglio K, Sheather S: Acid retention accompanies reduced GFR in humans and increases plasma levels of endothelin and aldosterone. *Am J Physiol Renal Physiol* 300: F830–F837, 2011
11. Wesson DE: Does an acid-milieu in chronic kidney disease contribute to its increased cardiovascular mortality? *Am J Nephrol* 43: 408–410, 2016
12. Raphael KL, Carroll DJ, Murray J, Greene T, Beddhu S: Urine ammonium predicts clinical outcomes in hypertensive kidney disease. *J Am Soc Nephrol* 28: 2483–2490, 2017
13. Wesson DE, Pruszynski J, Cai W, Simoni J: Acid retention with reduced glomerular filtration rate increases urine biomarkers of kidney and bone injury. *Kidney Int* 91: 914–927, 2017

See related article, "Urine Ammonium Predicts Clinical Outcomes in Hypertensive Kidney Disease," on pages 2483–2490.

Turning the Tide: Improving Fluid Management in Dialysis through Technology

Jennifer E. Flythe
Division of Nephrology and Hypertension, Department of Medicine, University of North Carolina Kidney Center, University of North Carolina School of Medicine, Chapel Hill, North Carolina; and Cecil G. Sheps Center for Health Services Research, University of North Carolina, Chapel Hill, North Carolina

J Am Soc Nephrol 28: 2260–2262, 2017.
doi: https://doi.org/10.1681/ASN.2017050491

Over the last decade, components of fluid management have emerged as some of the most important modifiable risk factors for morbidity and mortality among individuals on maintenance dialysis. Hypervolemia, either chronic from long-term volume overload or episodic from large interdialytic weight gains, may increase the risk of left ventricular hypertrophy and its adverse downstream cardiovascular consequences.[1,2] Conversely, hypovolemia from either too voluminous or too rapid of fluid removal may lead to multiorgan ischemia and associated clinical sequelae.[3,4] Experts recognize the need for balance between the extremes of volume status and ultrafiltration, but inter-relationships among volume-related components, lack of data on their relative importance, and absence of relevant clinical trials hinder consensus guideline development. Notwithstanding the paucity of trial evidence in this arena, international experts and United States dialysis organization leaders concur that putting "volume first" is essential if the dialysis community is to successfully "turn the tide" on the unacceptably poor outcomes experienced by our patients.[5,6]

Although the importance of volume control has been long appreciated in places like Tassin, France and Izmir, Turkey, the interest in fluid management in the United States has taken root in the last 5 years. The two largest United States dialysis providers recently implemented fluid management clinical programs. In 2013, DaVita launched FluidWise, a program advocating close attention to target weight prescription and attainment, BP control, standardized dialysate sodium, sodium and fluid dietary restrictions, and use of a clinic fluid advisor. The program includes risk stratification tools and individual- and facility-level fluid reports.[7] In late 2016, Fresenius Medical Care, North America released the Fluid Management Dashboard, an electronic medical record tool that identifies patients with postdialysis weights $\geq$1 kg above or below their prescribed target weight and patients with ultrafiltration rates $>$13 ml/h per 1 kg in $>$30% of recent treatments. The dashboard, accessible on the hemodialysis machine, provides clinicians easy, single-screen access to recent pre- and postdialysis weights, prescribed target weights, prescribed and delivered treatment times, and postdialysis BPs.

Although each of these initiatives is important, the programs share two crucial deficiencies: (*1*) lack of tools that assess patient volume status objectively and (*2*) lack of randomized, controlled trial data showing that the proposed clinical interventions improve patient outcomes. Volume status estimation is essential for clinicians to accurately prescribe target weight, gauge ultrafiltration tolerance, and effectively balance the consequences of volume and fluid removal extremes. Physical examination findings contextualized with BP patterns and dialysis treatment tolerance are instructive but imprecise, and they often fall short in busy dialysis clinic environments. Objective volume assessment tools, such as biomarkers (*e.g.*, B-type natriuretic peptide), relative plasma volume (RPV) monitoring, lung ultrasound, and bioimpedance (BIA) technology, exist. However, to date, clinical uptake has been restrained. Biomarker results have been disappointing. The one randomized, controlled clinical trial of RPV monitoring found that patients randomized to RPV monitoring had

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Jennifer E. Flythe, University of North Carolina Kidney Center, 7024 Burnett-Womack CB #7155, Chapel Hill, NC 27599-7155. Email: jflythe@med.unc.edu

worse outcomes than those in the conventional monitoring group.[8] Lung ultrasound used to measure extravascular lung water holds promise and is the subject of an ongoing European randomized, controlled trial (the Lust Study; NCT02310061).

