



January 2, 2020

Kim Wittenberg
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality
5600 Fishers Lane
Rockville, MD 20857

Dear Ms. Wittenberg:

The Renal Physicians Association (RPA) is the professional organization of nephrologists whose goals are to ensure optimal care under the highest standards of medical practice for patients with kidney disease and related disorders. RPA acts as the national representative for physicians engaged in the study and management of patients with kidney disease.

RPA welcomes the opportunity to provide comments on the ***End-Stage Renal Disease in the Medicare Population: Frequency and Duration of Hemodialysis and Quality of Life Assessment Draft Report***. RPA appreciates the scope of work undertaken by AHRQ, particularly highlighting the disconnect between payment policies and treatment, but we have concerns with AHRQ's assessment of insufficient or low evidence to support more frequent dialysis or dialysis of increased duration. Furthermore, RPA is concerned that the negative effects of increased access issues were presented without grading the evidence.

RPA's input and specific recommendations are provided below.

Overview

Abundant observational data spanning over 35 years from more than 100 peer-reviewed abstracts and journal articles consistently shows associations with clinical benefits of longer and/or more frequent treatments. This is the case whether the therapy is performed as short daily hemodialysis (SDHD) or as nocturnal hemodialysis (NHD). Conversely, data showing harm related to longer and/or more frequent treatments is scarce. Three of the concerns that have emerged are increased vascular access complications in patients receiving in-center HD 6 days a week, infection-related hospitalizations in those receiving short daily HD, and caregiver burden for those patients doing longer and/or more frequent treatments at home [1,2]. It is notable that decades of data adjusted for relevant confounders have shown no increased mortality associated with longer treatment time (TT).

Furthermore, although longer TT and/or more intensive dialysis may not be the best choice for all ESRD patients, more intensive dialysis may be of particular benefit to certain groups of ESRD patients [3]. These groups include patients with sleep apnea, difficult to manage hypervolemia, symptomatic hypotension or cramping during dialysis, and pregnant women. Patients who are obese and need longer TT to meet adequacy targets may also benefit. Patients with a smaller vascular access may also need longer TT at lower blood flows to meet adequacy targets. In addition to the many clinical benefits, quality of life can be improved for some patients with schedules of nocturnal home treatments or frequent but short, self-scheduled treatments that leave much or all of their days free for school, work, or family care.

Although much of the data is observational, the statistical analyses are rigorous and thoughtful, with control for relevant variables, and appropriate adjustments between groups. Home dialysis patients and those receiving longer or more frequent in-center HD may have characteristics such as better mobility, more resources, and less frailty, that also contribute to improved survival. A prospective RCT that is adequately powered to detect a difference in the isolated and sole primary outcome of survival, is needed. However, until results of such a definitive study are available, the RPA believes that current evidence, and the weight of expert opinion, support our recommendations.

There is general consensus among nephrologists and other subspecialists that for certain specific conditions such as congestive heart failure (CHF), pregnancy, and calciphylaxis, longer or more frequent hemodialysis is well justified with coverage policies in the United States currently supporting payment [4]. However, barriers still exist regarding the frequency with which additional treatments outside of the traditional thrice-weekly schedule are reimbursed, and this constraint represents a significant impediment to implementation of non-traditional treatment schedules. The recent US Department of Health and Human Services (HHS) initiative “Advancing American Kidney Health” is an effort to improve care for patients with chronic kidney disease (CKD) [5]. The initiative seeks to improve kidney care in the US, in part by improving options for renal replacement therapy, including expanding utilization of home dialysis. RPA strongly believes that payment policies that facilitate patient access to home therapies should be expanded in Medicare, Medicaid and by commercial payors.

Associations between longer TT and fewer hospitalizations, and with decreased use of anti-hypertensives and phosphorus binders (PB), suggest the possibility of global cost savings with this treatment approach [6-8]. Reductions in hospitalizations alone would impart significant savings to Part A Medicare, although provision of more frequent dialysis would cause some increase in Part B, expenditures. Nevertheless, a net savings to the system is anticipated, based upon experience elsewhere [9]. RPA posits that this net cost saving provides a compelling argument for the integration of Medicare Part A and B cost-analysis and finances, particularly for patients with ESRD.

