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See related article, “Physician Visits and 30-Day Hospital Readmissions in Patients Receiving Hemodialysis,” on pages 2079–2087.

Mind the Gap

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There are known knowns. These are things we know that we know.

There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns.

There are things we don't know we don't know.

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Donald Rumsfeld, February 2002 US Department of Defense News Briefing

The gap in clinical outcomes between all forms of kidney transplantation and the putative best forms of dialysis is large. This gap is made even more evident in the report by Tennankore *et al.* in this issue of *JASN*,¹ in which all categories of transplantation (expanded criteria deceased donor, standard criteria deceased donor, and living donor) outcomes were compared with intensive home hemodialysis (IHHD) of at least 16 hours per week. Rigorous matching and analytics were used and we cannot fault the authors' methods or conclusions. Thus, we are left explaining such outcome differences between the “least good” transplant strategy (expanded pool deceased donors) and the “best” dialysis strategy (IHHD). We must “mind this gap.”

The authors are not transplant specialists; however, we are surrounded by such specialists, and we agree that when transplantation is available, it is the most desirable and preferred form of kidney replacement therapy. Obviously, the scarcity of organs and the ineligibility of some patients leave us with the need to replace kidney function with dialysis. Perhaps IHHD, the comparator to transplantation in the study by Tennankore *et al.*, is not the best form of dialysis.

If case mix–adjusted peritoneal dialysis and standard hemodialysis outcomes are similar as evidence suggests,² then the question becomes whether more intensive hemodialysis, which includes IHHD, is superior to standard hemodialysis. The Hemodialysis (HEMO) trial was unable to show that its version of more intense dialysis (per-session delivered Kt/V of 1.53 versus 1.16) was superior to standard dialysis.³ However, the HEMO trial was only three sessions per week. The non-randomized Following Rehabilitation, Economics, and Everyday-Dialysis Outcome Measurements trial suggested that more frequent hemodialysis (five or six sessions per week) might be superior.⁴ The randomized Frequent Hemodialysis Network (FHN) trial⁵ was designed to compare in-center thrice-weekly hemodialysis to six in-center sessions per week without a major difference in total dose and is further discussed below. However, we cared for two FHN trial patients randomized to six sessions per week, and both patients claimed to have felt better but both reverted back to their thrice-weekly in-center schedule at the end of the trial. The patients attributed this decision to the “hassle” of frequent in-center hemodialysis. Had this trial compared home hemodialysis three times per week versus six times per week, perhaps the hassle would have been less influential in the patients' decision to reduce the frequency of their sessions back to thrice weekly. In addition to the tedium, there is evidence of more vascular access (VA) problems with more frequent hemodialysis.⁶ Therefore, why dialyze more frequently?

Mortality is increased on the first day back after the long interdialytic interval of the weekend,⁷ which fueled the suggestion that more frequent treatments with narrower shifts in

volume and electrolytes might improve survival, as further discussed below. However, because of the hassle of frequency, perhaps longer treatment time could compensate. In the absence of a definitive randomized controlled trial of longer treatment time and survival, we must rely on abundant observational data over 3 decades from different countries, different patient populations, and analysis by a variety of investigators, which support the association between longer hemodialysis treatment time and better patient outcomes.^{8–10} Indeed, some would argue that from a purely academic and statistical perspective, the observational data have the strength and consistency to support a causal relationship.¹¹

Biologic plausibility is one of the characteristics of strong, robust observational data, and several studies point toward more optimal cardiac physiology in patients who have longer treatment times per week. First, hemodialysis-induced myocardial stunning very likely leads to chronic left ventricle (LV) damage and seems to be associated with greater volume removal.¹² Frequent hemodialysis schedules are associated with lower ultrafiltration volumes and ultrafiltration rates (UFRs), and are also associated with less myocardial stunning.¹³ A recent observational study shows an association between rapid UFR, defined as >13 ml/h per kg, and higher all-cause and cardiovascular-related mortality.¹⁴ For a 70-kg patient, removal of 3 liters in 4 hours, instead of in 3 hours, decreases the UFR from 14.3 ml/h per kg to 10.7 ml/h per kg. A treatment time of 5 hours reduces the UFR to 8 ml/h per kg, which is the group in this study with the lowest risk of death. It is biologically plausible that the lower UFRs that can be achieved with either more frequent hemodialysis or longer treatment time, or both, thereby minimizing LV stunning and hypertrophy and perhaps improving survival.