In recent years, BIA spectroscopy has garnered increased attention. BIA devices pass an electrical current through the body and use measured tissue resistance to estimate body fluid volume. There are numerous approaches to BIA measurement and reporting, including segmental versus total body measurements, single versus multiple frequencies, and differences in normalization methods. Recent small randomized trials suggest that multifrequency, whole-body BIA (versus clinical judgement) may be helpful in improving volume status and associated outcomes.[9,10]

In this issue of the *Journal of the American Society of Nephrology*, Zoccali *et al.*[11] examine the associations of baseline fluid overload and 1-year cumulative fluid overload (separately) with all-cause mortality in a 26-country cohort of 39,566 patients on incident hemodialysis. Volume status was measured by the Body Composition Monitor (BCM; Fresenius Medical Care, Germany), a multifrequency BIA spectroscopy device that relies on a three-compartment physiologic tissue model on the basis of physiologic tissue hydration constants. The device, used predialysis, quantifies extracellular volume and fluid overload. Within 2 minutes of attaching electrodes to one hand and one foot and entering height and weight data, the device computes hydration status, lean tissue mass, and adipose tissue mass among other measures. The BCM is approved for use in many countries outside the United States.

In the study by Zoccali *et al.*,[11] relative fluid overload (fluid overload/extracellular volume) was defined as ≥15% in men and ≥13% in women, approximately equivalent to an absolute fluid overload of 2.5 L. More than 200,000 BIA measurements were recorded in the 5-year study. In adjusted analyses, individuals with baseline fluid overload (assessed within 3 months of hemodialysis initiation) had a 26% excess risk for mortality compared with patients who were not fluid overloaded. Models stratified by predialysis BP yielded similar results. Individuals who were fluid overloaded with lower (<130 mmHg) and higher (>160 mmHg) BPs exhibited the greatest mortality risks. In separate analyses restricted to individuals who survived the first year of dialysis (n=22,845), cumulative exposure to fluid overload was calculated by the area under the curve of fluid overload measurements recorded in the first year of dialysis. This approach attempts to account for the effects of long-term risk factor exposure. Cumulative fluid overload was associated with greater mortality risk across all categories of predialysis BP. Risk was greatest among individuals with fluid overload and predialysis BPs <130 or >160 mmHg. Death hazards from the cumulative fluid overload analyses were notably higher than those from the baseline fluid overload analyses, suggesting that chronic fluid overload is a stronger predictor of mortality than baseline fluid overload. Results were robust across clinical subgroups, dialysis type (hemodialysis or hemodiafiltration), and country.[11]

By considering both baseline and cumulative fluid overload as measured by whole-body BIA in such a large international cohort, the study authors have admirably confirmed and extended the evidence base supporting an association between fluid overload and mortality among individuals on hemodialysis. Lack of data on cause-specific outcomes and residual kidney function as well as the inability to distinguish harm related to higher ultrafiltration rates administered to patients who were fluid-overloaded from harm related to fluid overload itself are limitations of this study but do not materially diminish the overall message.

Importantly, the data are observational and neither establish a causal relationship between BIA-measured volume overload and outcomes nor provide insight as to whether BIA-directed fluid management may improve outcomes. In fact, a recent Canadian review of the clinical effectiveness, cost-effectiveness, and evidence-based guidelines for BIA use among patients on dialysis found insufficient evidence to support widespread BIA adoption.[12] A 2015 United Kingdom analysis reached similar conclusions.[13] Such uncertainty in the face of the sizable, well conducted, prospective cohort study by Zoccali *et al.*[11] underscores the need for large-scale, randomized, controlled clinical trials designed to determine if optimizing volume status *via* BIA or other methods improves clinical outcomes.

Notably, no BIA device is US Food and Drug Administration approved for the indication of body composition determination among patients on dialysis. Beyond the aforementioned evidence gaps linking BIA-directed fluid management to clinical outcomes, issues regarding BIA validity remain. The BCM was validated against several gold standards: bromide dilution (extracellular water), deuterium dilution (total body water), dual energy x-ray absorptiometry (lean tissue mass), and others.[14] However, the majority of validation analyses were conducted in healthy individuals, raising reasonable question about their translation to individuals with ESRD. Also, thresholds differentiating fluid overload from nonfluid overload come from small studies that, again, rely on normohydration references from healthy controls. Substantial body composition differences between healthy controls and individuals with ESRD likely exist. Furthermore, it is plausible that optimal thresholds defining fluid overload may differ across subgroups other than sex, supporting the need for additional investigation of hydration cut points.

Despite these uncertainties, there is substantial cause for optimism. Accumulating evidence linking suboptimal fluid management to outcomes, like that provided by Zoccali *et al.*,[11] coupled with both dialysis provider and patient interest in improving fluid-related outcomes have spurred remarkable community momentum. Experts often cite absence of accurate volume status measures as one of the most essential unmet needs of the modern dialysis era.[6] Meaningful collaborations across academicians, industry leaders, innovators, and regulatory bodies, all informed by the patient voice, have the potential to stimulate consequential innovation

in fluid management. Beyond BIA-based devices, real-time blood volume monitoring (*e.g.*, hematocrit or tracer techniques) and dialysis machine ultrafiltration biofeedback represent potential technologies for additional investigation. Advancements in this regard will represent landmark achievements in not only nephrology but also, disciplines such as cardiology and critical care, and most importantly, they will have an enduring effect on the quality of life of our patients.