Clinical Benefits of More Intensive Hemodialysis

In general, increased TT and more frequent hemodialysis provide identifiable physiologic benefits. These include less extreme fluctuations in volume and solute, slower ultrafiltration rates, and increased clearance of small and middle-size molecules and protein-bound molecules. A sample of studies describing associations between increased frequency and/or duration of HD and various clinical outcomes is summarized in the sections that follow.

Cardiovascular Benefits

Blood pressure (BP) control

Several studies performed in patients undergoing both short daily HD (SDHD) as well as nocturnal HD (NHD) show that BP goals are more readily met by patients receiving dialysis through these modalities as compared to patients on conventional thrice weekly HD. [10-16]. In many cases, BP control was achieved with either fewer medications or with cessation of all BP medications. The Frequent Hemodialysis Network (FHN) Daily Trial prospectively randomized patients to HD six times per week, or three times per week. Frequent HD was associated with improved HTN control after 1 year of intervention [1]. An RCT of frequent nocturnal HD vs. conventional HD supports the FHN finding of reduced BPs, with reduction or discontinuation of medications in over half the patients in the frequent nocturnal HD arm [10]. Another smaller RCT of extended weekly HD vs. standard HD did show a reduction in BP medication use after one year but did not demonstrate a difference between the two arms in mean BPs or LV mass. However, this study was designed to test quality of life, and it may have been underpowered to detect a difference in BP or LV mass between the two arms [17].

Left Ventricular Mass and Geometry

Several separate studies, including an RCT, have shown reduction in left ventricular mass index (LVMI) as measured by either echocardiography or magnetic resonance imaging with longer or more frequent HD [1,11,12,14,15]. In several of these studies, CHD patients were followed prospectively after conversion from standard HD to short daily dialysis or nocturnal hemodialysis; this change generated more hours of HD per week, and LV mass was reduced.

Malnutrition and Inflammation

Several studies have shown increased appetite, weight gain and muscle mass in patients converted from CHD to daily dialysis [18-20]. A detailed study of nitrogen kinetics in patients on NHD revealed that, compared CHD, there was no decline in total body nitrogen as measured by in-vivo neutron activation despite the larger amounts of amino acids lost in the dialysate with HHD [21]. The implication of this finding is that the greater catabolism associated with more hours of HD may be balanced by improved nutrition.

Phosphate and Bone Metabolism

Short daily hemodialysis (SDHD) is associated with significant improvements in net phosphate removal. With NHD delivered 4-7 nights a week, phosphate removal is approximately twice that of CHD and phosphorus levels are usually reduced. Depending on the number of hours of HD per week and individual diet, some patients no longer need phosphate binders or dietary phosphorus restriction, and some may even require phosphate supplementation [1,10,22-25]. The recently published ACTIVE Dialysis study randomized 200 participants to HD treatments of ≥ 24 hours/week or ≤ 18 hours/week. Extended hours of dialysis were associated with lower phosphate, independent of serum calcium and PTH levels [26].

Quality of Life (QOL) and Patient Reported Outcomes (PROs)

Patients on CHD typically report relatively poor quality of life, and the majority of ESRD patients do not work. Several studies report positive changes in QOL when patients make the switch from

CHD to more intensive therapy [10,18,27,28,29]. Improved QOL has also been reported in studies comparing frequent dialysis to conventional dialysis [1,7,30]. The FREEDOM study showed improvements in clinical outcomes including reduction of depressive symptoms [31]. A study by Unruh et al showed more frequent hemodialysis should be considered as an additional novel approach to improve the psychosocial health of patients treated with maintenance hemodialysis [32,33].