One physiologic gap in this observational chain of inference is filled in by data from the randomized controlled FHN trial.⁵ The patients assigned to in-center hemodialysis six times per week had lower ultrafiltration per treatment, as well as a statistically significant decrease in LV mass, compared with patients assigned to in-center hemodialysis three times per week. The statistical significance in LV mass reduction was achieved although 14% of patients randomized to six treatments per week attended <65% of their expected sessions. As mentioned earlier, patients randomized to six sessions per week complained of the hassle of leaving home. Consider the potential differences if the dialysis had been performed at home with fewer missed sessions.

Several studies of pregnancy outcomes provide evidence suggesting that patients who receive dialysis for a longer treatment time have better overall health. A recent study demonstrated a significantly higher birth rate associated with more intensive treatment, and was able to show a dose-response relationship between the number of dialysis hours per week and the live birth rate, as well as longer gestational age and a greater infant birth rate.¹⁵ To further support the argument for better generalized health with longer treatment time, daily

hemodialysis has been associated with improved nutrition and improved growth in children with ESRD.¹⁶

Ikizler argued that the selection of healthier patients to longer treatment time may introduce bias favoring the outcomes of longer treatment time.¹⁷ In the only observational multinational study to date showing higher mortality in patients receiving daily hemodialysis compared with those receiving conventional hemodialysis, the authors speculate that some of the French patients may have been assigned daily hemodialysis as rescue therapy and thus were actually sicker than those who received conventional hemodialysis.¹⁸ In addition and most crucially, this analysis could not be fully adjusted for the number of central venous catheters, a variable associated with mortality.¹⁹ After matching, 115 patients were missing VA information in the daily hemodialysis group, in contrast with only four patients missing VA information in the conventional hemodialysis group. If some of the 115 patients with missing VA data had catheters, then the percentage of patients with catheters would be higher in the daily hemodialysis group, a bias that would favor worse outcomes. It is notable that 30% of the patients in the daily hemodialysis group switched back to conventional hemodialysis. It is not clear whether these patients were healthier; however, if they were, then their removal from the daily hemodialysis group would leave a sicker residual population and thus generate bias toward a worse result in the daily hemodialysis group. The mean follow-up time was only 1.5 years and thus the study may simply not have been adequately powered to show better survival in the daily hemodialysis arm.

Many of the studies that show improved outcomes with more intensive dialysis follow patients receiving >20 hours of dialysis per week.^{9,20} Sessions of such duration are likely to have the cardiovascular safety of slow UFR as well as enhanced removal of slowly diffusible molecules, with unknown, but presumed, benefits. Part of the explanation for the gap may lie in better survival with extended treatment time using existing technology. Several investigators are minding the gap by working to invent new technologies to bridge it. William Fissell, David Humes, Victor Gura, and Claudio Ronco, to name a few, are working on dialytic or biologic devices to correct uremia. This progress is slow. Anemia and hyperparathyroidism were incriminated as problems affecting outcomes and currently both have pharmacologic therapies, but improved outcomes are not so certain. Even in randomized controlled trials, benefit to some patients and harm to others can lead to cancelling out of these opposite outcomes. Many aspects of the uremic condition are not understood. We have identified many known unknowns and have acknowledged that there are unknown unknowns in the gap between forms of dialysis and transplantation. It really is time to mind the gap.

DISCLOSURES

None.

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