However, there is also substantial cause for immediate action. Zoccali *et al.*[11] confirm a clinical notion that has been believed and arguably, known for a long time: fluid overload is disadvantageous. Technologic advancement with associated regulatory approval is a lengthy endeavor. Existing data show that judicious target weight challenge can reduce fluid overload.[15] Reliance on our longitudinal patient relationships that are enriched with abundant BP, weight, treatment tolerance, and if we take the time to ask, symptom data may facilitate safe reductions in hypervolemia as we simultaneously develop and test more precise methods for hydration status estimation. Now is the time to turn the tide on fluid management.

ACKNOWLEDGMENTS

J.E.F. is supported by grant K23 DK109401 from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.

DISCLOSURES

J.E.F. has received investigator-initiated research funding from the Renal Research Institute (New York, New York), a subsidiary of Fresenius Medical Care, North America. J.E.F. has received speaking honoraria from Dialysis Clinic, Incorporated (Nashville, Tennessee); American Renal Associates (Beverly, Massachusetts); the American Society of Nephrology (Washington, District of Columbia); the National Kidney Foundation (New York, New York); Baxter (Deerfield, Illinois); and multiple universities.

REFERENCES

1. Kalantar-Zadeh K, Regidor DL, Kovesdy CP, Van Wyck D, Bunnapradist S, Horwich TB, Fonarow GC: Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. *Circulation* 119: 671–679, 2009
2. Chazot C, Wabel P, Chamney P, Moissl U, Wieskotten S, Wizemann V: Importance of normohydration for the long-term survival of haemodialysis patients. *Nephrol Dial Transplant* 27: 2404–2410, 2012
3. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM: Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol* 26: 724–734, 2015
4. Burton JO, Jefferies HJ, Selby NM, McIntyre CW: Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol* 4: 1925–1931, 2009
5. Hecking M, Karaboyas A, Antlanger M, Saran R, Wizemann V, Chazot C, Rayner H, Hörl WH, Pisoni RL, Robinson BM, Sunder-Plassmann G, Moissl U, Kotanko P, Levin NW, Säemann MD, Kalantar-Zadeh K, Port FK, Wabel P: Significance of interdialytic weight gain versus chronic volume overload: Consensus opinion. *Am J Nephrol* 38: 78–90, 2013
6. Weiner DE, Brunelli SM, Hunt A, Schiller B, Glassock R, Maddux FW, Johnson D, Parker T, Nissenson A: Improving clinical outcomes among hemodialysis patients: A proposal for a "volume first" approach from the chief medical officers of US dialysis providers. *Am J Kidney Dis* 64: 685–695, 2014
7. Van Wyck D, Brunelli S: FluidWise program focuses on fundamentals to improve patient care. *Nephrol News Issues* 29: 36–38, 2015
8. Reddan DN, Szczech LA, Hasselblad V, Lowrie EG, Lindsay RM, Himmelfarb J, Toto RD, Stivelman J, Winchester JF, Zillman LA, Califf RM, Owen WF Jr: Intradialytic blood volume monitoring in ambulatory hemodialysis patients: A randomized trial. *J Am Soc Nephrol* 16: 2162–2169, 2005
9. Hur E, Usta M, Toz H, Asci G, Wabel P, Kahvecioglu S, Kayikcioglu M, Demirci MS, Ozkahya M, Duman S, Ok E: Effect of fluid management guided by bioimpedance spectroscopy on cardiovascular parameters in hemodialysis patients: A randomized controlled trial. *Am J Kidney Dis* 61: 957–965, 2013
10. Onofriescu M, Hogas S, Voroneanu L, Apetrii M, Nistor I, Kanbay M, Covic AC: Bioimpedance-guided fluid management in maintenance hemodialysis: A pilot randomized controlled trial. *Am J Kidney Dis* 64: 111–118, 2014
11. Zoccali C, Moissl U, Chazot C, Mallamaci F, Tripepi G, Arkossy O, Wabel P, Stuard S: Chronic fluid overload and mortality in ESRD. *J Am Soc Nephrol* 28: 2491–2497, 2017
12. Canadian Agency for Drugs and Technology in Health: Bioimpedance Devices for the Assessment of Body Fluid Volume for Patients Undergoing Dialysis: A Review of the Clinical Effectiveness, Cost-Effectiveness and Guidelines – An Update, 2015. Available at: https://www.cadth.ca/bioimpedance-devices-assessment-body-fluid-volume-patients-undergoing-dialysis-update. Accessed May 3, 2017
13. National Institute for Health and Care Excellence: The BCM – Body Composition Monitor for Managing Fluid in People Having Dialysis, 2015. Available at: https://www.nice.org.uk/advice/mib41. Accessed May 3, 2017
14. Fresenius Medical Care: BCM- Body Composition Monitor. Available at: http://bcm-fresenius.com/22.htm. Accessed May 3, 2017
15. Agarwal R, Alborzi P, Satyan S, Light RP: Dry-weight reduction in hypertensive hemodialysis patients (DRIP): A randomized, controlled trial. *Hypertension* 53: 500–507, 2009

See related article, "Chronic Fluid Overload and Mortality in ESRD," on pages 2491–2497.