RPA Recommendations

Individualized therapy is key to providing patient-centered care. The provision of more frequent and/or intensive dialysis exemplifies this approach for patients with dialysis-dependent ESRD. Changes in delivery of care structures, reimbursement models and payment policies of CMS and other third-party payors to support therapies other than the dominant in-center, thrice-weekly, 3-4 hours treatment paradigm are needed. RPA's specific recommendations are provided below:

1. Longer and more frequent dialysis should be an option available to all patients for whom there is potential for clinical and quality of life benefits. Nephrologists should assess their patient population for those patients who might benefit from more intensive hemodialysis.
2. Medicare, Medicaid, and commercial health insurers should adopt payment policies that increase the availability of more intensive dialysis therapies (either SDHD or NHD) to patients as prescribed by the patient's nephrologist.
3. Funding both in the form of Medicare reimbursement for dialysis through the ESRD Prospective Payment System (PPS) and research funding to NIH should be provided to advance technologies that promote the practice of more intensive hemodialysis, whether at home or in-center, for its convenience and cost effectiveness, but mostly for the clinical benefits it provides.
4. CMS and NIH should support well designed large RCTs to further evaluate this matter, but these studies should not preempt the provision of the best care possible based on current evidence.

As always, RPA welcomes the opportunity to work collaboratively with AHRQ in its efforts to improve the quality of care provided to the nation's kidney patients. Any questions or comments regarding this correspondence should be directed to RPA's Director of Public Policy, Rob Blaser, at 301-468-3515, or by email at rblaser@renalmd.org.

Sincerely,

A handwritten signature in black ink, appearing to read "Jeffrey A. Perlmutter", followed by a small mark that looks like "mm" or a stylized flourish.

Jeffrey A. Perlmutter, MD
President

References:

1. Chertow GM, for the FHN Trial Group: In-Center Hemodialysis Six Times per Week versus Three Times per Week. *N Eng J Med* 363: 2287-300, 2010.
2. Kraus MA, Kansal S, Copland M, et al. Intensive hemodialysis and potential risks with increasing treatment. *Am J Kidney Dis.* 68: S51-S58, 2016.
3. Zoccali C, Dounousi E, Abd ElHafeez S, Tripepi G, Mallamaci F. Should we extend the application of more frequent dialysis schedules? A 'yes' and a hopeful 'no'. *Nephrol Dial Transplant* 30(1):29-32, 2015.
4. Wilk AS, Hirth RA, Messana JM. Paying for Frequent Dialysis. *Am J Kidney Dis* 74(2):248-255. 2019.
5. Executive Order 13879. "Advancing American Kidney Health". Available at <https://www.federalregister.gov/documents/2019/07/15/2019-15159/advancing-american-kidney-health>. Signed 7/10/2019.
6. Nesrallah GE, Lindsey RM, Cuerden MS, et al. Intensive Hemodialysis Associates with Improved Survival Compared with Conventional Hemodialysis. *J Am Soc Nephrol* 23: 696-705, 2012.
7. Tentori F, Zhang J, Li Y, Karaboyas A, Kerr P, Saran R, Bommer J, Port FK, Akiba T, Pisoni RL, Robinson BM: Longer dialysis session length is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 27: 4180-4188, 2012.
8. Bakris GL, Burkart JM, Weinhandl ED, McCullough PA, Kraus MA. Intensive Hemodialysis, Blood Pressure, and Antihypertensive Medication Use. *Am J Kidney Dis* 68(5S1):S15-S23, 2016.
9. Walker R., Marshall MR, Morton RL, McFarlane P, Howard K. The cost-effectiveness of contemporary home haemodialysis modalities compared with facility haemodialysis: a systematic review of full economic evaluations. *Nephrology* 19(8):459-70, 2014.
10. Culleton BF, Walsh M, Klarenbach SW, et al. Effect of frequent nocturnal hemodialysis vs. conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA* 298:1291-1299, 2007.
11. Pierratos A. Nocturnal home hemodialysis: an update on a 5-year experience. *Nephrol Dial Transplant* 14: 2835-2840, 1999.
12. Chan CT, Floras JS, Miller JA, Richardson RM, Pierratos A. Regression of left ventricular hypertrophy after conversion to nocturnal hemodialysis. *Kidney Int* 61: 2235-2239, 2002.
13. Nesrallah G, Suri R, Moist L, Kortas C, Lindsay RM. Volume control and blood pressure management in patients undergoing quotidian hemodialysis. *Am J Kidney Dis* 42:13-17, 2003.
14. Fagugli RM, Pasini P, Pasticci F, Ciao G, Cicconi B, Buon cristiani U. Effects of short daily hemodialysis and extended standard hemodialysis on blood pressure and cardiac hypertrophy: a comparative study. *J Nephrol* 19:77-83, 2006.
15. Walsh M, Culleton B, Tonelli M, Manns B, A systematic review of the effect of nocturnal hemodialysis on blood pressure, left ventricular hypertrophy, anemia, mineral metabolism and health-related quality of life. *Kidney Int* 67: 1500-1508, 2005.
16. Chan CT, Floras JS, Miller JA, Pierratos A. Improvement in ejection fraction by nocturnal hemodialysis in end-stage renal failure patients with coexisting heart failure. *Nephrol Dial Transplant* 17:1518-1521, 2002.

17. Jardine MJ, Zuo L, Gray N, et al. A Trial of Extending Hemodialysis Hours and Quality of Life. *J Am Soc Nephrol* 28: 1898-1911, 2017
18. McPhatter LL, Lockridge RS Jr., Albert J, et al. Nightly home hemodialysis: improvement in nutrition and quality of life. *Adv Renal Replace Ther* 6: 358-365, 1999.
19. Spanner E, Suri R, Heidenheim AP, Lindsay RM. The impact of quotidian hemodialysis on nutrition. *Am J Kidney Dis* 42: 30-35, 2003.
20. Galland R, Traeger J, Arkouche W, et al. Short daily hemodialysis rapidly improves nutritional status in hemodialysis patients. *Kidney Int* 60: 1555-1560, 2001.
21. Pierratos A, Ouwendyk M, Lindsay RM. Total body nitrogen increases on nocturnal hemodialysis. *J Am Soc Nephrol* 10: 299A, 1999.
22. Musci I, Hercz G, Uldall R, et al. Control of serum phosphate without any phosphate binders in patients treated with nocturnal hemodialysis. *Kidney Int* 53: 1399-1404, 1998.
23. Yuen D, Richardson RM, Chan CT. Improvements in phosphate control with short daily in-center hemodialysis. *Clin Nephrol* 64: 364-370, 2005.
24. Toussaint N, Boddington J, Simmonds R, et al. Calcium phosphate metabolism and bone mineral density with nocturnal hemodialysis. *Hemodialysis Int* 10: 280-286, 2006.
25. Rocco MV, Lockridge RS, Beck GJ, et al. The effects of frequent nocturnal home hemodialysis: The Frequent Hemodialysis Network Nocturnal Trial. *Kidney Int* 80:1080-1091, 2011.
26. Zhan Z, et al. Effect of extended hours dialysis on markers of chronic kidney disease-mineral and bone disorder in the ACTIVE Dialysis study. *BMC Nephrology* 20:259, 2019.
27. Sachdeva M, Barta V, Thakkar J, et al. Pregnancy outcomes in women on hemodialysis: a national survey. *Clin Kidney J* 10(2):276-281. 2017.
28. McFarlane PA, Bayoumi AM, Pierratos A, Redelmeier DA. The quality of life and cost utility of home nocturnal and conventional in-center hemodialysis. *Kidney Int* 64: 1004-1011, 2003.
29. Heidenheim AP, Muirhead N, Moist L, Lindsay RM. Patient quality of life on quotidian home hemodialysis. *Am J Kidney Dis* 42: 36-41, 2003.
30. Tennankore K, Nadeau-Fredette AC, Chan CT: Intensified home hemodialysis: clinical benefits, risks and target populations. *NDT* 29:1342-1349, 2014.
31. Jaber BL, Lee Y, Collins AJ et al. Effect of daily hemodialysis on depressive symptoms and postdialysis recovery time: interim report from the FREEDOM (Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements) Study. *Am J Kidney Dis* 56:531-539, 2010.
32. Unruh ML, Larive B, Chertow GM, et al. Effects of 6-timesweekly versus 3-times-weekly hemodialysis on depressive symptoms and self-reported mental health: Frequent Hemodialysis Network (FHN) Trials. *Am J Kidney Dis*. 2013;61:748-758.
33. Fischer MJ, Porter AC, Lash JP. Treatment of Depression and Poor Mental Health Among Patients Receiving Maintenance Dialysis: Are There Options Other Than a Pill or a Couch? *Am J Kidney Dis*. 2013;61:694-697.